ACID-CATALYSED PROTIUM-DEUTERIUM EXCHANGE

ACID-CATALYZED PROTIUM-DEUTERIUM EXCHANGE IN NORBORNYL AND AROMATIC SYSTEMS

By

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A Thesis

Submitted to the School of Graduate Studies

in Partial Fulfilment of the Requirements

for the Degree

Doctor of Philosophy

McMaster University

Fall, 1973

DOCTOR OF PHILOSOPHY (1973)
(Chemistry)

McMASTER UNIVERSITY
Hamilton, Ontario

TITLE: Acid-Catalyzed Protium-Deuterium Exchange in Norbornyl and Aromatic Systems

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NUMBER OF PAGES: ix, 234.

SCOPE AND CONTENTS:

Solvolysis of nortricyclyl bromide (9a), nortricyclyl chloride (9b), nortricyclanol (9c), 5- and 7-norbornenols (10b, 15), syn-7-hydroxy-exo-2-norborneol (18a) and exo-2,3-epoxynorbornane (19) in a sealed tube at 250° in 10% v/v CH_3COOD-D_2O or D_2O alone in the case of the halonortricyclanes yields multiple but incomplete deuteration of the products 2-(cyclopentene)-acetaldehyde (11), 3-(cyclopentene)acetaldehyde (12), 3-(cyclohexene)carboxaldehyde (13) and norcamphor (14). Similar results are obtained with norbornadiene (21).

Treatment of norbornene (53), nortricyclane (54), norbornyl acetate (55) and exo-norborneol (56) with 10% v/v CH_3COOD-D_2O at 250° yields primarily completely deuterated 2-norborneol in reasonable yields. In contrast, treatment of benzonorbornadiene (64) under identical conditions results in selective deuteration of the aromatic ring of the product, benzonorborneol (65, 66).

Treatment of phenol (76), benzene (84), biphenyl (85), o- and m-xylene (86, 87), benzoic acid (101) and pyridine (102) with 4% v/v conc. HCl (conc. DCl) in D_2O or D_2O alone in the case of aniline hydrochloride (70)

at temperatures between 200-275°C results in selective deuteration of the aromatic nucleus with excellent isotopic incorporation and quantitative yields in most cases.

The high temperature-dilute acid (HTDA) exchange procedure described in the thesis is much superior to presently reported acid-catalyzed deuterium exchange techniques. The method presents substantial advantages, as compared with all other deuterium labelling procedures because of cost, simplicity of procedure, selectivity, freedom from steric effects and side reactions, high degree of isotope incorporation, essentially quantitative yields and most importantly, adaptability to large scale preparations. This process constitutes a new rapid one-step method of not only labelling organic compounds with deuterium and/or tritium but also provides a route for the preparation of ^{18}O labelled phenols.

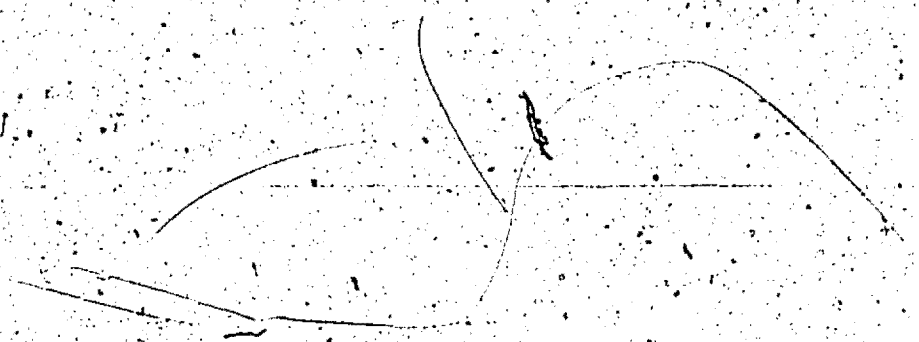
ACKNOWLEDGMENTS

I wish to express my sincere gratitude to Dr. N. H. Nerstiul for his valuable advice, guidance and encouragement throughout the course of this thesis and for his friendship during my stay at McMaster University.

Financial support from the Government of Ontario, Department of University Affairs, and the Department of Chemistry, McMaster University is appreciated.

I wish to thank Miss Susan Hawley for typing this thesis rapidly and accurately.

Finally, I wish to thank Krista, John and Janice, who were frequently orphaned and widowed during most of the past years.



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CHAPTER I

INTRODUCTION

A. Uses of Deuterium Labelled Compounds

The discovery and isolation of deuterium in 1932 has led to its wide use in both pure and mission-oriented research. The tremendous growth in the use of deuterium labelling in the last decade has been, in part, associated with the increased availability of deuterated reagents and the advance of physical techniques (nuclear magnetic resonance and mass spectrometry) to determine the extent of deuterium incorporation. Deuterated organic compounds are useful:

(a) for investigating reaction mechanisms and for structure elucidation[1];

(b) for studying vibrational spectra[2];

(c) for studies in mass spectrometry[3];

(d) for studies in nuclear magnetic resonance spectroscopy[4];

(e) for studying biological consequences of deuterium substitution in drugs[5];

(f) as high-temperature solvents[6];

(g) as lubricants[6];

(h) as reagents or intermediates for further synthesis[3];

(i) in biological systems and biosynthetic studies[7].

B. Methods of Preparing Deuterated Molecules

The introduction of one or more deuterium atoms into organic molecules can usually be accomplished by one of many possible methods, depending upon the nature of the organic molecule and the extent and

stereospecificity of deuteration desired. Some common procedures are:

I. Exchange Reactions

(a) Direct Exchange in the Inlet System of a Mass Spectrometer[8]

For the qualitative detection of active hydrogens such as OH, NH, SH or CO_2H, it is only necessary to introduce a slurry of the sample in heavy water into the inlet system of the mass spectrometer. It is difficult to perform such an exchange in a quantitative manner unless great care is first taken in equilibrating the instrument with deuterium oxide. Otherwise, partial back exchange with traces of water on the walls of the inlet system leads to low values. This type of exchange may even be observed with less exchangeable hydrogens, such as those α to a carbonyl group.

(b) Base-catalyzed Exchange

(a) Carbonyl-containing compounds

Exchange of enolizable hydrogens is one of the most common procedures for the introduction of deuterium. Virtually complete exchange can usually be achieved by repeated or extended treatment of the carbonyl compound with deuterated solvents and a basic catalyst. For the lower molecular weight ketones, cyclohexanones, and so on, an alkali metal carbonate or deuteroxide in a mixture of heavy water and an organic solvent (such as tetrahydrofuran, dioxan or glyme) is the most common method employed. Higher molecular weight ketones require more drastic conditions for the reaction to go to completion, probably because of the lower solubility. Provided the compounds are stable to alkali, it is preferable to use base-catalyzed rather than acid-catalyzed exchange, which is much slower[9]. The less recent methods used for ketone exchange to give fully α-deuterated compounds normally employed multiple

exchange stages necessitating large excesses of heavy water or deuterated solvents. This type of exchange is used extensively if partially-deuterated ketones are required or if small quantities of fully deuterated ketones are required. For the large scale production of fully deuterated carbonyl compounds, Jullien and Fréaville[10] have developed a countercurrent system.

(b) Via carbanions

Weak carbon acids, such as indene, exchange protons in deuterated solvents under basic conditions. In general, the more acidic the proton, the more facile the base-catalyzed exchange. Exchange of acidic protons is commonly accomplished by carbonate or deuteroxide catalysis whereas exchange of weakly acidic protons is facilitated by using amide ion in liquid ammonia[11]. Weldon and Wilson[12] have shown that when aromatic compounds are heated up to 400° with calcium deuteroxide, some deuterium incorporation occurs. This method has been employed for the successful perdeuteration of aromatic compounds such as naphthalene[13], biphenyl[14a], and anthracene[14b] which are stable up to temperatures around 400°. For systems that are unstable at these high temperatures, the exchange can be enhanced by raising the basicity of the medium by the addition of sodium deuteroxide[2].

The main disadvantages of base-catalyzed exchange via carbanions are:

(i) Sometimes side reactions (elimination[15a], cyclization[15b], decarboxylation[15c], carbene formation[15d], loss of substrate[15e], etc.) occur faster than exchange and reagents must be chosen carefully to block out undesired side reactions.

(ii) Often very strongly basic (KND_2-ND_3) and/or high temperature (CaOD - at 400°) conditions must be used in order to get an effective exchange process to occur. However, this can become very expensive and incon-

venient.

(iii) Acid-catalyzed Exchange

(a) Carbonyl-containing compounds

Hydrogen atoms at enolizable positions in ketones can be exchanged for deuterium in acid as well as basic medium. Acid catalysis is particularly suited for deuterium exchange of ketones which are prone to undergo base-catalyzed self-condensation[16] and which will not stand drastic basic treatment. Although camphor undergoes complete deuteration under basic conditions, complete deuteration is also accomplished when the ketone is heated with CF_3COOD-D_2O at 130° for nine days[17].

(b) Via carbonium ions

Discussed under section "Acid-catalyzed Deuterium Exchange via Carbonium Ions".

(iv) Chromatographic Exchange

Deuterium exchange can be achieved by column chromatography. Exchange is accomplished by passing substrates with active methylene groups adjacent to carbonyl groups through an aluminum oxide column which has been pretreated with deuterium oxide[18].

Analogously, gas-liquid chromatography can also be used as a labelling technique. Both basic[19] and acidic[20] gas chromatographic columns have been used to exchange enolizable hydrogens. It should be pointed out that labelled ketones can be chromatographed, without loss of deuterium, on neutral Carbowax or other supports[21]. In addition, aromatic protons can also be exchanged by gas-liquid chromatography[22].

(v) Metal-catalyzed Exchange

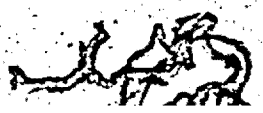
Catalytic exchange was one of the earliest methods used to introduce

deuterium into organic molecules[23,24,25]. It is still one of the most commonly used techniques for deuterating saturated hydrocarbons and other hydrocarbons, especially if selectivity is not desired. Exchange reactions on a metal surface are related to the reactions involved in catalytic hydrogenation and double bond isomerization. The source of deuterium in catalytic exchange is either deuterium gas or deuterium oxide with the latter possibly dissociating on catalyst surfaces. Catalytic exchange can be classified, as discussed below, into heterogeneous and homogeneous metal catalysis.

(a) Heterogeneous metal catalysis

Although there are marked differences in the rate of deuterium exchange on metal catalysts of differently placed hydrogen atoms in a molecule, these differences are usually inadequate for selective deuteration of organic compounds where selectivity is desired. Hence catalytic exchange can only be used in rare cases[26] to prepare specifically and partially deuterated compounds. However, several techniques in heterogeneous catalysis are available to prepare perdeuterated compounds. Three general techniques are: exchange with deuterium in the gas-phase, liquid-phase exchange with deuterium and exchange with deuterium oxide. The results of liquid-phase exchange are generally different from gas-phase exchange. However, this is not surprising since different mechanisms[27] are involved and different catalysts and conditions are used.

Dixon and Marr[28] have developed a vapor-phase exchange apparatus for the exchange of aliphatic hydrocarbons. The method consists of passing the deuterium gas and hydrocarbon over a nickel on kieselguhr catalyst at 300°. The major disadvantage of this procedure is that a large complicated apparatus is required. Atkinson et al.[29] have developed a more useful

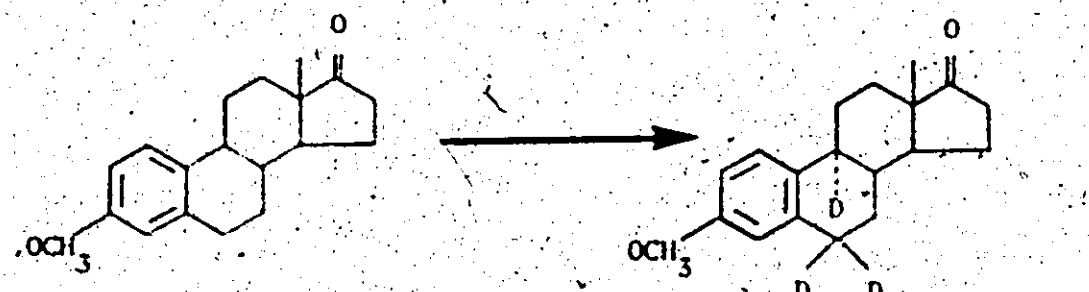


liquid-phase technique for perdeuterating hydrocarbons, especially for those with boiling points above 200°. The method consists of passing deuterium gas through an exchange cell containing the hydrocarbon and the catalyst, 2% palladium on charcoal. In this manner n-hexadecane and pristane are 99.4% deuterated after 316 and 700 hr. respectively. Unsaturated hydrocarbons require longer exchange periods.

Exchange techniques on catalysts employing deuterium gas are only useful for the preparation of saturated hydrocarbons, owing to the reduction and rearrangement reactions that take place with unsaturated systems. Catalytic exchange with deuterium oxide rather than deuterium gas is much more useful. By heating the substrate at moderate temperatures (50-250°) in the presence of a metal catalyst (Adam's catalyst, platinum black, etc.) and deuterium oxide, one can effect perdeuteration of many compounds. Benzene-d_6[30], aniline-d_7[31] and glycine-d_5[32] have been prepared in this manner. The addition of hydrogen peroxide has been found to assist the exchange[33] and its addition to Adam's catalysts in deuterium oxide at 240° is the recommended method for the perdeuteration of aliphatic mono- or diacids, ketones, hydrocarbons and aromatic compounds. Anthracene-d_{10} in 99% isotopic purity and 86% yield was prepared in this manner.

In general, platinum appears to be the preferred metal for general catalytic labelling because of its generally higher activity[34] and because side reactions are frequently less extensive (e.g., ring-opening in cyclobutanes[35]). The reactivity of platinum may be increased without altering its selectivity by reducing platinum chloride with sodium borohydride[36]. This sodium borohydride activated platinum catalyst has been used to ring deuterate alkylbenzenes.

As mentioned previously, catalytic exchange is rarely used for specific partial deuteration. However, by carefully adjusting the exchange conditions, it has been possible to selectively exchange benzylic or aromatic protons. When an ethyl acetate solution of estrone methyl ether (1) was shaken in a deuterium atmosphere in the presence of palladium on charcoal, the 6,6,9-d_3-estrone methyl ester (2) in 83% isotopic purity was obtained[8].



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Nickel and silica-supported nickel catalysts have been used to selectively exchange benzylic protons over aromatic protons in toluene[37] and p-xylene[38].

Aromatic protons can be exchanged for deuterium[39,40] by equilibration with deuterium oxide in the presence of platinum oxide catalyst. In this manner, tetralin (3) has been transformed into the 5,6,7,8-d_4 derivative (4). Selective replacement of aliphatic hydrogens by deuterium is difficult and can

3 4

usually be accomplished only with tertiary hydrogens using deuteriosulfuric acid[41].

By far the most important metal catalyst for selective deuterium exchange of organic compounds, nickel deposited on kieselguhr, was chiefly developed by MacDonald and Shannon[42]. Deuterium exchange catalyzed by nickel on kieselguhr[42,43] has been used to partially exchange

(i) the alkyl protons in toluene (2.7 D), m-xylene (5.0 D) and ethylbenzene (4.1 D);

(ii) the ring protons in p-t-butylbenzene (1.9 D), p-hydroxyanisole (1.9 D) and aniline (1.7 D); and

(iii) the alkyl and ring protons in p-toluidine (4.6 D), N-methylaniline (2.2 D) and N-methyltoluidine (5.6 D).

The incompleteness of the exchange after one cycle appears to be a major disadvantage of this catalyst.

(b) Homogeneous metal catalysis

Homogeneous metal catalysis utilizes prereduced group VIII transition metals as catalysts, platinum being the most active.

The importance of homogeneous metal catalysis was stressed when Garnett and Hodges[44] reported a simple one-step procedure for the exchange of a large number of aromatic compounds in the presence of homogeneous metal catalysts such as platinum (II) salts. In a typical procedure, a solution of acetic acid-d_1, heavy water, deuterium chloride, the organic compound and disodium platinum tetrachloride (Na_2PtCl_4) as catalyst is allowed to react in an evacuated sealed tube at a temperature within the range 25-120°, this being determined by the isotope used and the enrichment required. Acetic acid is essential to the medium to ensure homogeneity of phase. The acidity of the solution is critical since this should be high enough to minimize reduction of the catalyst complex and thus prevent precipitation of platinum. However,

the acidity should not be too high, otherwise the homogeneous metal-catalyzed process is inhibited and only acid exchange occurs in those compounds where this is possible. If platinum does precipitate from the reaction mixture, it is found that the inorganic acid present poisons subsequent heterogeneous exchange on the surface of the precipitated catalyst. This procedure has been used to label benzene (10.7% D), fluorobenzene (5.9% D), toluene (4.7% D), biphenyl (5.0% D) and naphthalene (3.6% D)[44b]. These results clearly indicate, as in heterogeneous metal catalysis, that the major disadvantage is the low deuterium incorporation.

With certain compounds, such as mesitylene, where the ring hydrogens readily exchange under acid conditions, it is possible to label both methyl and ring hydrogens in one step by effecting a compromise in acidity such that both metal- and acid-catalyzed isotope incorporation occur[44b], although the efficiency of the two processes is reduced under these conditions.

Of the very large number of compounds that have been examined by the present technique, aromatics are generally quite reactive whereas aliphatics such as cyclohexane exchange very slowly.

More recently, Garnett et al.[45] reported a new, simple method for rapid and selective aromatic deuteration using organoaluminum dichloride catalysts and deuterated aromatic compounds, such as perdeuteriobenzene, as the deuterium source. Typically, a mixture of ethylaluminum dichloride, perdeuteriobenzene and aromatic substrate are mixed for a few minutes at room temperature before all aromatic positions are equilibrated. However, alkanes, alkenes, as well as oxygen- and nitrogen-containing compounds (e.g., pyridine, anisole, phenol, aniline, etc.) do not exchange.

Although metal-catalyzed (homogeneous and heterogeneous) exchange

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% D refer to atom % excess D.

is the most popular exchange method it suffers from the following deficiencies:

(i) irreproducibility of catalytic surfaces and results[46a];

(ii) the catalyst surface has many different types of sites available to the molecule and each of these may have its own characteristics in isotopic exchange reactions[47b];

(iii) incidental poisoning of the catalyst by the organic molecule being exchanged or poisoning by an accidentally or deliberately introduced extraneous species[29];

(iv) complicated and expensive apparatus[28];

(v) steric hindrance[46c];

(vi) side reactions such as coupling of aromatic rings[46d]; and

(vii) low deuterium incorporation, thus making it necessary for multi-stage equilibrations using fresh catalyst and deuterium oxide[42].

II. Reductive Methods

(i) Catalytic Deuteration of Double Bonds

(a) Heterogeneous Catalysis

Catalytic deuteration (e.g., palladium on charcoal in ethyl acetate) in simple straight-chain olefins, such as methyl oleate[47], is a very unsatisfactory method for the selective introduction of the isotope, owing to extensive scrambling. This is presumably due to the effective migration of the double bond on the surface of the catalyst. More selective deuteration can be accomplished in those olefins where the double bond is less mobile for structural or stereochemical reasons. Excellent molecules for specific double-bond deuterations are bicyclic systems (where the double bonds are

fixed) such as norbornadiene and norbornene[48].

(b) Homogeneous Catalysis

Probably the most extensively used catalyst for the homogeneous addition of deuterium to double bonds is tris(triphenylphosphine)chlororhodium[49]. It has been shown that this catalyst is fairly sensitive to stereochemistry[50] but it has the advantage of being highly stereospecific[51] and being fairly insensitive to some of the common metal catalyst poisons[52].

In order to overcome some of the difficulties of catalytic deuteration of double bonds (rearrangement and exchange in other parts of the molecule), alternative approaches have frequently been employed to give exclusively cis (or trans) addition of deuterium. Dideuteriodiimide[53] is most commonly used to effect cis reduction.

(ii) Dissolving Metal Reductions

Saturation of the double bond in α,β-unsaturated ketones by means of lithium (or other alkali metals) in liquid deuterioammonia usually proceeds in a stereospecific manner and offers a convenient means of introducing deuterium stereospecifically into the β-position of ketones[54]. Sodium (with or without alcohol) in liquid deuterioammonia can be used to reduce benzene rings to deuterated cyclohexadiene derivatives (the Birch Reduction)[55].

(iii) Metal Deuterides

Reductions with metal deuterides (lithium aluminum deuteride[56], sodium borodeuteride[57], dialkylaluminum deuterides[58], organotin deuterides[59], borondeuteride[60] as in deuteroboration, etc.) are generally highly specific and are well suited for the introduction of deuterium at well-defined sites. Reductions with lithium aluminum deuteride and sodium

borodeuteride (and other metal deuterides) are used analogously to the corresponding protio reductions to make deuterated alcohols from aldehydes, ketones, acids and their derivatives and amines from nitriles. The versatility[61] and the availability of lithium aluminum deuteride makes it one of the most commonly used reagents to prepare a host of deuterium labelled substrates. Only a few representative examples will be listed here:

(a) Ketones and Aldehydes

The familiar reduction of carbonyl compounds is the method of choice for labelling a carbon atom bearing a hydroxy group ($RR'C{=}O \rightarrow RR'CDOH$).

(b) Esters

Lithium aluminum deuteride reduction of esters is convenient to prepare labelled primary alcohols ($RCO_2R' \rightarrow RCD_2OH$).

(c) Sulfonate Esters

Mesylates and tosylates, notably of primary alcohols, are readily transformed into the corresponding hydrocarbon (RCH_2OMs or $RCH_2OTs \rightarrow RCH_2D$) in which the methyl group has been labelled with deuterium.

(d) Halides

The reduction of alkyl halides with $LiAlD_4$ is analogous to that of sulfonate esters.

(e) Epoxides

The reductive opening of epoxides with $LiAlD_4$ offers an excellent path to the introduction of a single deuterium atom adjacent to an alcohol function.

(f) Tosylhydrazones

The reduction of tosylhydrazones (derived from aldehydes and ketones) to hydrocarbons lends itself particularly well to the introduction of deuterium

at the site of a carbonyl function. This method is thus an alternative to the desulfurization of mercaptals.

(g) Amides

Either aliphatic or cyclic amides are reducible to the corresponding amine with lithium aluminum deuteride. This affords the simplest means of introducing two deuterium atoms adjacent to an amino function ($-NCOR \rightarrow -NCD_2R$).

III. Miscellaneous Methods

There are numerous other methods of incorporating deuterium into a molecule and only a few of these will be mentioned:

(i) Replacement of a halogen by a metal atom and the subsequent quenching of the organometallic compound with deuterium chloride or deuterium oxide ($RX \xrightarrow{Mg} RMgX \xrightarrow{D_2O} R\text{-}D$; $R\text{-}Br \xrightarrow{Li} RLi \xrightarrow{D_2O} R\text{-}D$)[62].

(ii) Catalytic (deuterated Raney nickel) desulfurization of thioketals[54].

(iii) Photochemical techniques[63].

(iv) Methylation of phenols[64] and carbon-nitrogen[65] bonds.

(v) Biological techniques[66] such as

(a) biological perdeuteration of amino acids, sugars, steroids, nucleic acids, etc.;

(b) biological oxidations and reductions; and

(c) biological addition of labelled ammonia and water to double bonds.

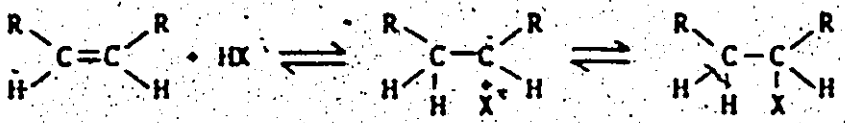
Of all the preceding methods of preparing deuterated molecules, only metal-catalyzed (homogeneous and heterogeneous) exchange, base-catalyzed exchange via carbanions and acid-catalyzed exchange via carbonium ions have been used extensively for perdeuteration.

C. Acid-catalyzed Deuterium Exchange via Carbonium Ions

I. Exchange via Olefins and Cyclopropanes

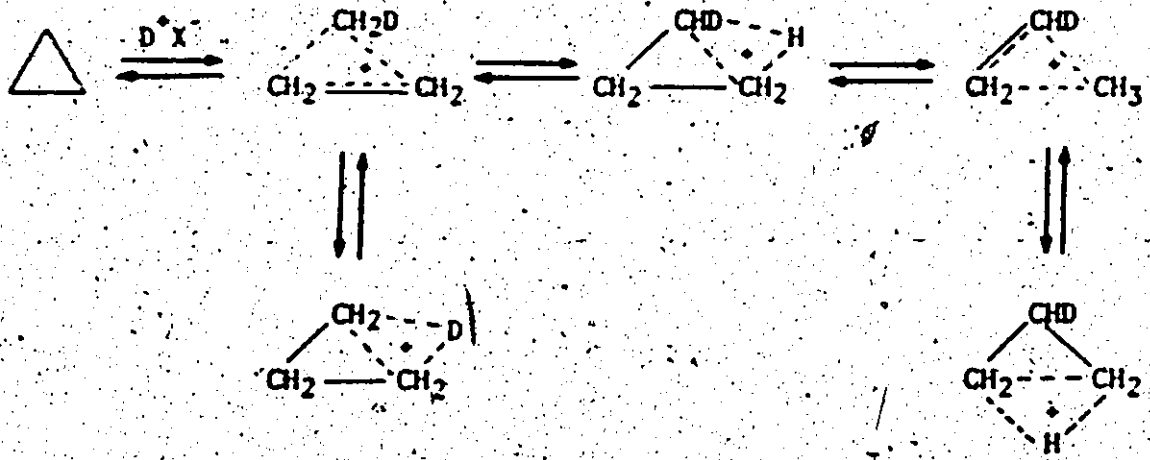
Originally[67], it was thought that the carbonium ion could exchange directly; however, in 1964 Deno[68] followed reactions by n.m.r. and showed that exchange in carbonium ions occurred by intervention of double bonds. Recently this idea has received considerable support from several other sources[69,70]. The mechanism of exchange through an intermediate olefin is an addition-elimination reaction with DX (Scheme I-1) and is quite similar to the acid-induced electrophilic exchange of aromatic compounds which will be discussed later.

SCHEME I-1

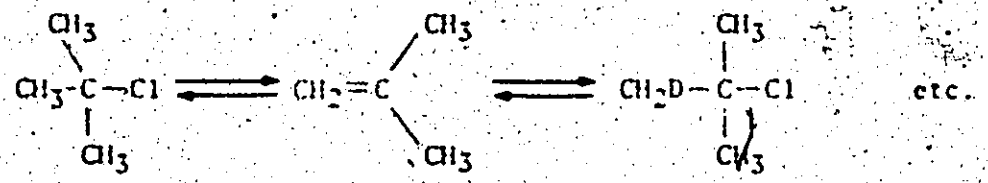


Exchange via a cyclopropane may be envisaged as follows (Scheme I-2):

SCHEME I-2



Once it was established that olefins were intermediates in deuterations involving carbonium ions, the acid-catalyzed reactions became easier to apply. Stephens and Leitch[71] prepared fully deuterated t-butyl chloride by treating t-butyl chloride with 10 N DCl. They also showed that isobutene exchanged deuterium on addition of deuterium chloride, so the sequence of events can be presumed to be as follows:



however, acid-catalyzed deuterium exchange of hydrocarbons are quite often of little preparative use because a fantastic maze of alkylation-dealkylations, rearrangements and hydride transfers are involved and usually the carbon framework of the products and the number of carbons bear little relation to that of the reactants[72]. Metal-catalyzed exchange is most frequently used for incorporating deuterium into hydrocarbons.

Garnett and co-workers used HCl-D_2O at 130°[73] in an attempt to find a general method of labelling cycloalkanes. They found that

(a) the exchange was relatively slow, and many cycles would be required for complete exchange;

(b) aromatic compounds exchanged poorly;

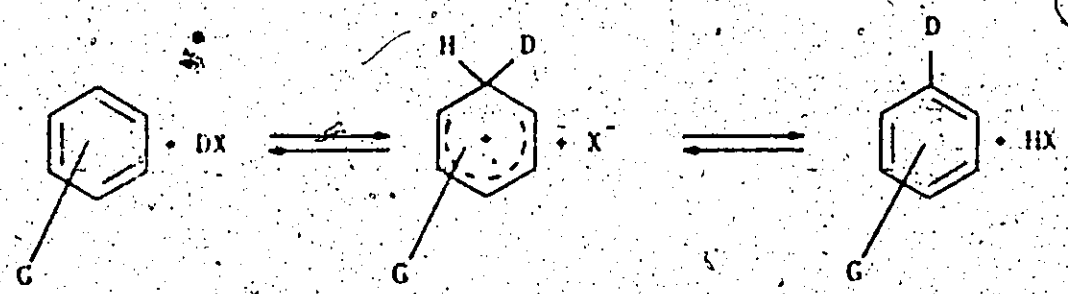
(c) terpenes and dienes exchanged under these conditions but the yields were very low because of isomerization and polymerization; and

(d) temperatures greater than 110° are needed for elimination and perdeuteration since at temperatures less than 110° only addition of DX occurs to give monodeuterated species.

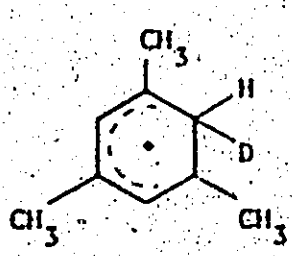
II. Exchange in Aromatic Systems

Ingold et al.[74,75] showed that anisole and other aromatic compounds exchanged their ortho- and para-hydrogens more rapidly than the meta-protons and also more readily than benzene in the presence of strong acids such as deuteriosulfuric acid. They suggested that acid-catalyzed deuterium exchange of aromatics proceeded in the same manner as simple aromatic electrophilic substitution. The reaction involves electrophilic attack on the aromatic ring by the D^+ species and proceeds in the following manner (Scheme I-3):

SCHEME I-3



For instance, 1 mole of mesitylene, boron trifluoride and deuterium fluoride yields a solid σ complex having structure (5), which yields deuteriomesitylene (6, 60% d_1) when warmed above its melting point (-10°)[76]. As expected, the rules governing acid-catalyzed-deuterium exchange of aromatic systems are generally similar to those of aromatic substitution[77,78].



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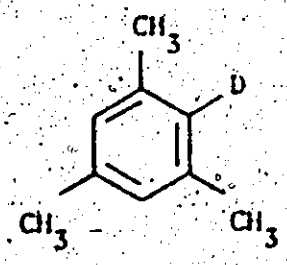

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III. Factors Affecting Rate of Exchange

The introduction of deuterium by acid-catalyzed exchange depends upon: (i) the acid strength;

(ii) the substituents in the substrate;

(iii) the nature of the solvent; and

(iv) the temperature.

Variations in one or all of these factors can be used to prepare a large number of specifically deuterated or perdeuterated compounds.

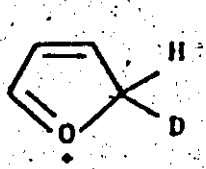
(i) Acidity

In general, for any given substrate, the more acidic (protonating power) the medium is, the greater the rate of exchange[79;80,170] and hence most, if not all, acid-catalyzed exchange methods which increase the extent and the rate of deuterium incorporation are concerned with raising the acidity of the deuterium source while trying to maintain a minimum amount of decomposition that this increase of acidity may cause. Gold[81] has given a full account of the various mixtures used, some of which are liquid deuterium bromide, acetic acid-d_1 with stannic chloride, deuterated phosphoric acid-boron trifluoride complex in liquid sulfur dioxide, 50-80% deuteriosulfuric acid in water, fluorosulfonic acid-antimony pentafluoride complex ("magic acid"), etc.

Complete perdeuteration of cyclopentane and cyclohexane derivatives in 10-80% yields have been obtained via refluxing the derivatives in 44% DBr-D_2O[82]. Best and Wilson[83] demonstrated that in the reaction between aniline hydrochloride and heavy water at 107°, the ortho- and para-positions of the aromatic molecule are the only nuclear positions which participate in the hydrogen exchange; no exchange of meta-hydrogens could be detected. In

the exchange of bromobenzene with 50-80% D_2SO_4[83], the ortho-, and para-hydrogens exchanged fairly rapidly while the meta-protons exchanged slowly but at the same rate as sulfonation. This prevented the use of this exchange reaction for the preparation of pentadeuteriobenzene. Preparation of benzene-d_6, however, can be accomplished by treating benzene with 51% D_2SO_4 at room temperature for 10 days[84] or with DCl-$AlCl_3$ for 60 h in a complicated glass apparatus[85]. In contrast, the weaker acid medium, aqueous hydrochloric acid, is essentially incapable of catalyzing the deuterium exchange of benzene at room temperature[84]. In general, 80% D_2SO_4 in D_2O at room temperature for 1 to 2 days completely deuterates only aromatic positions in polyalkyl benzenes. Naphthalene-d_8 can be prepared by shaking the protio species with four cycles of 50% D_2SO_4 at 120° for 50-100 h[86]. Acid-catalyzed exchange of biphenylene has failed because the high concentrations of D_2SO_4, gaseous deuterium chloride, liquid deuterium bromide and other Lewis acids cause extensive decomposition.

Acid-catalyzed exchange of simple five-membered ring heterocyclic compounds (e.g., pyrrole, thiophene, furan, etc.) with one heteroatom takes place more easily than benzene. The mechanism of these exchanges involves onium ions of the type 7. However, acid-catalyzed exchange of furans[87] and pyrroles is accompanied by decomposition while thiophene[88] does not exchange completely, even after 6 cycles for 1,212 h. Thus base-catalyzed



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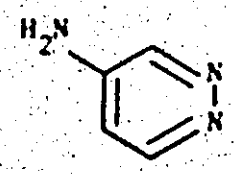

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exchange is frequently preferable, although one can envisage cases when the acid-catalyzed reaction will give more specific exchange, particularly since benzylic hydrogens are generally inert to acid-catalyzed but not to base-catalyzed exchange. Pyridine[89a] and 4-aminopyridazine (8)[89b] must be heated up to temperatures of 215° and 186° respectively in the presence of acid before exchange (which is incomplete) occurs.

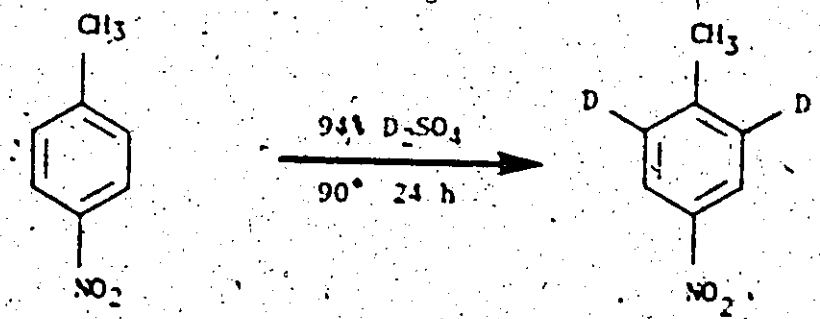
Although there is usually a large difference in the reactivity of the ortho-para-positions relative to the meta-positions in the aromatic nucleus, much smaller differences in the reactivities of the ortho- relative to the para-position have been observed with different acid reagents. For instance, the reactivity of the ortho- relative to that of the para-position in tritiotoluene during detritiation varies markedly with the medium; the reactivity ratio is 1.05 in 75% sulphuric acid at 25°, 0.49 in anhydrous trifluoroacetic acid at 70° and 0.49 in anhydrous heptafluorobutyric acid at 70°[90a]. Similar differences in the relative reactivities of the ortho- and para-positions of t-butylbenzene[90a], and biphenyl[90b] with different acids have also been observed. Hence the reactivity of aromatic positions can vary, depending upon the reactivity of the attacking acid. However, the small differences in reactivities between the ortho- and para-positions are of little synthetic use for specific labelling of the ortho- or para-positions.

(ii) Substituent Effect

In general, electron releasing (inductively or by resonance) substituents will facilitate exchange while electron withdrawing groups destabilize the intermediate carbonium ion and retard the rate of hydrogen exchange. That is, substituents can raise or lower the energy of activation for exchange. Thus, the directive effects of substituents in the exchange in aromatic systems are

analogous to those in aromatic electrophilic substitution. For example, Leitch et al.[91] have prepared 4-nitrotoluene-2,6-d_2 by treating p-nitrotoluene with 94% deuteriosulfuric acid at 90° for 24 h (Scheme I-4).

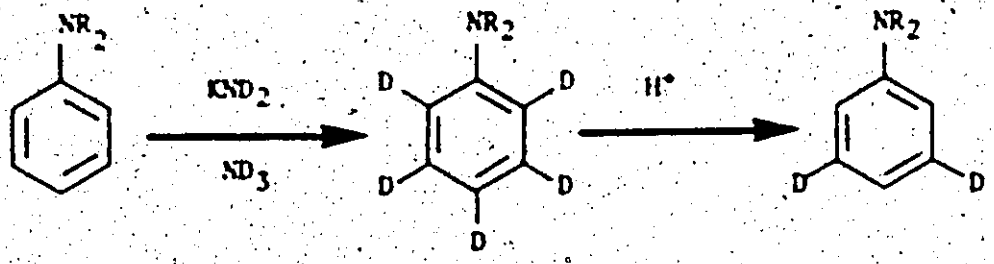
SCHEME I-4



1

In contrast to base-catalyzed exchange of aromatic amines where all positions of the ring are exchanged, acid-catalyzed exchange (temp. < 200°) accomplishes exchange predominantly in the ortho- and para-positions. This fact can be used to prepare specifically meta labelled amines by first exchanging all hydrogens by base-catalysis and then by treating the fully deuterated species with acid to remove the o- and p-deuterons (Scheme I-5).

SCHEME I-5



Shatenshtein et al.[92] have used this technique (first KND_2-ND_3 and then CF_3COOH) to prepare tris-(phenyl-3,5-d_2)amine.

Ring substituted anilinium salts are very useful starting materials for preparing deuterated aromatics because the amino group can be diazotized

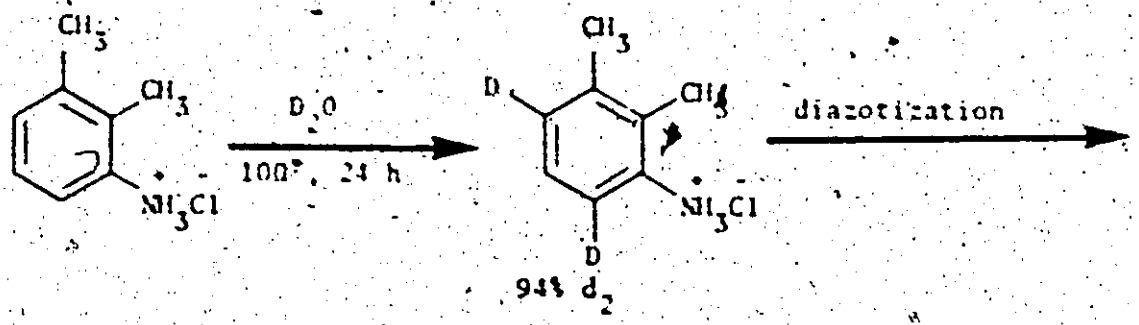
and the resultant diazonium salt can then be converted to a large number of other deuterated compounds. There are, however, conflicting reports about the loss of deuterium in the diazotization step. Numerous authors[93,94] have reported diazotization stages without alteration of the deuterium content. The great utility of anilinium salts for preparing specifically perdeuterated compounds can be illustrated by the work of Cooks et al.[93] (Scheme I-6). It is not necessary to give an endless list of the effect of substituents on deuterium exchange but only to mention that well-known directing substituents lead to well-defined (deuterated) products.

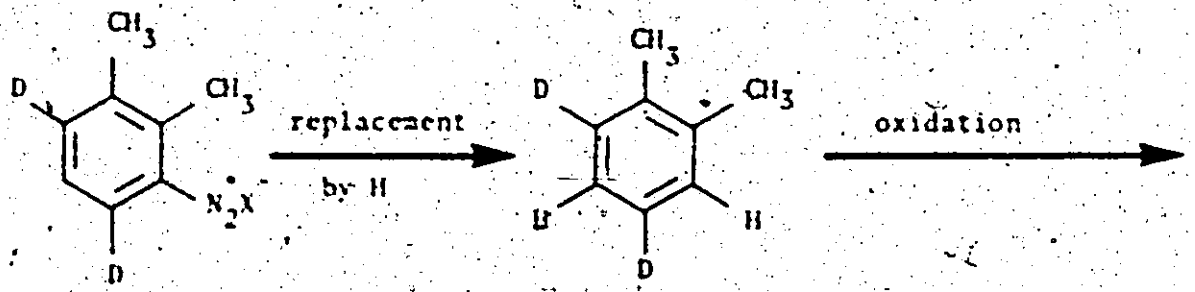
(iii) Solvent Effect

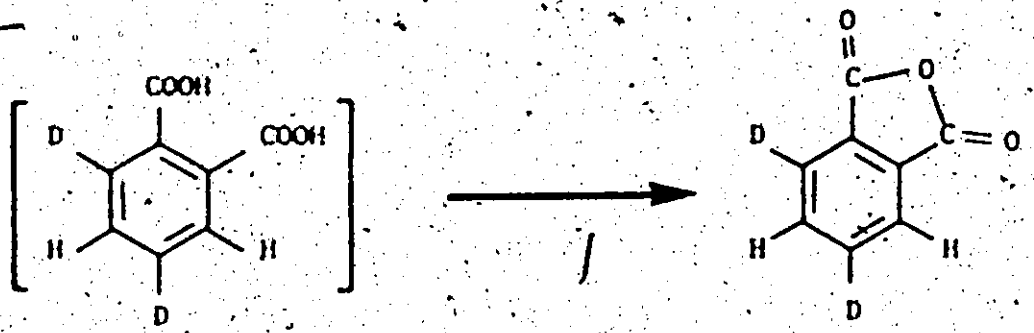
Very little work has been done on the role of solvent in electrophilic deuterium exchange reactions and hence the role of solvent is usually overlooked or neglected. However, general effects of solvent on carbonium ion reactions (solvolysis, etc.) can be found in Kosower's book[95].

Shatenshtein's Russian group is the primary researcher on the role of solvent in acid-catalyzed deuterium exchange reactions. They have reported[96] that the exchange rates increase on going from hexane (1) to carbon tetrachloride (1.2) to benzene (5.1) to dichloroethylene (13) to benzyl chloride (42), where these relative rates (in parentheses) were measured on the relatively rapidly exchanging pentamethyl-benzene-d_1 in trifluoroacetic acid. Garnett et al.[73] have observed rate enhancements by the inclusion of acetic acid in DCl-D_2O exchange mixtures. This is not surprising since the presence of an organic solvent, or a stronger base (acid) or a higher temperature, or all of these enhance the rate[66]. Further studies on the rate of exchange in more polar solvents is presently being carried out by Shatenshtein's group and little more can be said presently.

SCHEME 1-6


CH_3
CH_3
NH_3Cl
D_2O
100°, 24 h
D
D
94% d_2
diazotization


CH_3
D
CH_3
N_2X
D
replacement
by H
H
oxidation


COOH
D
COOH
H
H
D
O
C
O
C
O
D
H
H
D
94% d_2

(iv) Temperature Effect

The rate of reaction (exchange) can be expressed as the product of three factors:

$$\text{rate} = \text{collision frequency} \cdot \text{energy factor} \cdot \text{probability factor} \qquad [1\text{-}1]$$

The energy factor, which depends upon the temperature and the characteristic energy of activation of each reaction, is the most important factor determining the rate of exchange. The exponential nature of the rate equation [1-2] leads to a very large change in rate for a small change in temperature

$$k = Ae^{-E_{act}/RT} \qquad [1\text{-}2]$$

k = rate constant

A = constant

R = 1.986 cal mole^{-1} deg^{-1} (gas constant)

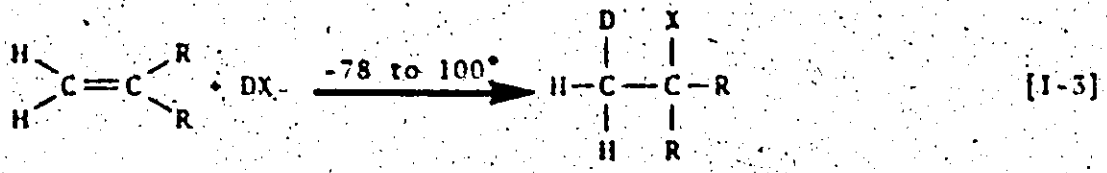
T = absolute temperature

and the greater the E_{act} is, the greater the effect of a given change in temperature. For example, a rise from 250° to 300°C, which is only a 10% increase in absolute temperature, increases the rate by one-half if E_{act} = 5 kcal, doubles the rate if E_{act} = 10 kcal, and triples the rate if E_{act} = 15 kcal.

In aromatic systems containing oxygen and nitrogen substituents which compete with protonation of the benzene ring, the temperature and even the solvent are instrumental in determining whether protonation occurs preferentially at the ring or at the substituent. For example, in a HF-BF_3 system at -83°, the ratio of ring protonated and O-protonated anisole is 3:2. If the temperature is increased to -8°, the equilibrium shifts in favour of

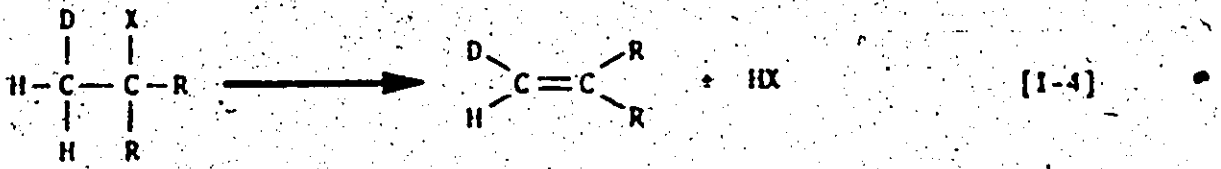
the C-protonated isomer, the fraction of O-protonated anisole is decreased to only 2%! The strong electron-releasing properties of hydroxy-, alkoxy- and amino-substituents raise the basicity of the benzene ring to such an extent that the carbon para to the substituent can successfully compete with the heteroatom for the proton[97].

At low temperatures (-78 to 100°), DX (or TX) usually adds to olefins in a stereospecific manner to yield monodeuterated (tritiated) species (equation I-3)[98,158].



[I-3]

However, in order to obtain perdeuterated (or tritiated) species, the temperature must be sufficiently high to cause elimination and regenerate the olefin function which can then undergo further exchange (Equation I-4). That is, for non-aromatic systems, the condition (temperature) must be such that a reversible addition-elimination exists (Scheme I-1). Garnett and collaborators[73] have



[I-4]

shown that at 80-100° in the presence of aqueous DCl, cycloalkanes add only one deuterium and that temperatures greater than 110° are required for multiple deuteration. Obviously, multiple exchange can also occur with any substrate such as an alkyl halide, alcohol, etc., which is capable of undergoing an elimination reaction (dehydrohalogenation, dehydration, etc.) to form an alkene

which is a necessary prerequisite for perdeuteration (tritiation). In general, the elimination reaction is favoured by high temperatures and by electron-withdrawing substituents suitably oriented in the molecule to increase the acidity of the proton being removed.

As previously mentioned, in spite of the voluminous literature on hydrogen-deuterium exchange, the majority of methods of perdeuterating organic molecules by acid catalysis involve highly acidic media and temperatures below 190°. However, many of these systems are unsatisfactory because of cost, complicated apparatus and procedures, slow or incomplete exchange and low yields (due to decomposition or side reactions). In contrast, exchange under conditions of high temperature (>200°)[79,80] and dilute acid have not been explored in any detail[99,100,101]. This is surprising since the exponential nature of the rate equation [1-2] predicts that a small change in temperature causes a large change in the rate of exchange. In addition, very strong acids shift the equilibrium of Scheme 1-3 to the benzonium ion intermediate and on quenching can lead to monodeuteration or a decrease in the rate of perdeuteration. Complete exchange can perhaps be better accomplished by using weak (dilute) acid and high temperature conditions.

It is my purpose to examine the utility of high-temperature and dilute acid (HTDA) conditions as an economical and versatile method of acid-catalyzed selective deuteration and/or perdeuteration of norbornyl and aromatic systems.

Many aspects of deuterium, such as uses and labelling methods (especially those based on isotope exchange reactions) can equally well be applied to the heaviest hydrogen isotope, tritium. General methods of labelling organic compounds with tritium have been reviewed elsewhere[102]. Tritium has been used in exchange reactions with alkanes, cycloalkanes, olefins, aromatic hydrocarbons,

amino acids, alcohols, etc.[103,104]. In spite of the many resemblances that exist between deuterium and tritium, the β-emitting characteristics (radioactivity) of tritium must be considered, not only its hazard to health but also its high sensitivity (the sensitivity of detection of the radioisotope is much greater than for stable deuterium). This latter fact makes tritium labelling very useful in cases where the degree of isotope incorporation is low.

CHAPTER II

RESULTS AND DISCUSSION

A. Norbornyl Systems

1. Solvolysis of Substituted Nortricyclanes and Norbornenes

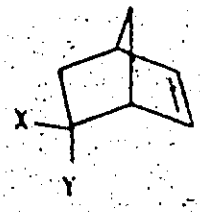
Solvolysis of 3-substituted nortricyclanes (9a and b) and 5-substituted norbornenes in 80% ethanol-water[105], acetic acid[106a,b], or methanol[107] at 25-55° gives 3-nortricyclyl (9c, f and g) and exo-5-norbornenyl products (10c, d and e) via the cationic species 16 or 17. In deuterated media (DOAc-D_2SO_4, DCl, DBr, etc.), stereospecifically monodeuterated products are observed.[108] The studies described herein establish that solvolysis of nortricyclyl bromide (9a), nortricyclyl chloride (9b), nortricyclanol (9c), endo-5-norbornenol (10b), anti-7-norbornenol (15), syn-7-hydroxy-exo-2-norborneol (18a) and exo-2,3-epoxynorbornane (19) in sealed tubes at 250° in 10% v/v acetic acid-water or water alone in the case of the halonortricyclanes yields 2-(cyclopentene)-acetaldehyde (11), 3-(cyclopentene)acetaldehyde (12), 3-(cyclohexene)carboxaldehyde (13) and norcamphor (14). When the solvolyses are carried out in deuterated medium, multiple deuteration of 11, 12, 13 and 14 results.

Norcamphor and 3-(cyclohexene)carboxaldehyde were identified by comparison of i.r., n.m.r., m.s. and g.l.p.c. retention time data with those of authentic samples. The (cyclopentene)acetaldehydes were identified in the following manner. That cyclopentenyl and aldehydic moieties were present was indicated by the i.r. of 11 + 12 which showed bands at 3052, 1612 and 2710 cm^{-1}. The n.m.r. spectrum showed absorptions at δ 9.50 and 5.68 and supported this premise. Since the 2- and 3-(cyclopentene)acetaldehydes are not separated

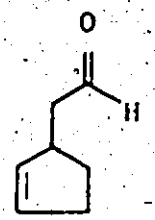
by g.l.p.c., the solvolysis method as described by Trahanovsky[109] was employed for ratio determination. Reduction of 11 + 12 to the (cyclopentene)-ethanols, preparation of the nosylates of the mixture, followed by acetolysis gave the exo-norbornyl (84%), 2-(cyclopentene)ethyl (14%) acetates and 1% of an unknown as was determined by g.l.p.c. A control experiment with a mixture of 11 + 12 prepared by ceric ammonium nitrate oxidation of exo-norborneol[109] established a ratio 42:58 which compared favourably with the ratio of 48:52 determined for the same mixture by Trahanovsky et al.[109]. Closer scrutiny showed that i.r. fingerprint spectroscopy is a more direct method for determining the 11:12 ratio (Figures 1, 2 and 3 of Appendix D). A band at 910 cm^{-1} present in the spectrum of 2-(cyclopentene)acetaldehyde (11) was present in the i.r. of a mixture of 11 + 12. The relative area of the peak at 910 to that of the broad doublet at 718 (due to 11) and 666 (due to 12) determined for the 42:58 and 14:85 mixtures is 16% and 6%, respectively. Therefore to determine the percentage of 11 in a mixture of 11 + 12, the percent area of the 910 peak to the 718-666 doublet is multiplied by 2.6. When the procedure is applied to pure 2-(cyclopentene)acetaldehyde, the area of the 910 peak × 2.6 is within 3% of the area of the 718 peak and thus establishes the validity of the method (see Experimental A.I.(vii), (b), on I.R. Fingerprint Region Assay).

G.l.p.c. analysis of a typical run with nortricyclanol and the nortricyclyl halides showed 10-15 peaks of retention times in the region of authentic samples of syn- and anti-2,7-norbornanediol. In one run carried out in deuterated medium the diol fraction was converted to the corresponding diacetates with acetic anhydride in pyridine. Nuclear magnetic resonance and mass spectral studies and g.l.p.c. retention time data on a 10 ft × 1/8 in 10% Carbowax on Chromosorb W column established through the diacetates, that the syn-7-, anti-7-,

9 a, X = Br
b, X = Cl
c, X = OH
d, X = OBs
e, X = OEt
f, X = OAc
g, X = OMe



10 a, X = OH, Y = H
b, X = H, Y = OH
c, X = OEt, Y = H
d, X = OAc, Y = H
e, X = OMe, Y = H



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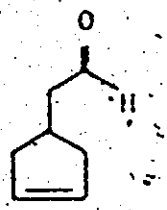

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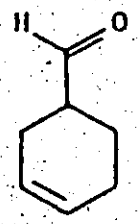

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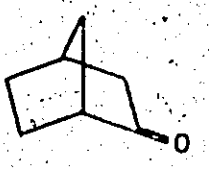

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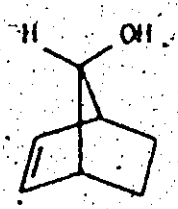

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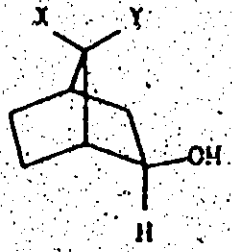

18 a, X = H, Y = OH
b, X = OH, Y = H

19

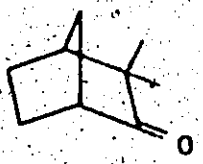

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Table I. Data for Solvolysis of Nortricyclyl Substrates

Substrate	Entry	Conditions[a]			Relative % Yields						% Yield[b]			D/molecule[c]		
		Solv.	Temp. (°C)	Time	11+12	13	14	9c	Diols	Other	11+12	13	14	11+12	13	14
9a	1	D*		4 h	t	t	90			10			32			3.20
9b	2	H*		10 min	1	1	2	3	90	3						
	3	H*		60 min	2	4	80	1	8	5						
	4	D*		1.3 h	1	2	85	1	5	6						3.60
	5	H_2O	250	1.5 h	t	t	90	-	5	5			38			
	6	H*	165	1.5 h	-	-	--	5	-	95						
	7	D*		4 h	-	-	93	-	-	7			30			3.75
9c	8	H*		10 min	1	1	2	45	45	6			40			
	9	H*		60 min	1	1	2	-	90	5						
	10	H*		4 h	15[d]	20	45	-	20	t						
	11	D*	300	1.5 h									35	2.40	2.20	1.90
	12	D*		9.5 h	15	23	52	-	8	2	9	15	33	2.15	2.00	1.75
	13	H_2O	250	1.5 h				100								
	14	D*·HCl		1.5 h									35			3.20

[a] H* = 10% v/v HOAc-H_2O at 250°; D* = 10% v/v DOAc-D_2O at 250°.

[b] Preparative g.l.p.c. was used to determine the yields. Each value is corrected for collection losses. For a description of the method see Appendix A.

[c] Greater than 90% of the enolizable deuterium was washed out. The mass spectral data (uncorrected relative intensities) are listed in Table I of Appendix C.

[d] A composite of 15% 11, 84% 12 and 1% of an unknown.

Table 2. Data for Solvolysis of Norbornenyl Substrates

Substrate[d]	Entry	Conditions[a]			Relative % Yields						% Yield[b]	D/molecule[c]
		Solv.	Temp. (°C)	Time (h)	11+12	13	14	9c	Diols	Other	14	14
10a+10b	1	H*		1.5	10	15	24	11	13	27		
	2	H_2O	250	1.5	-	-	-	11	-	89		
10b	3	D*		4	12	15	67	-	-	6	52	2.6
15	4	H*		1.5	3	5	16	t	70	6		
	5	H_2O	250	1.5	— starting material only							
	6	D*		9.5	3	14	71	-	-	12	63	2.8
18a+18b	7	H_2O	250	1.5					100			
	8	H*		1.5	4	3	8	-	80	5		
18a	9	D*		9.5	18	21	60	-	-	1	40	1.50
19	10	H*		4.5	-	8	76	-	-	16		
	11	H*		1.5	6	19	75	-	-	-		
	12	D*		4	3	10	69	-	-	18	62	2.05

[a] H* = 10% v/v HOAc-H_2O at 250°; D* = 10% v/v DOAc-D_2O at 250°.

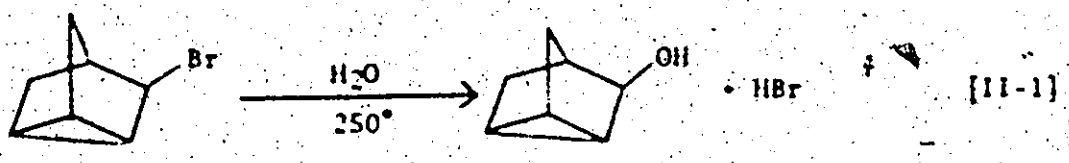
[b] Preparative g.l.p.c. was used to determine the yields. Each yield is corrected for collection losses as described in Appendix A (G.l.p.c. Collection Loss Determinations).

[c] Does not include the enolizable deuterium. The mass spectral data (uncorrected relative intensities) are listed in Appendix C, Table 2.

[d] Typically, a mixture of substrate and solvent was degassed and heated in a sealed glass tube at 250° in a Carius oven.

exo-5-, and endo-5-exo-2-norbornanediols are products. No attempt was made to identify all the components of higher retention time.

The data in Tables 1 and 2 show that acid (entries 10 and 13 of Table 1 and entries 1, 2, 4, 5, 7 and 8 of Table 2) and a temperature > 200° (entries 5 and 6 of Table 1) are required for the reaction. That is, nortricyclanol, exo-5-, endo-5-, anti-7-norbornenols, syn-7- and anti-7-hydroxy-exo-2-norbornenol are stable in water at 250°. When the reaction is carried out in 10% v/v HOAc-H_2O at temperatures below 200° the conversion to aldehydes and norcamphor does not occur detectably. Nortricyclyl bromide and nortricyclyl chloride are converted to 11, 12, 13, and 14 in water because HBr and HCl are generated during the solvolysis (Eq. II-1). In fact, nortricyclyl chloride is hydrolyzed to nortricyclanol in 85% yield by boiling water[110]. As shown by entries, 1, 5



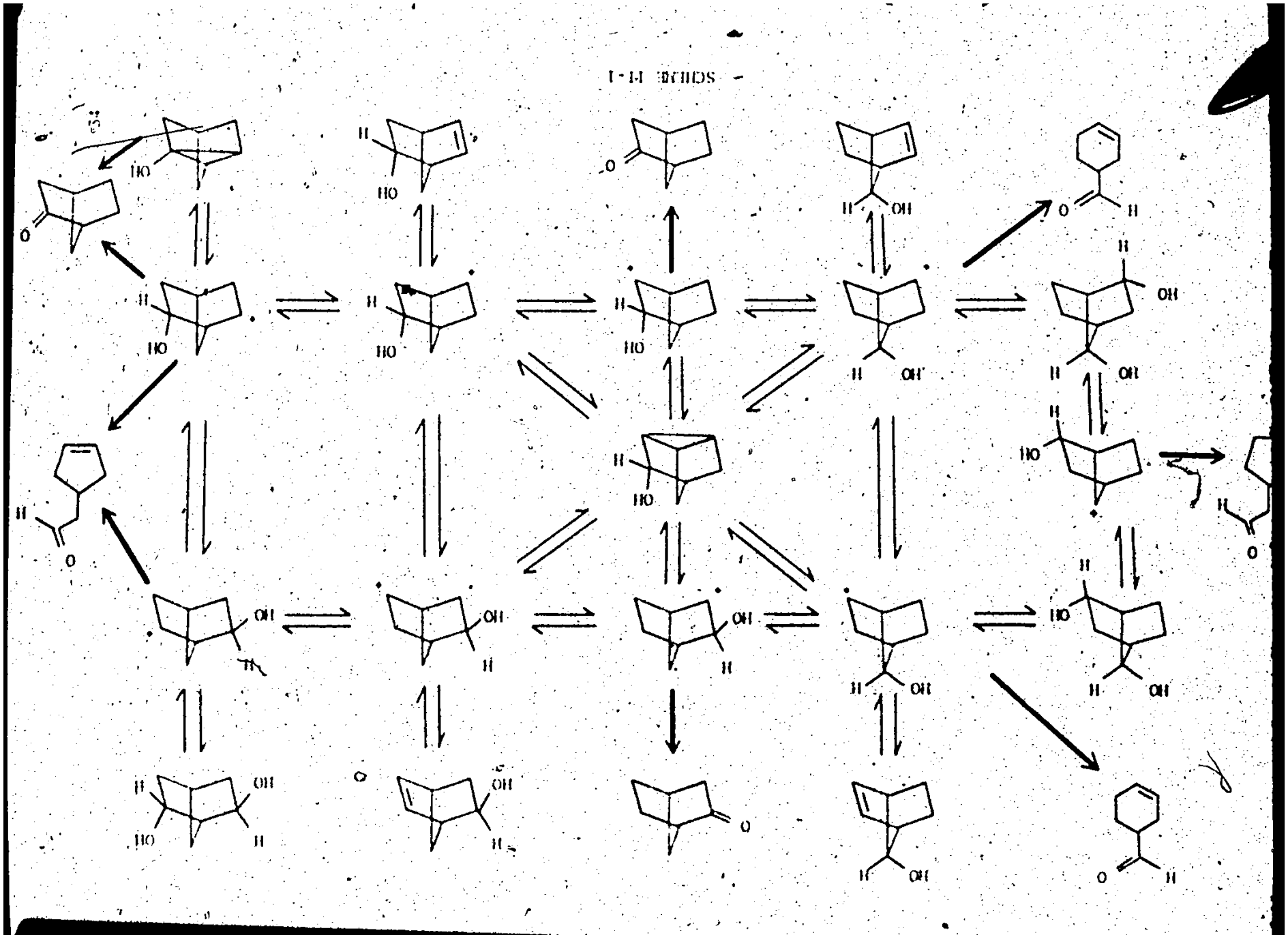
[II-1]

and 10 (Table 1) and control experiments, the aldehydes decompose in the presence of HBr and HCl and this accounts for the apparent formation of norcamphor only in reactions where HBr and HCl are generated. In the absence of the acids HBr and HCl, the aldehydes are reasonably stable in 10% v/v HOAc-H_2O (entries 10 and 12 of Table 1) and are isolated from the nortricyclanol reaction in 20-25% yield. Entries 2, 3, 8, 9, and 10 of Table 1 show that 9a, 9b and 9c initially yield diols which together with norbornenols are then converted to 11, 12, 13, and 14. G.l.p.c. analysis of the nortricyclyl bromide, chloride and nortricyclanol solvolyses showed that minor quantities of the norbornenols 10a, 10b and 15 were formed in each case. The yield of norbornenols is always low because the double bond is very readily protonated under the reaction conditions. As expected, the norborn-

enyl substrates, 10a, 10b, 15 (entries 1, 3, 4 and 6 of Table 2) also initially yield norbornanediols which are then converted to 11, 12, 13 and 14. In all cases, the diol concentration builds up and then decreases as the conversion to aldehydes and norcamphor occurs. Scheme II-1 represents various possible pathways for the formation of the aldehydes and norcamphor. This mechanistic scheme will be discussed in greater detail in Section II-A-III. However, the aldehydes and norcamphor clearly act as sinks for appropriately substituted norbornyl systems.

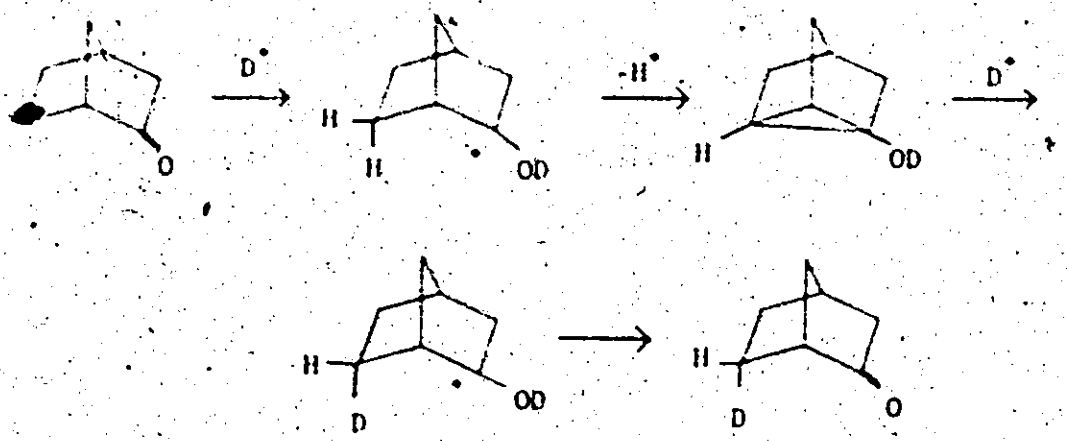
Deuterium is incorporated in the aldehydes and norcamphor when 9a, b, and c, 10a, 15, 18a and 19 are solvolyzed in deuterated medium. Mass spectral deuterium analysis of 14 (a composite of up to d_8 species) obtained from 9a and b and the aldehydes and norcamphor (a composite in each case of up to d_6 species) obtained from 9c establishes that the amount of deuterium incorporated depends on the acidity of the medium (entries 1, 4, 7, 11 and 12 of Table 1). When nortricyclanol is heated in the deuterated medium (DOAc-D_2O) with an equal molar concentration of HCl for 1.5 h, the norcamphor contains 3.20 deuterium atoms per molecule (entry 14, Table 1). Thus the more acidic medium, DOAc-D_2O-HCl, causes a substantial increase in deuteration. Variations in the temperature between 250-300° do not significantly alter the deuterium incorporation into norcamphor obtained from 9c (entries 11 and 12 of Table 1).

The control experiments in deuterated medium (DOAc-D_2O) show that (a) the aldehydes and norcamphor do not incorporate any deuterium, other than that by enolization α to the carbonyl; (b) isomerization of the double bond in 11 + 12 and 13 does not occur; and (c) deuterium is not incorporated into norcamphor via acid-catalyzed homoenolization (Scheme II-2)[111] or some



other pathway which involves HOAc-OAc. Attempts to homoenolize camphenilone (20) in the presence of CF_3COOD at 250° failed.

SCHEME II-2



The lack of deuterium incorporation into the aldehydes (via protonation of double bond) and their stability (no isomerization of the double bond) indicates that the cyclopentenyl and cyclohexenyl double bond is not protonated under these conditions of high temperature and dilute acid (10% v/v HOAc-D_2O). In contrast, the double bond of the more strained bicyclic system* is readily protonated. The heats of hydrogenation, listed in parenthesis[112], of cyclopentene (-25.7), cyclohexene (-28.6), nortricyclane (-32.1), norbornene (-33.0) and norbornadiene (-35.0 kcal/mol) establish that any olefinic substrate which has a heat of hydrogenation $\geq$32.1 kcal/mol will undergo protonation (deuteration) in 10% v/v HOAc-H_2O at 250°.

Other things being equal, our results indicate that cyclohexene and cyclopentene will not readily undergo protonation (exchange) in 10% v/v HOAc-D_2O at 250°. However, stronger acids and/or higher temperatures could possibly lead to protonation and even exchange of monocyclic systems.

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*Norbornenols, norbornene and norbornadiene are protonated in 10% v/v HOAc-D_2O at 250°.

whereas cyclohexene has been found to undergo little protonation and subsequent dehydration at 250° in 10% v/v DOAc-D_2O for 4 h, exchange occurs in 10% v/v DOAc-1% DCl-D_2O at 250° and in refluxing 44% DBr-D_2O.[82] For example, cyclopentyl bromide undergoes 99% exchange in four cycles in 44% DBr-D_2O at reflux with an overall recovered yield of 60%[82].

That protium-deuterium exchange occurs *via* protonation-deprotonation pathways (Scheme II-1) is supported by the fact that deuterium is incorporated into unreacted nortricyclanol and the *syn*- and *anti*-7-*exo*-, and *endo*-5-*exo*-2-norbornanediols.

In each case the deuterated norcamphor obtained from the solvolysis of 9a, 9b, 9c, 10b, 15, 18a and 19 was reduced to *endo*-norborneol and the distribution of deuterium was determined by area integration analysis in the presence of Eu $(DPM)_3$ as described in Section II-A-IV. The data are listed in Table 3. These results show that deuterium is incorporated in all positions of the norbornyl skeleton. This is accountable in terms of a combination of 1,2-Wagner-Meerwein shifts, 3,2- and 6,2-hydride (deuterium) shifts and 1,2 and 1,3 eliminations and/or protonated epoxides. One possible pathway is illustrated in Scheme II-3. This is supported by the fact that multiple deuteration (d_4 species) is observed in unreacted nortricyclanol.

The results in Table 3 also show that the deuterium is not equally distributed, indicating that equilibration of all positions in the norbornyl skeleton has not been achieved because hydroxy-cation fragmentation to the sink-compounds competes with exchange. From Scheme I-1, complete perdeuteration can only be accomplished by establishing a completely reversible reaction sequence. Although nortricyclanol, the norbornenols and the norbornanediols

---

The deuterium content of unreacted norbornenols can not be checked because they are only present in small quantities and thus can not be isolated for deuterium analysis.

Table 3. Deuterium Distribution in Norcamphor

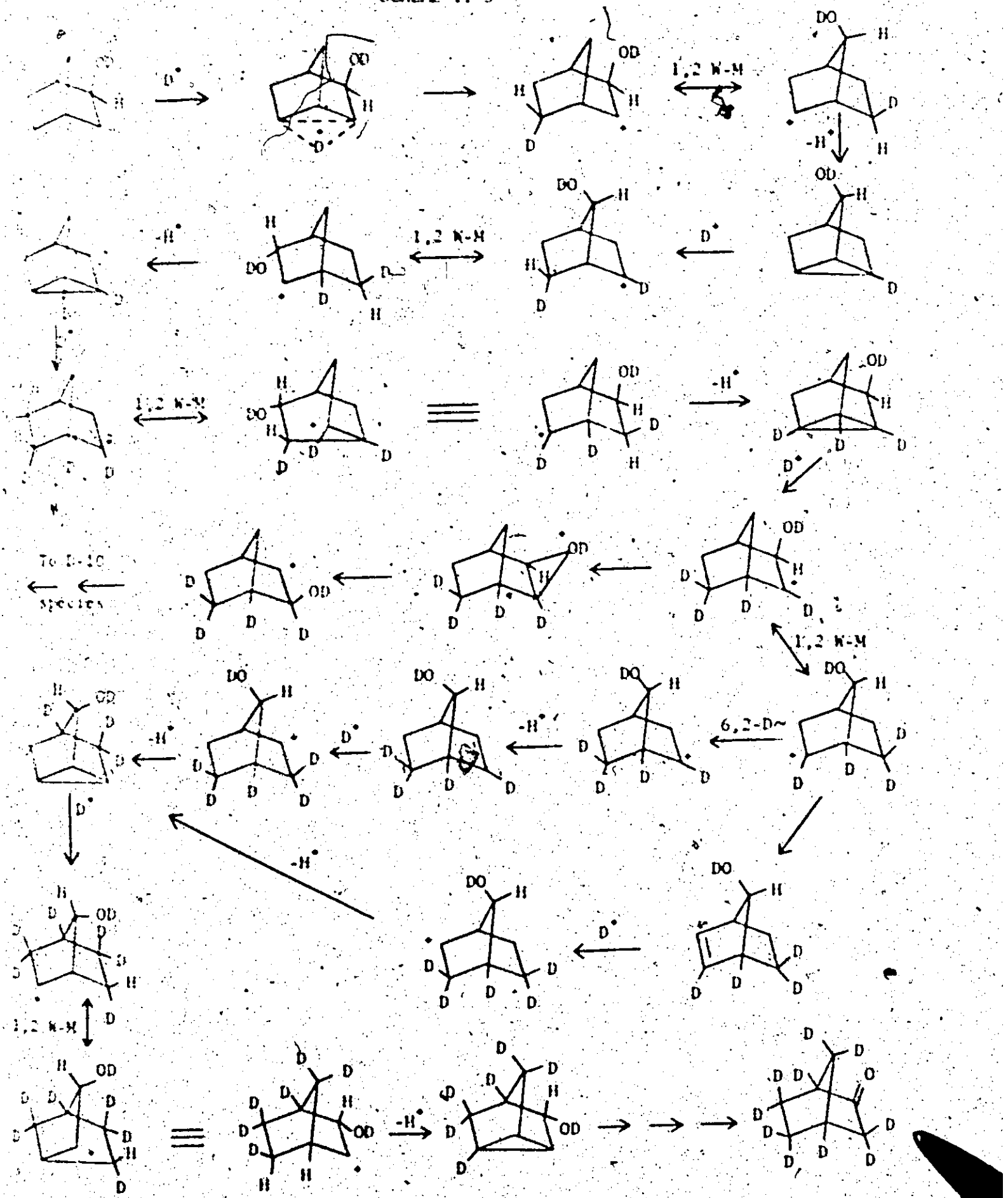
Substrate	Fraction of one deuterium at[a,b]							
	C(1)	C(4)	C(5)x[c]	C(5)n	C(6)x	C(6)n	C(7)a	C(7)s
9a	0.40	0.35	0.50	0.50	0.30	0.40	0.30	0.30
9b	0.40	0.30	0.55	0.55	0.55	0.50	0.25	0.60
9c	0.20	0.10	0.35	0.45	0.15	0.20	0.15	0.20
10b	0.35	0.20	0.20	0.45	0.30	0.45	0.25	0.25
15	0.35	0.30	0.35	0.40	0.25	0.35	0.25	0.50
18a	0.20	0.15	0.20	0.25	0.25	0.20	0.15	0.20
19	0.30	0.25	0.35	0.35	0.20	0.25	0.20	0.25

[a] Rounded to 0.05 of one deuterium.

[b] C-3-exo- and C-3-endo are omitted because deuterium is incorporated via acid-catalyzed enolization (usually 1.7 D).

[c] x = exo, n = endo, a = anti, s = syn.

SCHEME II-3



are intermediates in the reversible exchange sequence (Scheme II-1), the aldehydes and norcamphor are not. Therefore, any norbornyl system which generates hydroxy-cations which fragment to stable "sink" compounds will not undergo complete deuteration.

II. Hydration of Norbornadiene at 250°

When norbornadiene (21) is heated in 10% v/v CH_3COOD-D_2O at 250°, multiple deuteration is observed in the products 2- and 3-(cyclopentene)-

21

22

acetaldehyde, 3-(cyclohexene)carboxaldehyde and norcamphor. The results of our study are shown in Table 4.

That the reaction is acid-catalyzed is shown by entries 1 and 7. Entries 1, 2, 3 and 4 clearly show that norbornadiene rapidly gives norbornenols, nortricyclanol, and norbornanediols which are gradually converted into 11, 12, 13, and 14 via rearrangement and cleavage processes. As described in Section II-A-III, cleavage of a 1,6- or a 1,7- bond in a suitable hydroxy-cation would yield the aldehydes.

When norbornadiene is heated in deuterated medium (entry 5), 11 and 12 combined, 13, and 14 contain 2.55, 2.60 and 2.40 non-enolizable deuterium atoms, each a composite of up to d_6 species. As described in the previous section, control experiments have shown that (a) > 95% of the deuterium must be incorporated into 11, 12, and 13 prior to cleavage and (b) deuterium is not incorporated into 14 via acid-catalyzed homoenolization[111] or

Table 4. Data for the Hydration of Norbornadiene at 250°

Entry[a]	Time (h)	Relative % Yield[b]					% Yield[d]			D/molecule[e]		
		11+12	13	14	Diols	Other[c]	11+12	13	14	11+12	13	14
1	0.5	4	3	8	55	30						
2	1.5	15	18	40	20	7						
3	3	17	19	45	15	4						
4	5	14[f]	17	52	14	3						
5	9.5	14	17	54	14	1	8	13	33	2.55	2.60	2.40
6	18	1	6	92	-	1			23[h]			
7[g]	10	norbornadiene + polymer										

[a] Typically, a solution of 21 in 10% v/v HOAc-H_2O or 10% v/v DOAc-D_2O was degassed and heated in a sealed tube at 250° in a Carius oven.

[b] The relative percent yields were determined gas chromatographically on $\frac{1}{8}$ in x 10 ft 10% SE-30 and 10% Carbowax on Chromosorb W columns.

[c] The norbornenols and nortricyclanol are included here.

[d] The yields were determined by preparative g.l.p.c. Each is corrected for collection losses (See Appendix A).

[e] The enolizable deuterium in 11, 12, and 13 was washed out by three injections through a 3/8 in x 10 ft 5% KOH + 20% Carbowax column maintained at 170°. 14 was treated three times with a KOH-MeOH-H_2O solution.

[f] A composite of ca. 15% 11 and 85% 12 as determined by i.r. fingerprint region assay.

[g] The reaction was run in H_2O only.

[h] Isolatable yield by vacuum distillation from a large scale (125 g) reaction.

some other mechanism which involves HOAc-OAc⁻. That is, the exchange occurs prior to formation of the final products by protonation-deprotonation pathway which includes as steps 1,2-Wagner-Meerwein shifts, 2,6- and 2,3-hydrogen shifts and 1,2- and 1,3-elimination of a proton (Scheme II-1). Norbornadiene is only a special case of the nortricyclyl and norbornenyl derivatives. Quadricyclane (22) would also be expected to behave like 21, under the reaction conditions.

The acid-catalyzed additions of methanol and acetic acid to norbornadiene[107,113] at 25-230° yield a mixture of 9g, 10e and 9f, 10d, respectively. In deuterated medium, stereospecific nondeuteration of the norbornyl skeleton occurs, although some polydeuteration takes place in the acetoxy group, especially at higher temperatures. This, coupled with our results, shows that the temperature effect is a crucial factor for perdeuteration. At lower temperatures (≤ 230°), only addition products are formed, resulting in monodeuteration. Temperatures ca. 250° are required to accomplish elimination and thus establish the reversible addition-elimination sequence necessary for exchange (Scheme I-1). In spite of the high temperature which facilitates the 1,2 and 1,3 elimination, only partial exchange is achieved because suitably substituted norbornyl hydroxy-cation intermediates which are formed by protonation are converted to the sink-compounds 11, 12, 13 and 14.

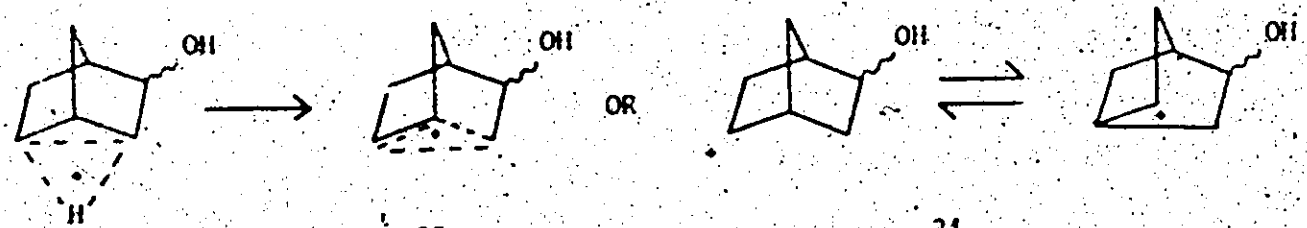
An added feature of these high temperature and dilute acid conditions is the synthetic applicability. The preparation of 13, 14 and especially 11 and 12 in one step from norbornadiene and aqueous acetic acid is remarkable. A large scale reaction, using readily available and inexpensive norbornadiene (125 g) in aqueous acetic acid at 250° (entry 6) has shown that these reaction conditions are a very economical method of producing norcamphor (33 g, 23%).

If HCl is added to the reaction medium, the aldehydes would be decomposed during the reaction to yield only norcamphor. If substituted norbornadienes are used, it may be possible to prepare substituted norcamphors.

III. Solvolysis of Hydroxy Tosylates and Brosylates - Mechanism of Product Formation

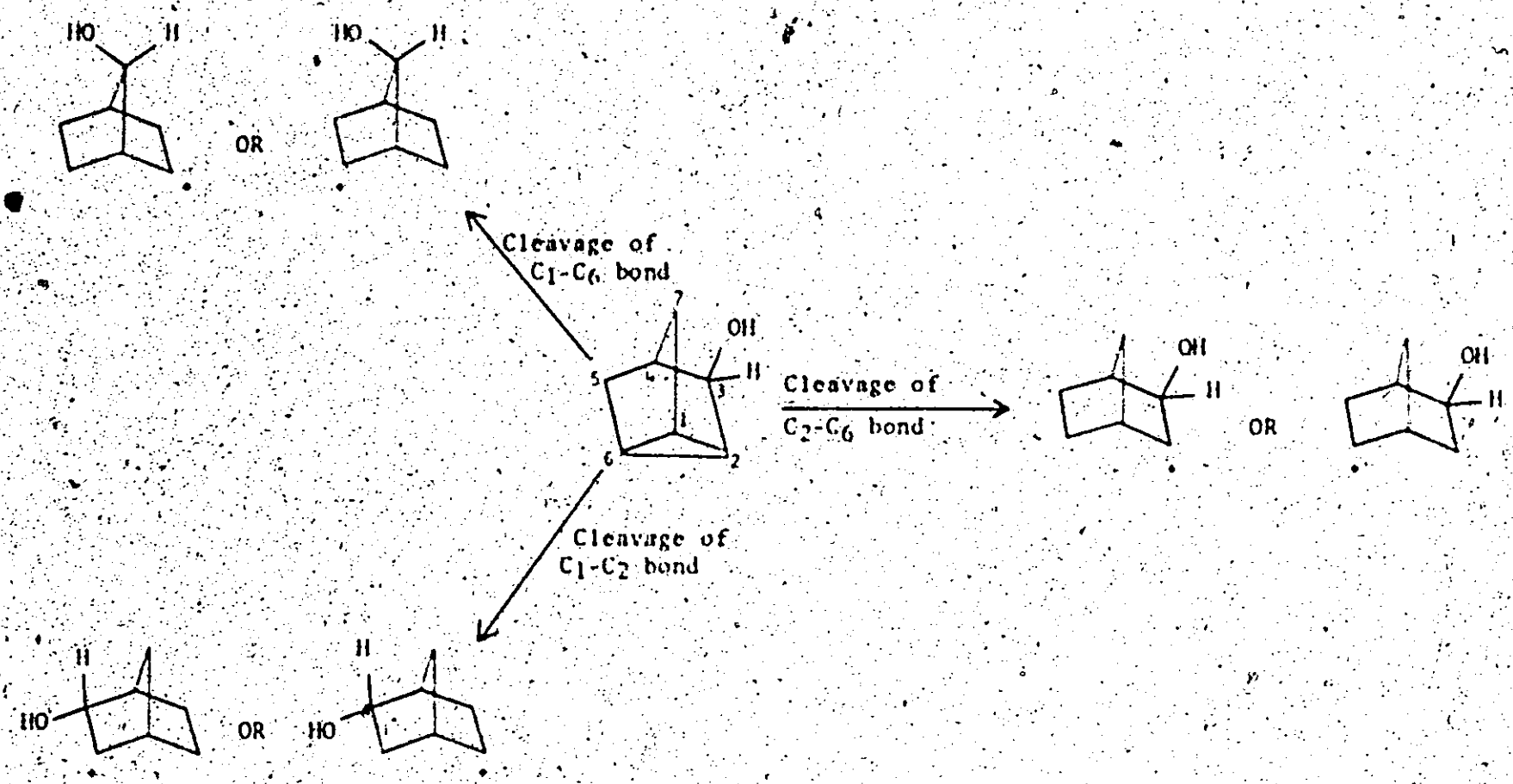
From Scheme II-1, the initial step in the reaction of nortricyclanol is the protonation of the cyclopropane ring. In unsymmetrically alkylated cyclopropanes, the proton usually attacks the least substituted center and ruptures the bond to give the most stable carbonium ion. In unsymmetrically substituted tricyclo[2.2.1.$0^{2,6}$]heptanes, such as 9c, any one of the three bonds may cleave to generate a cation, and Scheme II-4 shows these possibilities for 9c. Although no mechanistic information is available for nortricyclanol, Kerstiuk et al.[108] have shown that the σ bond farthest removed from an electron-withdrawing halogen in halonortricyclanes (9a and b) is cleaved preferentially.

The hydroxy-cation intermediates (Schemes II-1 and 4) may be non-classical, e.g., 23, or classical, e.g., 24. Classical cations are drawn only to facilitate understanding and are not intended to represent our view on the norbornyl cation problem.



23 24

SCHEME II-4


HO
H
OR
Cleavage of
C1-C6 bond
OH
H
Cleavage of
C2-C6 bond
Cleavage of
C1-C2 bond

There are three formal processes that lead to rearrangement: (a) a Wagner-Meerwein shift, (b) a 6,2-hydride shift, or (c) a 3,2-hydride shift. Low temperature and solvolytic studies have shown that, in general, the Wagner-Meerwein shifts are more rapid than 6,2-shifts while the latter are more rapid than 3,2-hydride shifts. However, cases have been reported where 6,2-shifts may proceed in the absence of Wagner-Meerwein shifts, especially when one member of the pair of cations is made comparatively much less stable than the other. Under solvolytic conditions Lee and co-workers[114] have suggested that the 6,2-hydride shift may also precede Wagner-Meerwein rearrangement. Fraenkel et al.[115] support this conclusion. Conversely, 6,2-shifts do not compete with the nominal Wagner-Meerwein shifts under conditions that limit the lifetime of carbonium ions.

It is widely accepted that 6,2-shifts occur in an endo to endo manner[116a,b]. The 3,2-shift occurs predominately exo - exo[117] but cases of endo - endo[118] are known. The 3,2- migration of an endo proton is stringently avoided and the system often reacts by circuitous pathways (W-M, 6,2-H-), after which the more favourable exo - exo shift may occur.

The stereochemistry of the 3,2- and 6,2- shifts and the competitive nature between the W-M shift and the 3,2- and 6,2- shifts is extremely important not only in the determining of the stereochemistry of the resultant product(s) but also in determining the number of products obtained in a particular reaction. This can be amply illustrated in the acid-catalyzed rearrangement of the endo- and exo-2,3-epoxy-2-phenylnorbornane (25 and 26)[119].

Reaction of the exo-epoxide (25) with m-chlorobenzoic acid for 1 h yielded a mixture of endo-2-phenylbornan-3-one (27) (23%), exo-2-phenylbornan-3-one (28) (8%), hydroxy olefin (29) (8%) and the unsaturated aldehyde (30)

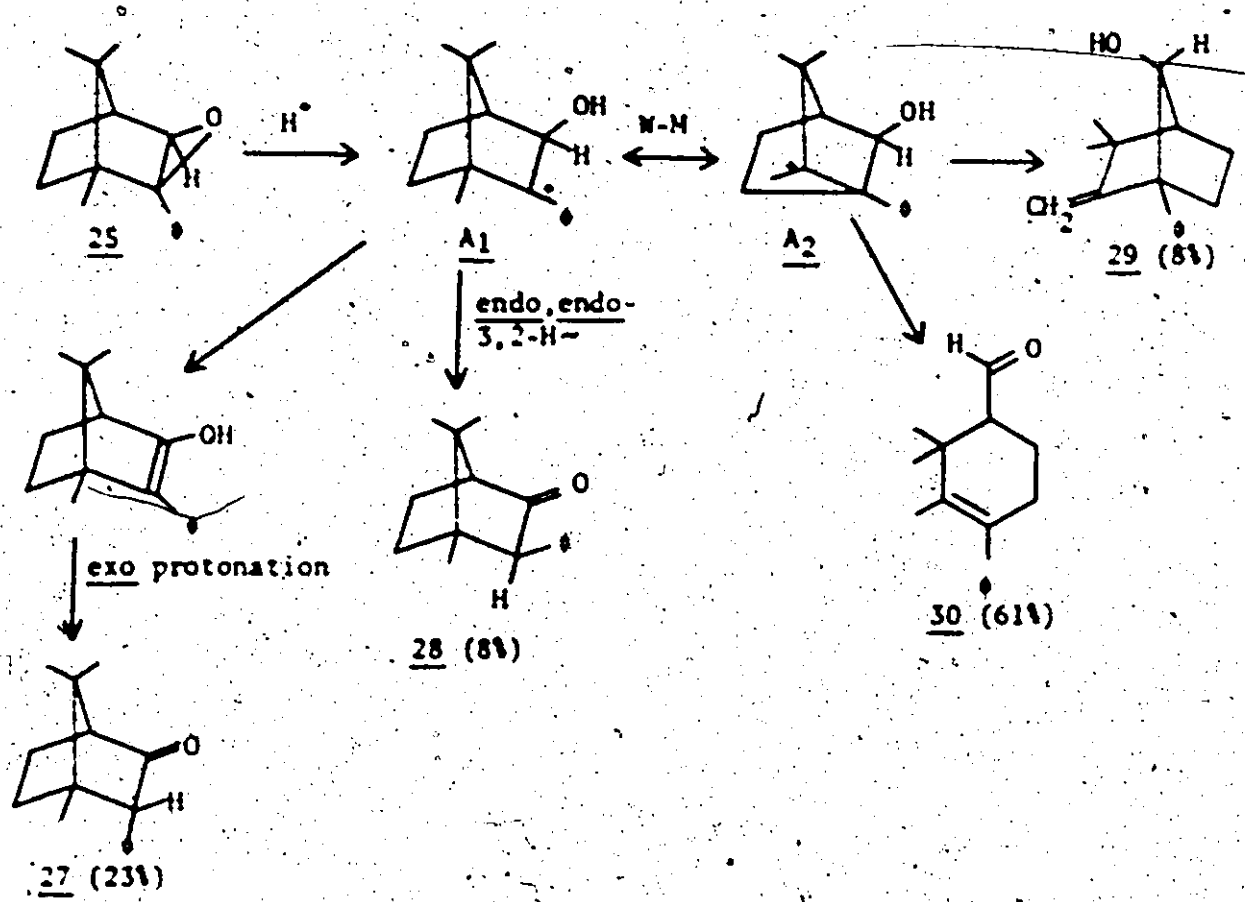
(51%) as shown in Scheme II-5. In contrast, treatment of the endo-epoxide (26) resulted in its quantitative conversion to endo-2-phenylborman-3-one (27) (Scheme II-6). In the endo-epoxide, 26, the geometry of the cation, B1, is such that the great facility of the exo,exo-3,2-hydride shift takes precedence over all other competing processes, even N-M rearrangement to B2. In A1, a direct exo,exo-3,2-hydride shift is not possible and thus the geometry of A1 dictates that numerous other processes occur as shown in Scheme II-5.

The formation of the sink-compounds (11, 12, 13, and 14), elimination products (10a, 10b and 15) and addition products (18a and 18b) may be rationalized if hydroxy-cations and the usual Wagner-Meerwein, 3,2- and 6,2-hydride shifts of the norbornyl system are considered (Scheme II-1).

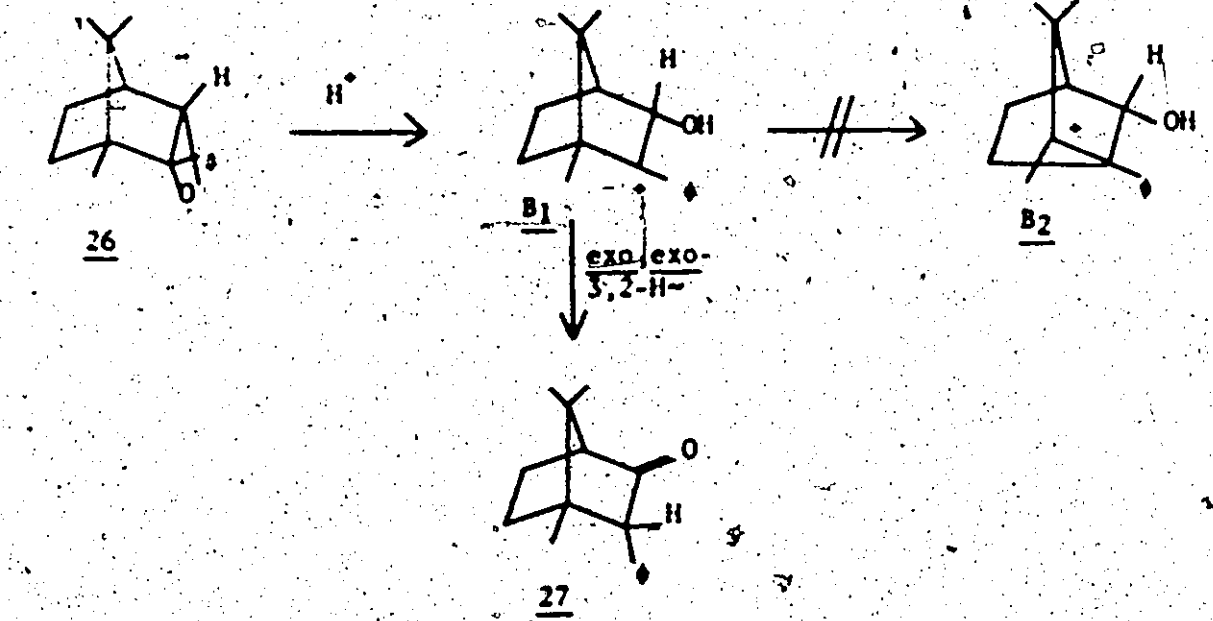
As discussed previously, the substituted nortricyclanes (9a, b, and c) and norbornenes (10a, 10b and 15) yield norbornyl diols* as the major products (18a and b in particular) and these are converted to unsaturated aldehydes and norcamphor. This indicates that nucleophilic capture of the appropriate cation to form diols is much more rapid than rearrangement to 11, 12, 13 and 14 via hydride shifts and fragmentations. In fact, Winstein et al.[120a] have shown that hydride shifts do not compete favourably with attack by an entering group in the highly nucleophilic solvent water. Berson and co-workers[120b] have shown that the amount of 6,2- and 3,2-hydride shift diminishes relative to solvent capture with increasing reaction temperature. Thus it is not at all surprising that the initially formed hydroxy-cations, in the presence of 10% v/v HOAc-H_2O at 250°, are rapidly trapped with solvent (H_2O) to yield diols.

*A total of 13 different norbornyl diols may be formed.

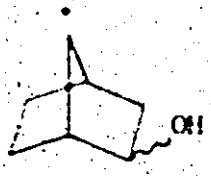
SCHEME II-5(119)



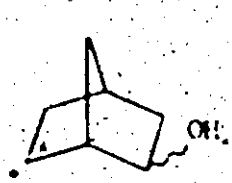
SCHEME II-6(119)



In our mechanistic studies, our attention will be primarily focused on the intermediate precursors of the sink-compounds 11, 12, 13 and 14 (Scheme II-1). For this purpose, the appropriate hydroxy-cations 31, 32, and 34 were generated solvolytically from 35, 36, and 37, respectively, in buffered acetic acid-water.



31



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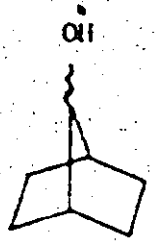
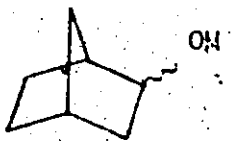
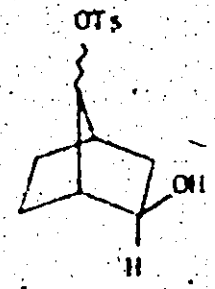


33



34



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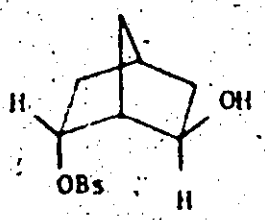
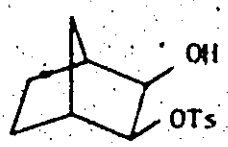


36



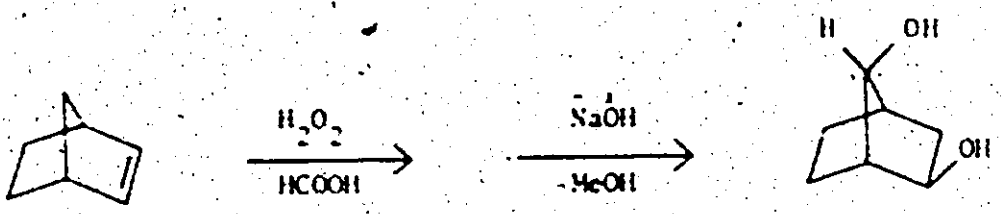
37

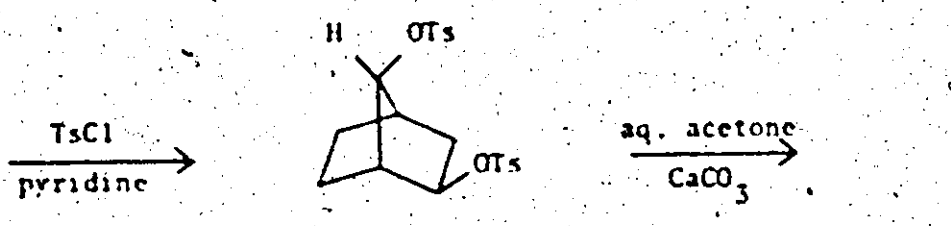
(i) Mechanism of 2-(Cyclopentene)acetaldehyde (11) Formation

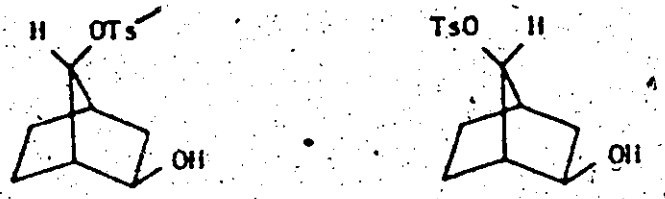
The exo-2-hydroxy-7-norbornyl cation (31a) was generated by the solvolysis of a 78:22 mixture of exo-2-hydroxy-syn- and anti-7-tosyloxy-norbornane (35) at 95° in a 10% v/v HOAc-H_2O solution buffered with 0.1 M NaOAc. The hydroxy tosylate was prepared as outlined in Scheme II-7. Pure exo-2-hydroxy-syn-7-tosyloxynorbornane can not be prepared by solvolysis of the ditosylate because 6,2-hydride shift competes with solvent capture to yield some of the anti- isomer. The extent of anti- isomer depends on the

SCHEME II-7

Synthesis of exo-2-hydroxy-syn- and anti-7-tosyloxynorbornane (35).







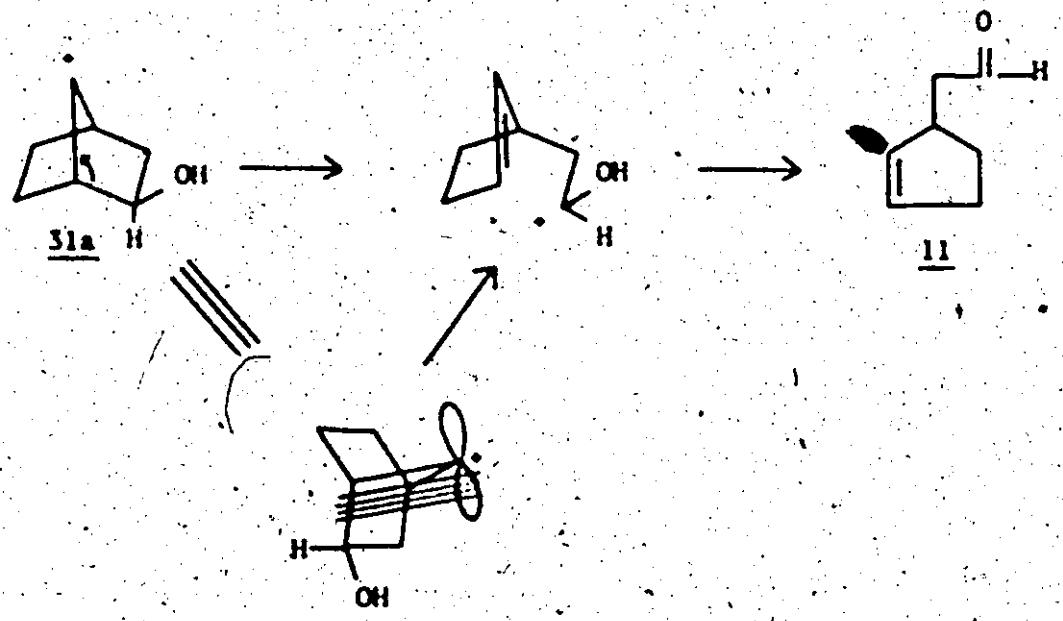
78%

22%

solvolysis conditions (see Experimental).

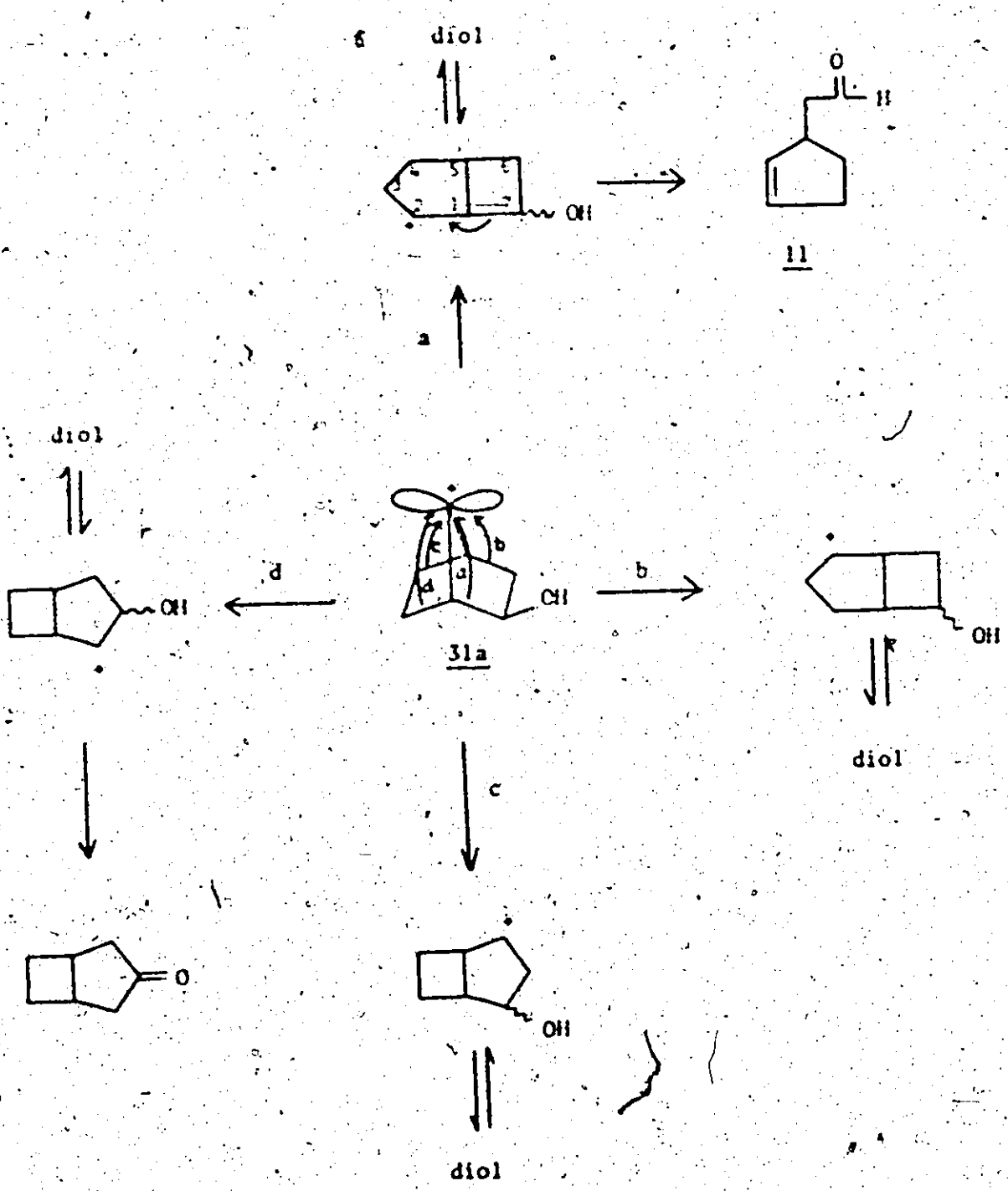
I.r. fingerprint region assay and analytical g.l.p.c. of the petroleum ether extract of the solvolysis product established that this extract contained only 11 (90% isolable yield as based on the hydroxy tosylate). The subsequent ether extract contained traces of 11 and unreacted hydroxy tosylate. This clearly indicates that 31a or the endo-isomer is a precursor to 11 (Scheme II-8). Interestingly, in this fragmentation overlap of the p-orbital at C-7 with the C-1 and C-2 bond is required.

SCHEME II-8



An alternative pathway to 11 could occur by alkyl chain migration in the 7-norbornyl cation as illustrated in path a of Scheme II-9. Gassman and co-workers[121] have shown that 1,2-alkyl chain migrations (analogous to pathways a - d) are possible in the 7-norbornyl cation as was demonstrated in the acetolysis of 7-tosyloxynorbornane which yielded small

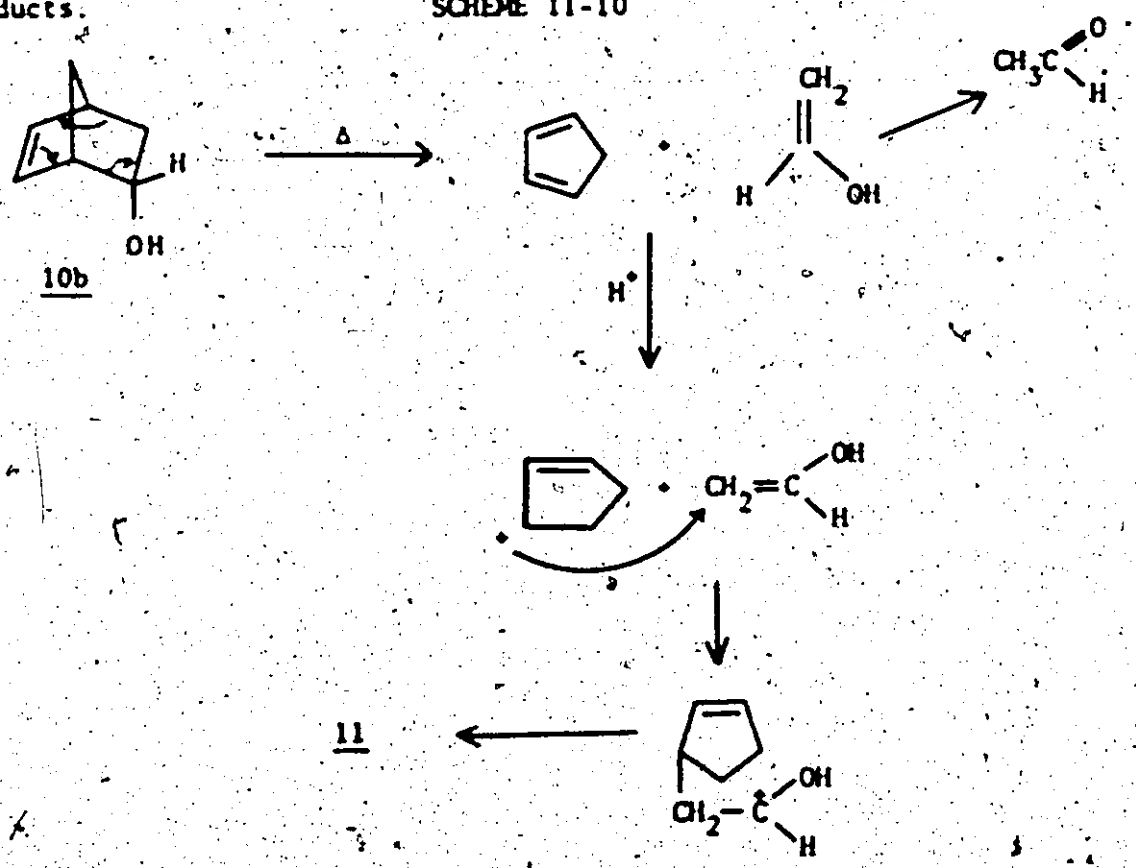
SCHEME II-9



amounts (3-5%) of 2-acetoxybicyclo[3.2.0]heptane. The formation of 11 as the sole isolable product (90% yield) excludes pathways b-d. Unfortunately, we can not distinguish between Scheme II-8 and path a of Scheme II-9 on the basis of presently available data. Regardless of which pathway yields 11, the presence of 11 only indicates that solvent capture and/or hydride shifts do not compete with fragmentation, which may be concerted. Also, since the isolated yield of 11 was 90%, both the syn- and anti-tosylate must yield 11. This indicates that the stereochemistry of the leaving group at C-7 is not a significant factor in determining the final product although further studies with the syn- and anti- hydroxytosylates would establish this exactly.

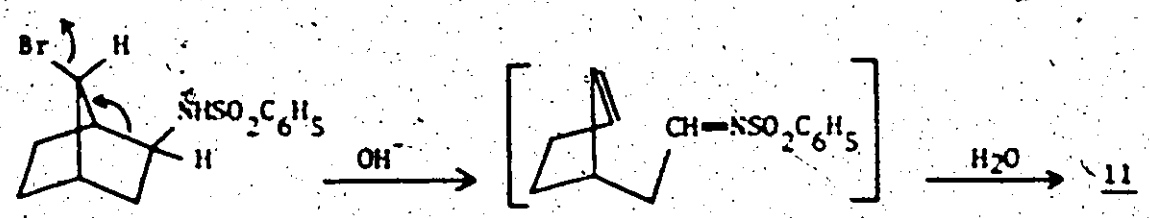
An acid catalyzed process (Scheme II-10) which involves a retro Diels-Alder is not important because 10b is stable in water at 250°. The fact that 11 was isolated in 90% yield is also a strong argument against any retro Diels-Alder reaction. Once acetaldehyde was formed it would certainly lead to other products.

SCHEME II-10



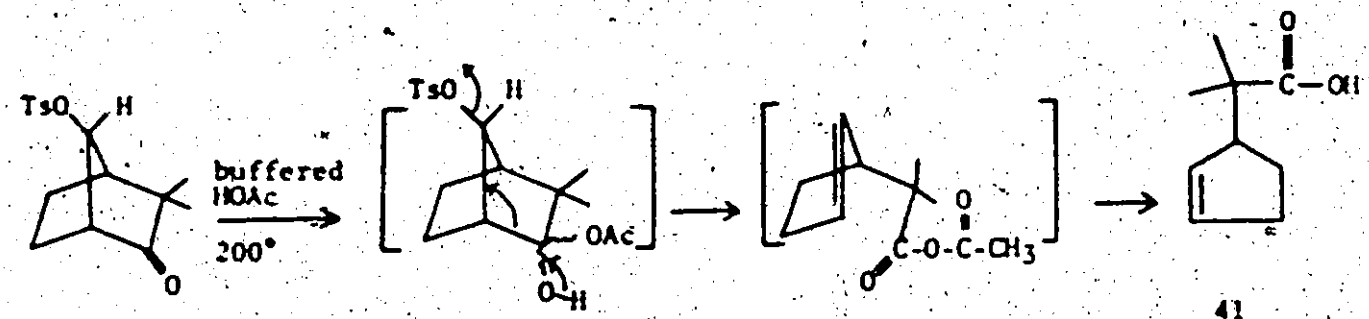
Cleavage of the 1,7 bond in the [2.2.1] system has been established in the conversion of anti-7-bromo-exo-2-benzenesulfonamidobicyclo[2.2.1]-heptane (39) to 11 (Scheme II-11)[122a,b] and 3,3-dimethyl-anti-7-tosyloxy-norbornan-2-one (40) to 2-(cyclopentene)-2,2-dimethylacetic acid (41) (Scheme II-12)[123].

SCHEME II-11[122a,b]



39

SCHEME II-12[123]



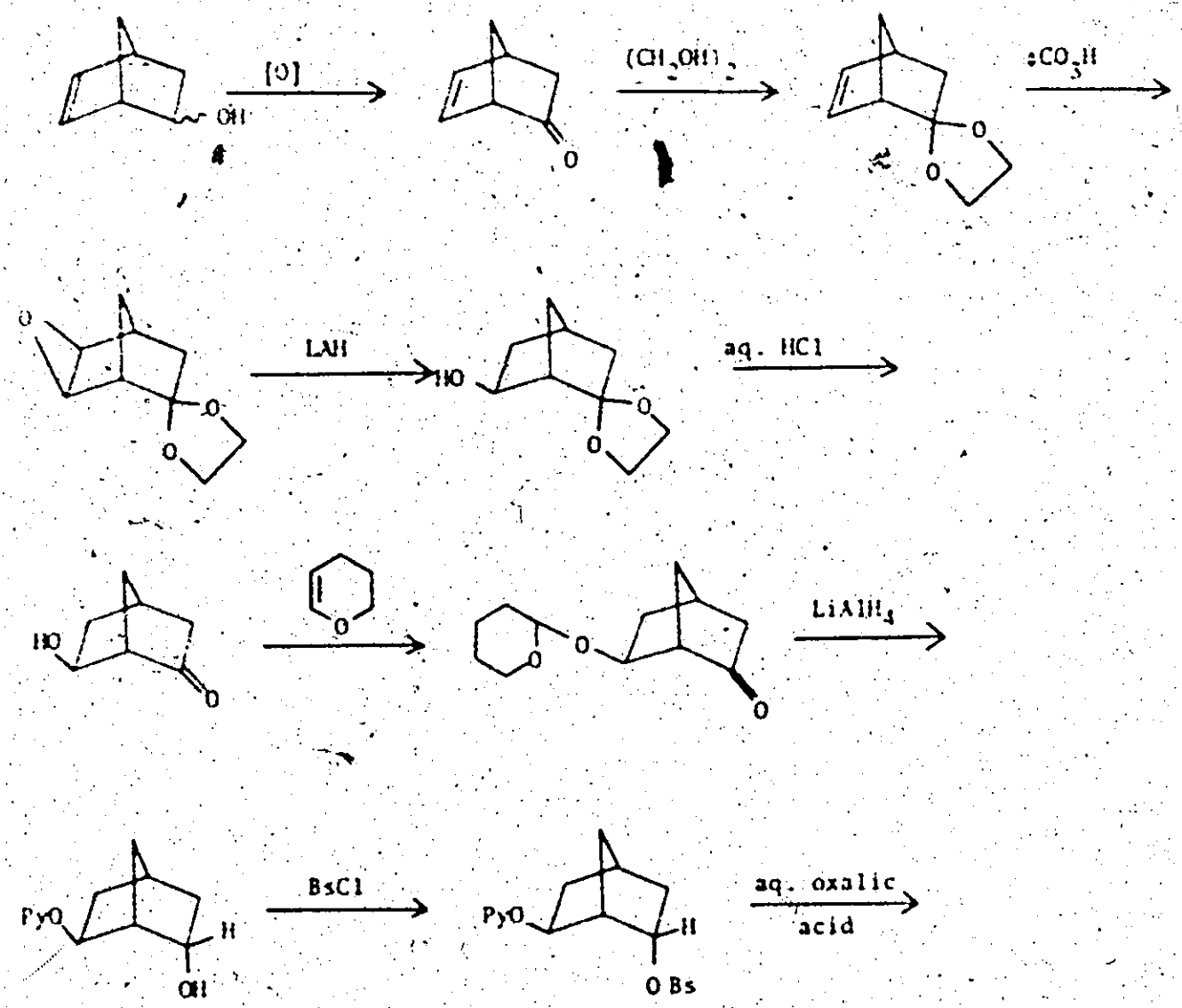
40 41

(ii) Mechanism of 3-(Cyclopentene)acetaldehyde (12) Formation

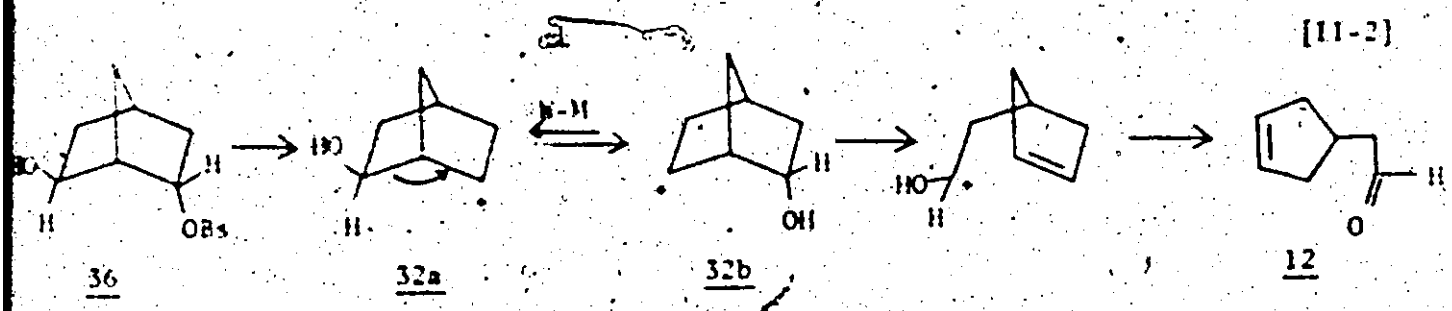
The exo-6-hydroxy-endo-2-brosyloxynorbornane (36), prepared as outlined in Scheme II-13, was solvolyzed at 95° in a 10% v/v HOAc-H_2O solution buffered with 0.1 M NaOAc. Analytical g.l.p.c. analysis of the pentane extract (the brosylate is insoluble in pentane) showed that from an overall

SCHEME II-13

Preparation of exo-6-hydroxy-endo-2-brosyloxynorbornane (36)



isolated yield of ~4%, the major product was 2- and/or 3-(cyclopentene)-acetaldehyde (94%) with some 3-(cyclohexene)carboxaldehyde (3%) and one other unidentified product (3%), which was not norcamphor. I.r. finger-print analysis (absence of peaks at 910 and 718 cm^{-1} and presence of peak at 660 cm^{-1}) of the pentane extract established that the major product was 12 and not 11. The ether extract yielded traces of a white solid (16 mgs), which by g.l.p.c. analysis was composed of 12 and nine other unidentified products which according to retention times were not 14 or norbornanediols. Since an acetone solution of 36 injected through the g.l.p.c. yielded only one peak with a retention time identical to 11 and/or 12 (presumably 12), the nine products from the ether extract were solvolysis products and not products resulting from reactions of 36 on the g.l.p.c. injector block and/or column. Thus on solvolysis of 36, and the generation of the hydroxy-cation, 32, the major product is 12 (Eq. II-2). The presence of 13 (3%)

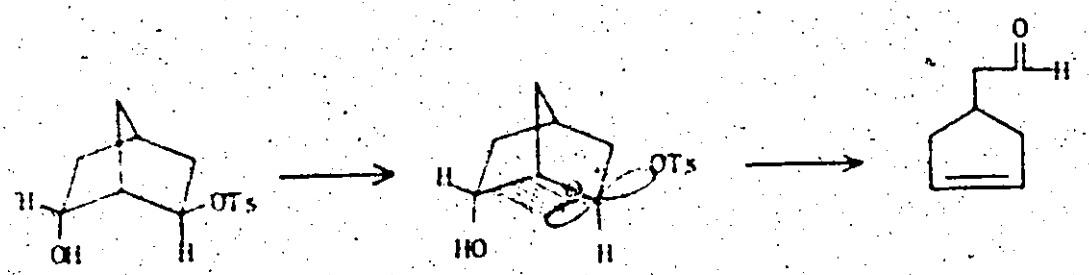


36 32a 32b 12 [II-2]

indicates that 6,2- and 3,2-hydride shifts together with Wagner-Meerwein rearrangement compete with fragmentation, but only to a small extent. In addition, the presence of nine unidentified products in the ether extract indicates that numerous other (undetermined) pathways (hydride shifts, elimination, etc.) also compete.

A tosylate or brosylate in an exo configuration should solvolyze

with participation of the C-6 and C-1 bond in an essentially concerted fashion to yield 12 as the sole product (Eq. II-3). With this in mind,



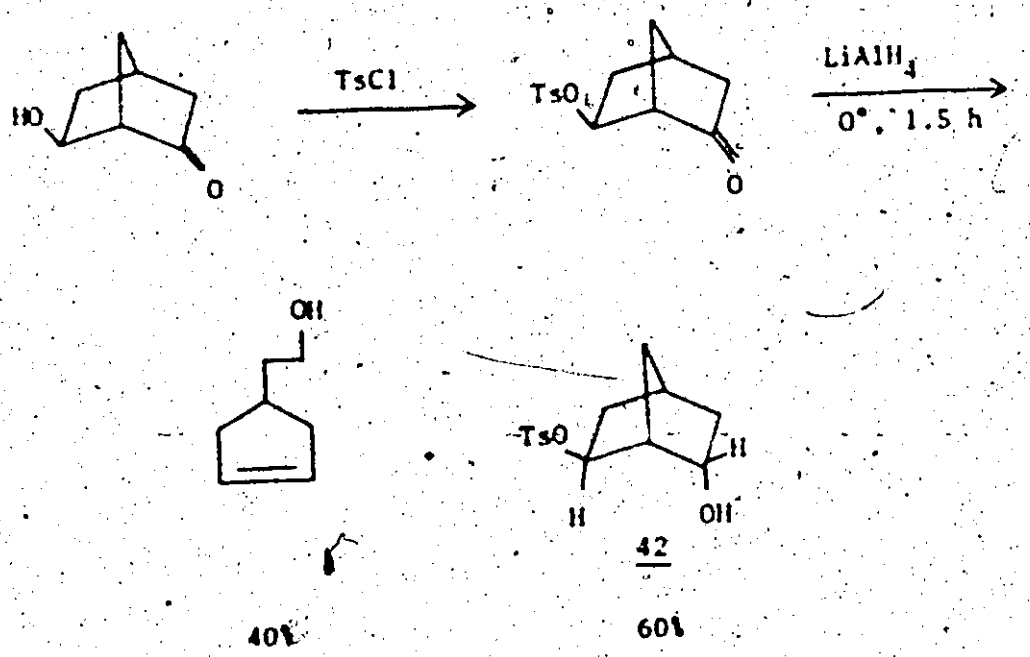
[II-3]

42 12

attempts were made to prepare the endo-6-hydroxy-exo-2-tosyloxynorbornane (42) as shown in Scheme II-14. However, in addition to our desired product,

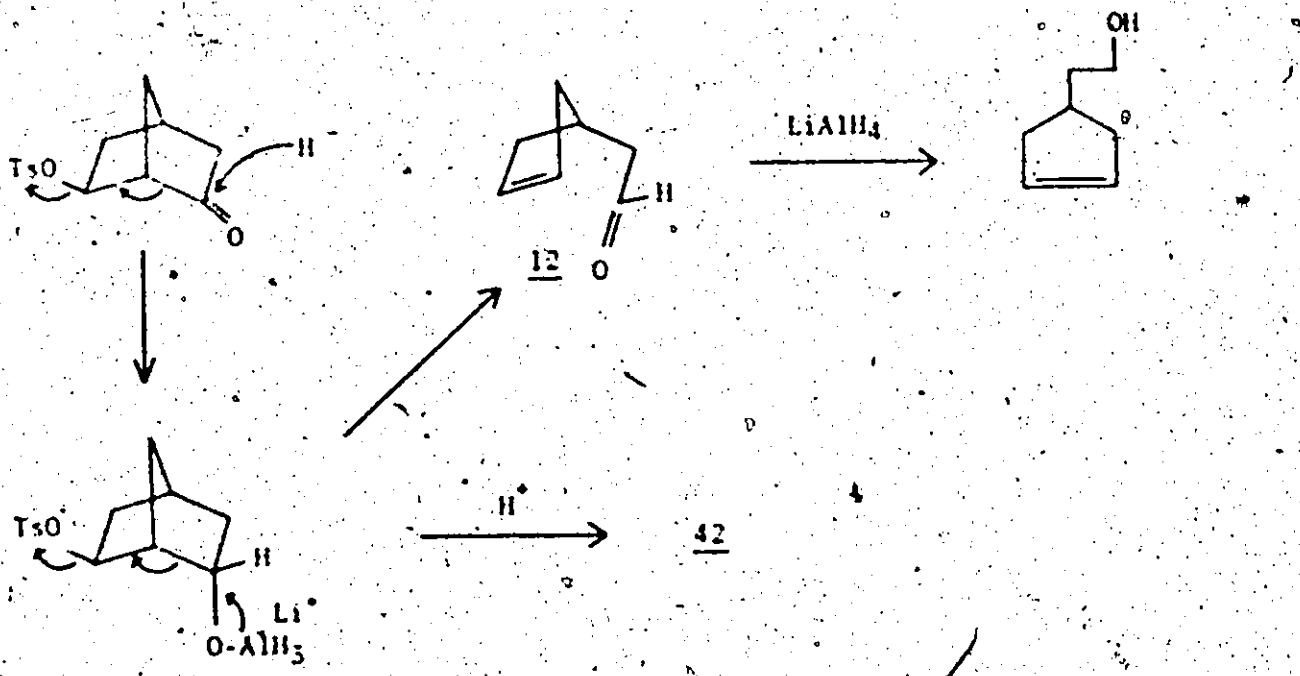
SCHEME II-14

Preparation of endo-6-hydroxy-exo-2-tosyloxynorbornane (42)



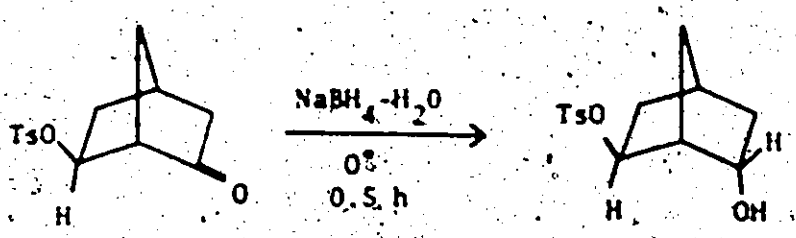
considerable amounts (40%) of a fragmentation product, 3-(cyclopentene)-ethanol, as determined by i.r. and n.m.r. were formed. Attempts to purify the hydroxy tosylate by recrystallization were unsuccessful. The presence of 42 indicates a step-wise process, as illustrated in Scheme II-15. This type of reductive fragmentation of the bicyclo system with $LiAlH_4$ has been well documented.[124a-c] In fact, any bicyclo system with a carbonyl and a tosylate (brosylate) in a 1,3 relationship fragments during reduction with $LiAlH_4$.[124a-c]

SCHEME II-15



Further attempts to prepare 42 by $NaBH_4/H_2O$ reduction of the keto-tosylate were made, as shown in Scheme II-16. In this case, i.r. and n.m.r. indicated that 42 was the major product with traces of unknown(s). However, again attempts to purify 42 by recrystallization were futile. Preparation of the corresponding brosylate also gave similar results. Gas chromatographic

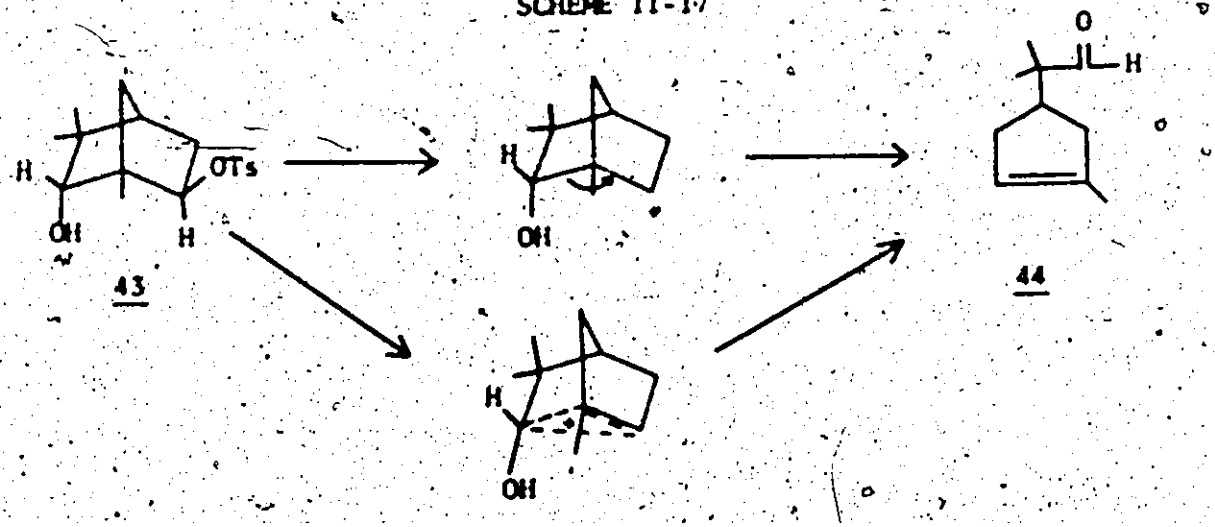
SCHEME II-16



analysis of an ether solution of crude 42 led to its conversion (pyrolysis) to 12, as determined by retention time.

The preceding results indicate that the 6,2-hydroxy-cation (32a) or its endo-isomer (32b) is certainly a precursor to 12. In contrast to the 2,7-hydroxy-cation (31a) which fragments to only one product, 11, the 6,2-hydroxy-cation undergoes competing reactions under solvolysis conditions to give numerous minor products, in addition to the major fragmentation product. Under solvolytic conditions, it has been shown that endo-6-hydroxy-exo-2-tosyloxyfenchane (43) fragments to only one product, 3-methyl-3-(cyclopentene)dimethylacetaldehyde (44) (Scheme II-17)[125]. This result suggests that 42 should give 12 as the only product. Competing processes, which are present in the endo-brosylate, 36, will not be important because the geometry is favourable for a concerted fragmentation. Similar types of

SCHEME II-17[125]

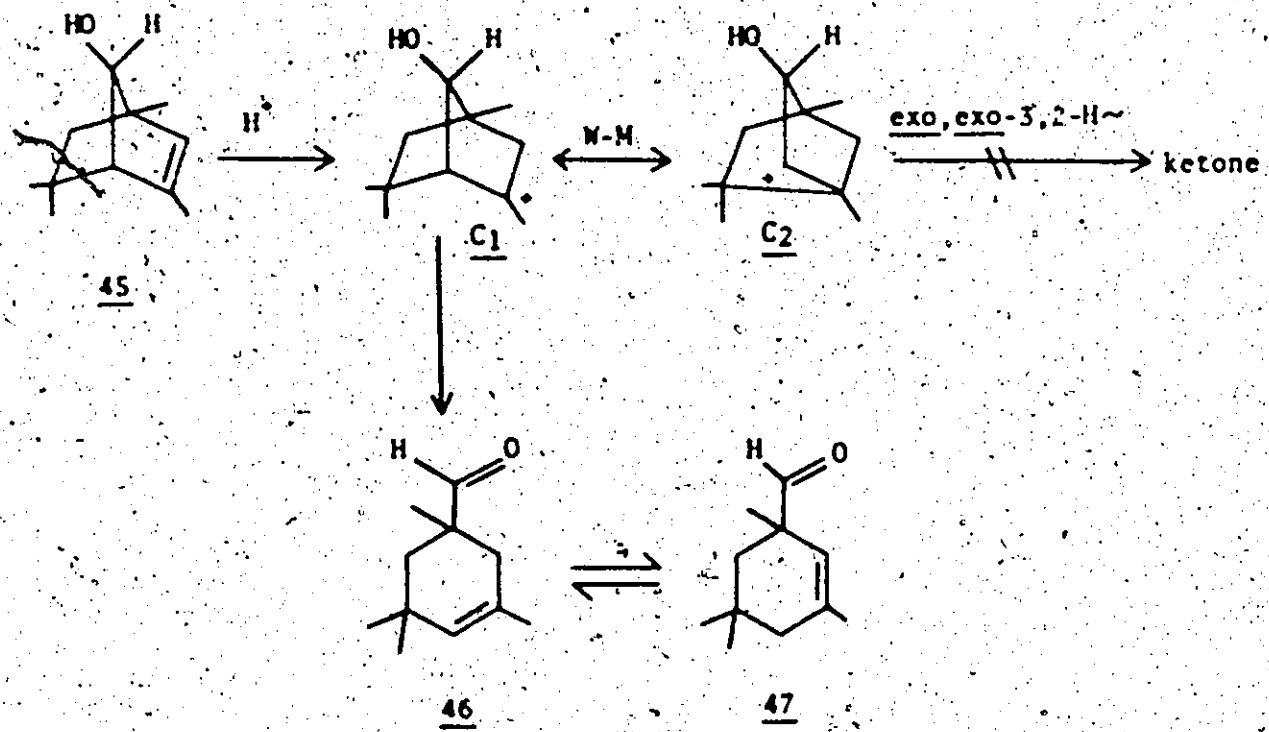


C-C cleavage processes of the norbornyl skeleton to give 3-(cyclopentene)-acetaldehyde derivatives have also been reported by other authors[126,127]. This type of fragmentation is also similar to acid-catalyzed cleavage of 1,3 diols[128].

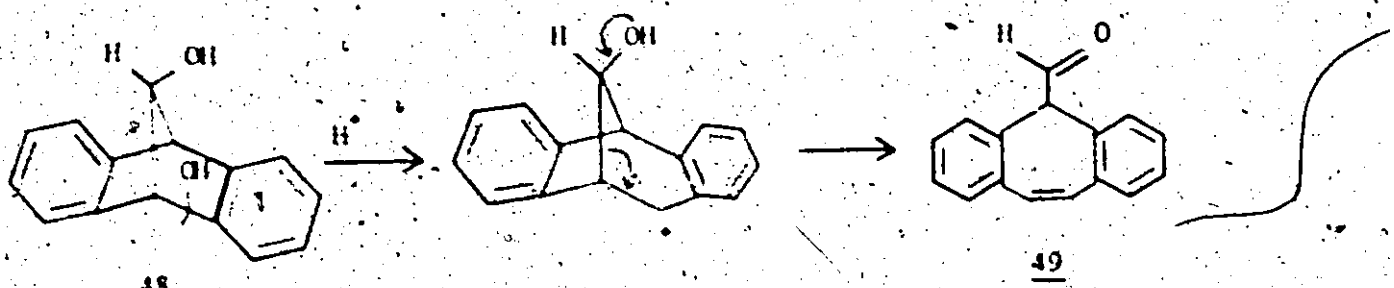
(iii) Mechanism of 3-(Cyclohexene)carboxaldehyde (13) Formation

Formal cleavage of the C-1 and C-7 bond of a bicyclic system to give 3-(cyclohexene)carboxaldehyde derivatives has been reported by numerous authors[119,129-133]. Typical examples are shown in Schemes II-18 - 20.

SCHEME II-18[129]

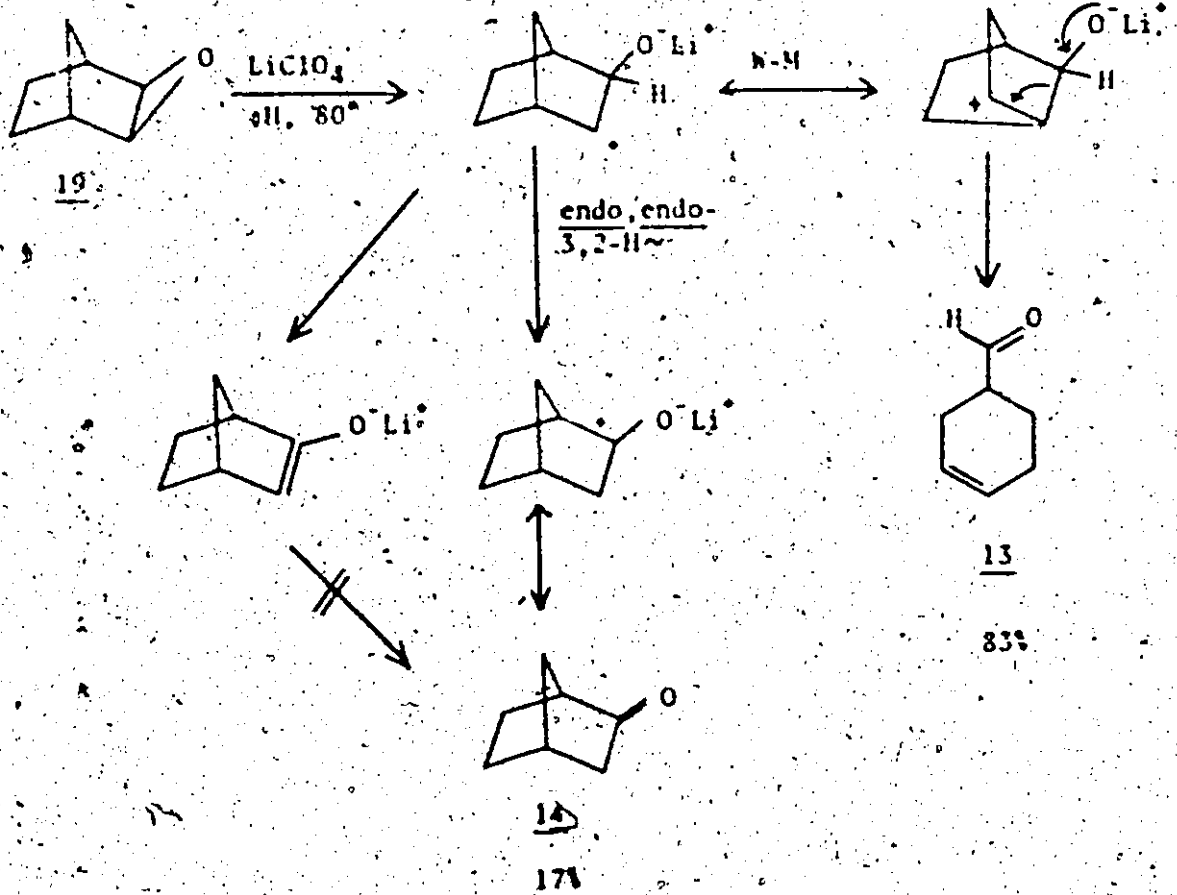


SCHEME II-19 [133]



48 49

SCHEME II-20 [132]



19 13 83% 14 17%

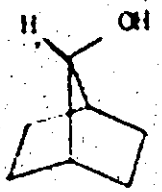
From these three examples several conclusions can be drawn about C-1 and C-7 fragmentation.

(i) Schemes II-18 and 19 show that if a syn- or anti-hydroxy-2-cation (33) is generated directly, it will fragment to only one product, the corresponding unsaturated aldehyde.

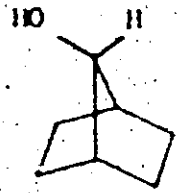
(ii) In cases where a 7-hydroxy-2-cation is generated indirectly through a series of hydride shifts or W-M rearrangements (Schemes II-5 and 20), other products will also be formed from the other hydroxy-cation precursors.

(iii) In cases where a 7-hydroxy-2-cation is generated indirectly, the percentage of fragmentation product (unsaturated aldehyde) formed will depend upon the ease with which the predecessor hydroxy-cations can form other stable products. For example, as described in Scheme II-6, exo,exo-3,2-H~ in B_1 to form 27 is so rapid that no other process competes. However, in Scheme II-5, the geometry of the cation, A_1, is such that W-M rearrangement (to a 7-hydroxy-2-cation) and elimination competes with the relatively slow endo,endo-3,2-hydride shift. A similar result was observed for 19 as described in Scheme II-20. In these two latter cases, the product distribution establishes that the W-M rearrangement and fragmentation are much more rapid than a 3,2-hydride shift required for ketone formation. As a point of interest, in Scheme II-20, norcamphor is not formed via the enolate since there is no proton source.

These preceding examples clearly establish that 3-(cyclohexene)-carboxaldehyde likely is formed from 9a, 9b and 9c via the intermediates 33a and 33b. However, other pathways such as a 7,2-Wagner-Meerwein shift



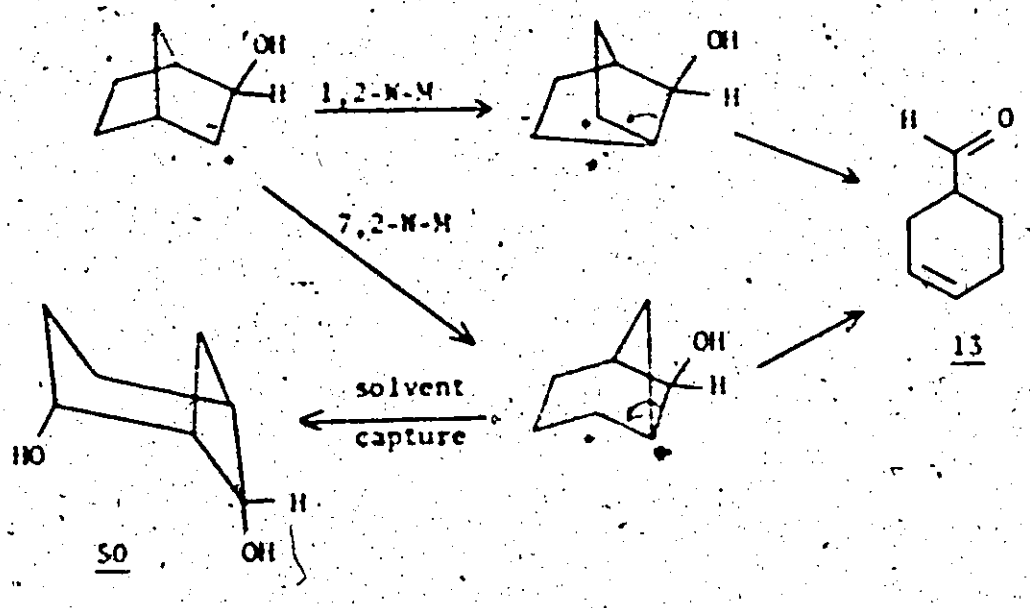
33a



33b

in Scheme II-21 must be considered and can not be ruled out presently and, in fact, the diol fraction may contain bicyclo[3.1.1] and [3.2.0] species.

SCHEME II-21



The existence of a 7,2-Wagner-Meerwein rearrangement in a norbornyl skeleton has been demonstrated by Collins et al.[134,135]

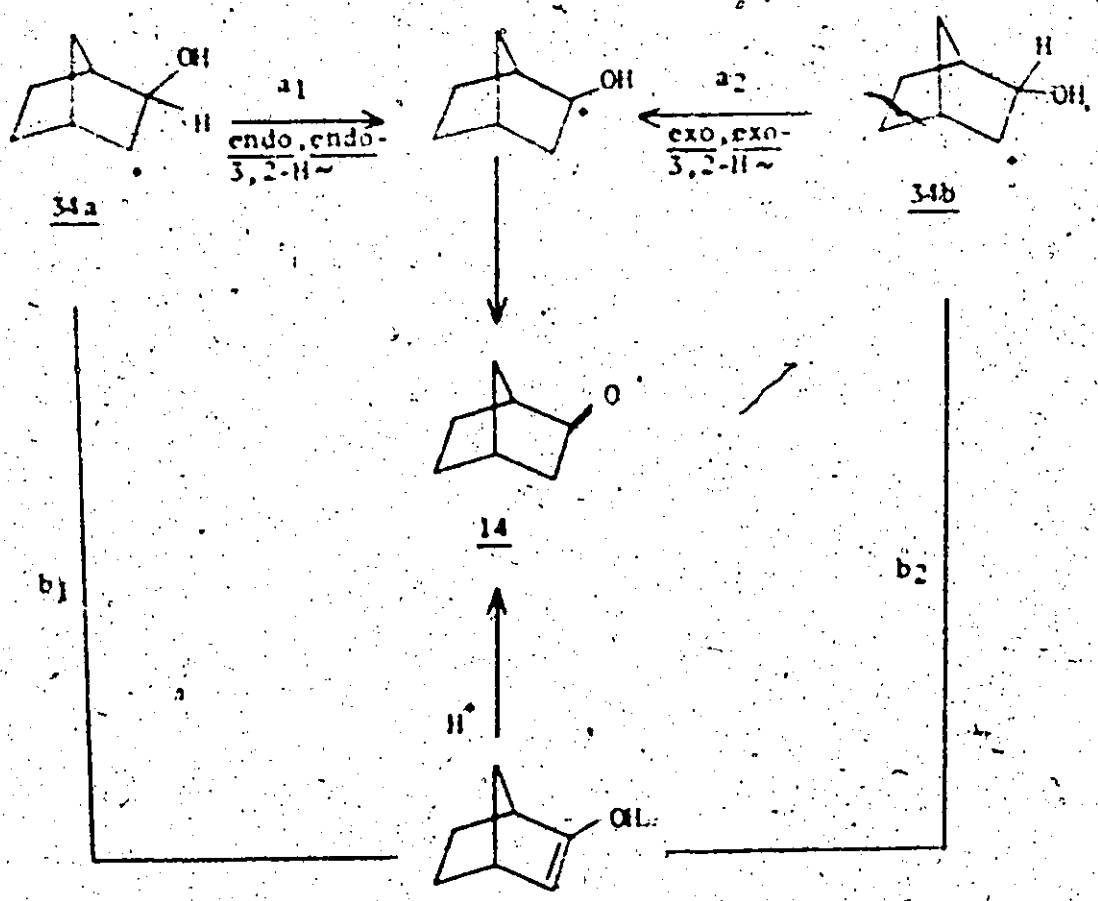
The detailed steps of the mechanism of product formation are not established and no attempt is made herein to do so, in terms of specific processes (hydride shifts, Wagner-Meerwein rearrangement, elimination, etc.) at the molecular level. However, our preceeding discussion demonstrates

that, regardless of the mode of formation, appropriate hydroxy-cations are precursors to the fragmentation products (Scheme II-1).

(iv) Mechanism of Norcamphor (14) Formation

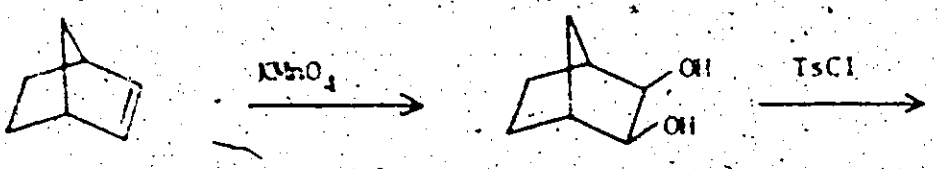
Scheme II-22 outlines some possible pathways for the formation of 14. All these pathways have direct analogies[119] and hence are possibilities. In order to explore these possibilities, cis-exo-3-hydroxy-2-tosyloxynorbornane (37) was prepared as shown in Scheme II-23 and solvolyzed at 95° in 10% v-v HOAc-H$_2$O buffered with 0.1 M NaOAc. After 7 days, work-up yielded a

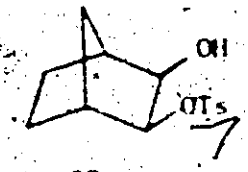
SCHEME II-22



SCHEME II-23

Synthesis of cis-exo-3-hydroxy-2-tosyloxynorbornane (37)

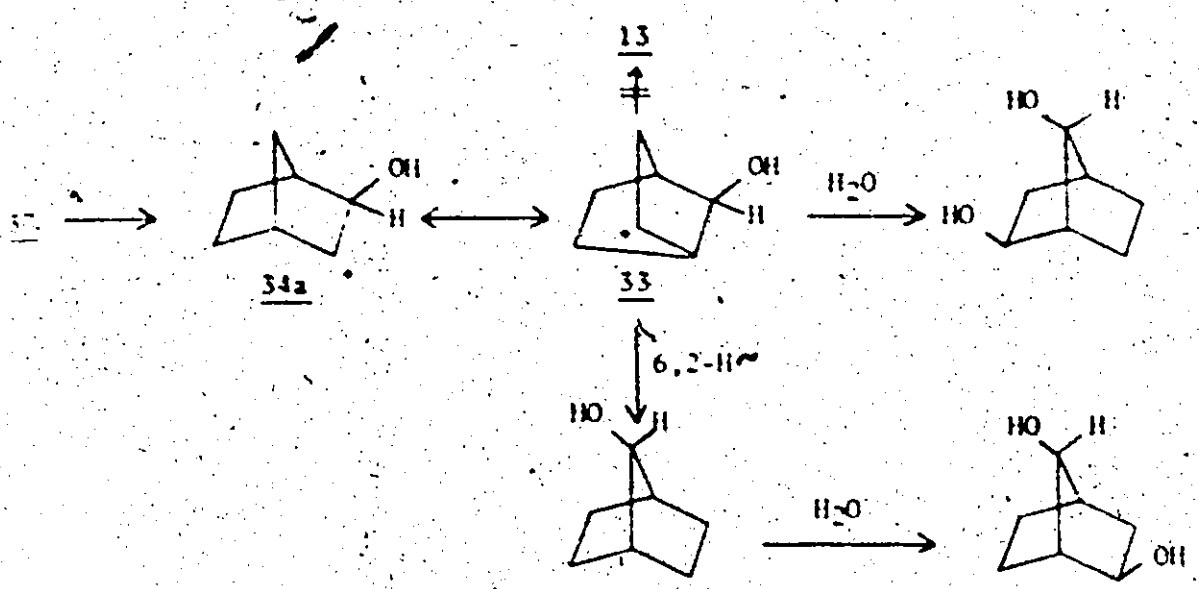




37

semi-solid (88% yield of norbornanediols) which contained traces of norcamphor (no unsaturated aldehydes) and nine other products with retention times in the region of norbornanediols as established by g.l.p.c. analysis. Two of the major products had retention times identical to syn- and anti-3-hydroxy-exo-2-norborneols (18a and b). This clearly indicates that pathways a_1 or b_1 do not occur to any appreciable extent. The exclusion of pathway a_1 is not surprising since endo,endo-3,2-hydride shifts are generally unfavourable. Apparently, under our solvolysis conditions, 34a undergoes solvent capture and/or rearrangement and subsequent solvent capture. The occurrence of a W-M rearrangement and 6,2-hydride shift can be substantiated by the appearance of 18a and b (Scheme II-24). Interestingly, fragmentation (33 → 13) does not compete with solvent capture at this temperature, in direct contrast to the solvolysis of 35 and 36 where solvent capture or even rearrangement do not compete effectively with fragmentation. This could possibly be attributed

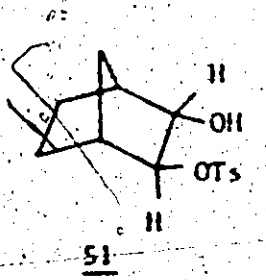
SCHEME II-24



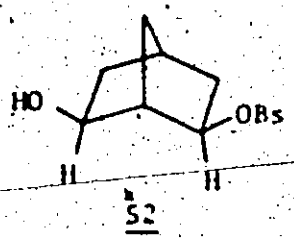
to a concerted fragmentation process in the latter two cases.

Solvolysis of the cis-exo-3,2-hydroxy tosylate at 250° yields 11, 12, 13 and 14. This is not surprising since the initially formed diols, which are stable at 95°, solvolyze at 250°, to form the sink-compounds.

Since exo,exo-3,2-hydride shifts are much more facile than the endo,endo analog, pathway a2 should be a major pathway to formation of 14. This could be checked by the solvolysis of 51, which would generate the



51



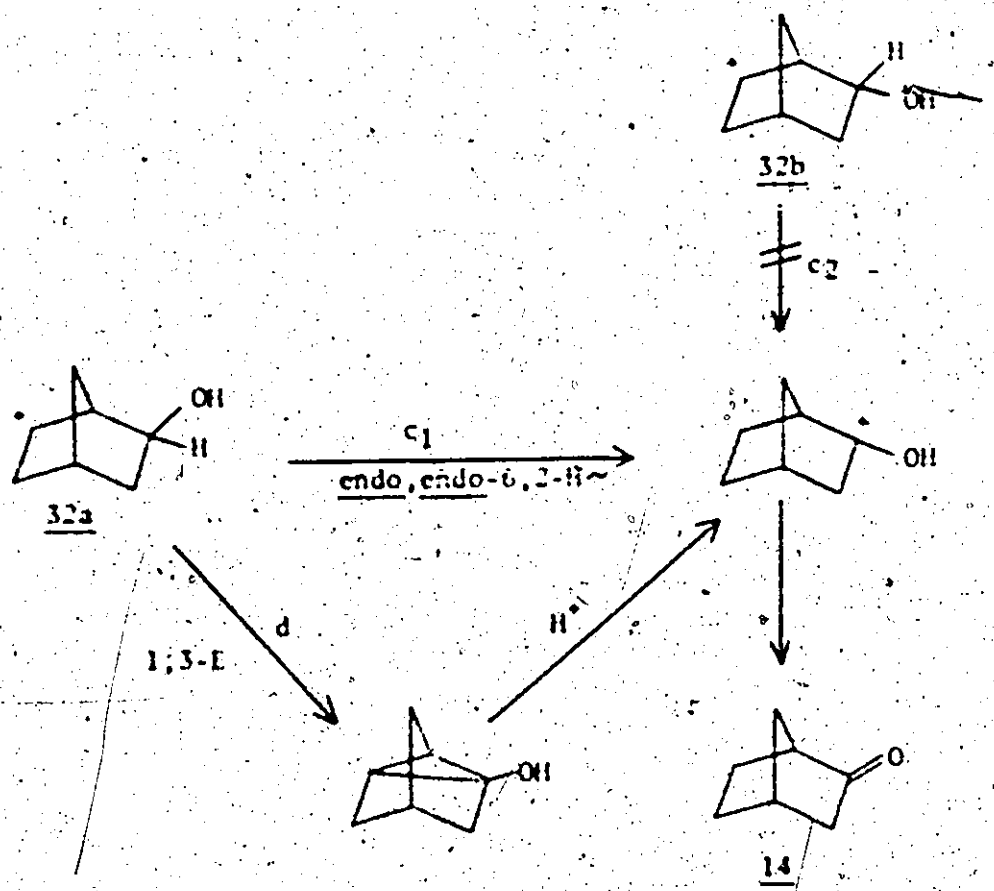
52

endo-3-hydroxy-2-cation (34b). This cation has the correct stereochemistry for an exo,exo-3,2-hydride shift and this should compete more favourably, if not exclusively, with solvent capture and/or rearrangement.

An alternative pathway for the formation of 14 has been represented

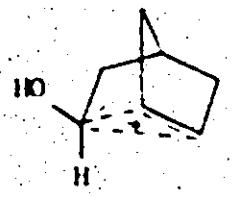
in Scheme II-25. However, the solvolysis of the exo-6-hydroxy-endo-2-brosylate (36), which generates the 6-hydroxy-2-cation (32a), yields only 12 and not 14. Clearly, a 6,2-H shift or a 1,3 elimination does not compete with fragmentation and thus the exo-6-hydroxy-2-cation is not a precursor to 14. Pathway c_2 is very unlikely because there is no precedence for an exo, exo-6,2-hydride shift.

SCHEME II-25



Although we have shown that a 6,2-hydride shift does not compete with fragmentation during the solvolysis of the exo-6-hydroxy-endo-2-brosylate (36), a 6,2-hydride shift might be faster in the exo-6-hydroxy-exo-2-brosylate

(52) and thus compete effectively with fragmentation to yield 14. However, this possibility can be ruled out, since Lee et al.[136] have shown by the tritium scrambling in the solvolysis of the exo- and endo-2-t-2-norbornyl brosylates that the rates of 6,2-hydride shifts in both the exo- and endo-isomer are essentially identical. That is, in the solvolysis of the exo- and endo-brosylates (52 and 36), fragmentation via D occurs preferentially over the 1,3 elimination and/or hydride shift required for the formation of norcamphor (Scheme II-25).



D

In conclusion, the most probable mechanism for the formation of norcamphor is pathway a; and/or b; of Scheme II-22.

Synthetic Utility

The formation of aldehydes 11 + 12 and 13 was somewhat surprising since examples involving the conversion of bicyclo[2.2.1]heptane derivatives to monocyclic products are reported to be relatively rare[122a,b,123,125-7]. In our studies herein, the driving force for fragmentation presumably resides in the generation of a very favourable leaving group, the conjugate acid of a carbonyl. Our process provides a unique synthetic route to 11 + 12 and 13.

The unsaturated aldehydes and especially norcamphor act as sinks for appropriately substituted norbornyl systems. Conceivably any appropriately

substituted bicyclic system which contains seven ring-carbon atoms and which yields hydroxy-cations on solvolysis or protonation is convertable to sink-compounds. Thus our high temperature and dilute acid conditions affords an alternative synthetic method for the preparation of substituted norcamphors and aldehydes.

If partially deuterated or tritiated norcamphors or unsaturated monocyclic aldehydes are required, the conditions described herein are extremely useful because the deuteration (tritiation) procedure is superior to other methods. Although incomplete exchange occurs in the sink compounds the degree of exchange can be controlled, to a limited extent only, by the acidity of the reaction medium.

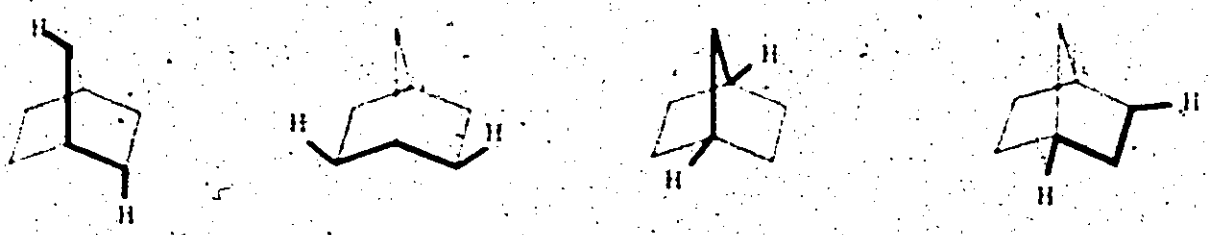
IV. N.m.r. Spectra Analysis of endo-Norborneol (57) in the Presence of the Chemical Shift Reagent, $Eu(DPM)_3$

Shift reagents can be used for (i) structural determinations[137a-d], (ii) assignment of ^{13}C n.m.r. spectra[138a,b], and (iii) determination of deuterium incorporation into organic molecules. Thus, in order to determine quantitatively the site and stereochemistry of the deuterium incorporated into the norbornyl skeleton, the deuterated norcamphor in each case was converted to endo-norborneol which was subjected to n.m.r. integration analysis in the presence of the shift reagent, $Eu(DPM)_3$.

As reported by Hinckley[139] and Sanders and Williams[140], association of $Eu(DPM)_3$ with organic molecules containing coordinating groups (alcohols, amines, esters, ethers, etc.) causes large paramagnetic shifts with only a very slight broadening[141] of the proton resonance signals of the molecules. Association with the Europium complex occurs via the lone-

pair electrons of the substrate and the induced shift decreases rapidly with increased distance of the proton from the lone-pair electron group[139]. Presently, there is no unanimous agreement in the literature[142a,b] regarding the exact nature of the factors which give rise to the shifts. Wahl and Peterson[143] applied $Eu(DPM)_3$ to the adamantanols and provided evidence that the mechanism of deshielding involves both interaction through space and through bonds. The latter is more important when only two or three bonds separate hydrogen and europium (e.g., OH and 2-H in endo-norborneol). The former effect becomes dominant when four or more bonds are involved and close approach of europium and hydrogen is possible. In many cases[139,140,144,145], increasing the amount of $Eu(DPM)_3$ increasingly resolves the spectrum of the substrate.

The idea that spin-spin splitting in n.m.r. spectroscopy is dependent upon indirect coupling of neighbouring nuclei via the electrons in a molecule is generally well accepted[146]. Theoretical and experimental progress has been made in understanding how spin-spin coupling constants vary with molecular structure when either two or three bonds separate a pair of interacting protons. Thus, the dependence of J-(coupling constant) on the geminal H-C-H angle[147] and on the vicinal H-C-C-H dihedral angle[148] is well known. Although it was generally stated that coupling between protons which are separated by more than three bonds in saturated systems was negligible (~1 cps)[149], numerous examples[150,151] contradicted this rule and led to the important concept of "long-range" spin-coupling[152,153]. In the bicyclo[2.2.1]heptane system, this coupling occurs between pairs of protons related according to the "W-letter rule" as illustrated below.



The rigidity of these molecules results in all protons being within five bonds of one another and in definite and fixed geometrical relationships.

Analysis of Spectra

The spectrum of endo-norborneol in carbon tetrachloride showed as separate signals only the OH, 2x and 3n protons. When tris(dipivalomethanato)europium is added to carbon tetrachloride solutions of endo-norborneol, well-resolved spectra (see Figures 1, 2 and 3) are obtained. The signals were assigned by a combination of first order analysis of the splitting patterns, double resonance experiments and by studying the spectrum of endo-2-norborneol-exo-5-exo-6-d, (Fig. 2).

A typical first order analysis affording a signal assignment is illustrated in Fig. 1. The 2x and 6n protons are farthest downfield since the induced shifts are greatest for protons nearest to the hydroxy group[139]. A double resonance experiment (Fig. 1) confirms the assignment of 6n; irradiation of the 6n proton collapses the 6x proton which in turn can be assigned via the dideuterated alcohol. The 3n signal consists of two symmetrical triplets due to coupling with the 3x, 2x and 7a protons. The 6n and 3n protons can clearly be differentiated in the dideuterated alcohol (Fig. 2). Here the 6n signal is a doublet due to coupling with only the 5n proton (loss of 6x coupling) while the 3n signal remains as two symmetrical triplets. The bridge-head protons are usually identified by their broad patterns. The

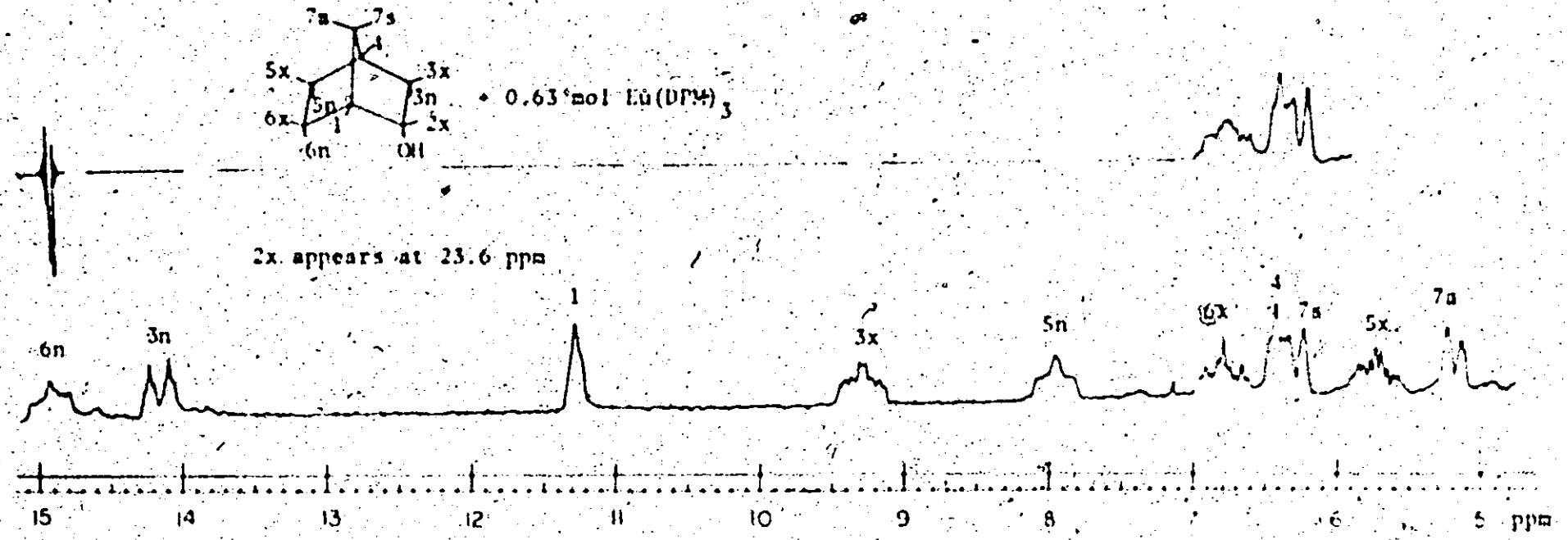


Fig. 1. Proton resonance spectrum of endo-norborneol in the presence of 0.63 mol Eu(DPM)$_3$ (mol. = molar ratio of Eu-complex to alcohol) in carbon tetrachloride recorded with 100 Mc Varian HA-100 spectrometer. The top spectrum is a double resonance experiment where the 6n signal is saturated by irradiation.

bridgehead proton at C-1 which is spatially close to the hydroxy group appears as a broad peak at 11.29 ppm at 0.63 mol. $Eu(DPM)_3$. The 3x proton is a complex multiplet; however, closer scrutiny on an expanded scale (Fig. 3) clearly shows a septet due to coupling with the 3n, 2x and 4 protons. Comparison of the deuterated and undeuterated endo-norborneol (Figs. 1 and 2) clearly establishes the assignment of the rest of the spectrum. The 5n and 6n protons have collapsed to doublets with some fine structure in the deuterated alcohol since they are now only strongly coupled to each other and weakly coupled to 7a; the couplings to 5x and 6x have disappeared. Conclusive proof for the assignment of the 5n proton is achieved by double resonance (Fig. 2); irradiation of the 6n proton collapses the 5n signal.

The signals due to 6x and 5x are absent in the deuterated analog confirming their assignment as shown in Fig. 1. The bridgehead proton at C-4 appears as a broad doublet (Figs. 1 and 2). The 7a and 7s protons appear as broad doublets (strong coupling with each other) with some fine structure (W coupling). Additional proof for the assignment is obtained by a double resonance experiment (Fig. 2); irradiation of the 7a proton collapses the 7s and 3n signals but not the 6n signal. The 7s proton is further downfield than the 7a proton because it is nearer to the hydroxy group; this is confirmed by the preceeding double resonance experiment and also by irradiating the 7s signal (No. 104, CCl_4) which collapses the 7a and 6n signals but not the 3n signal. At an $Eu(DPM)_3$/alcohol ratio (mol) of 0.63 (Fig. 1) the analysis shows that the 6x and 4 protons appear at δ 6.80 and 6.40 respectively, downfield from Me_4Si. This does not agree with Paasivirta's[144] assignments of δ 4.12 and 4.32 for 6x and 4, respectively, obtained at mole ratio of 0.33. However, $Eu(DPM)_3$ analysis on endo-2-norborneol-exo-5-exo-

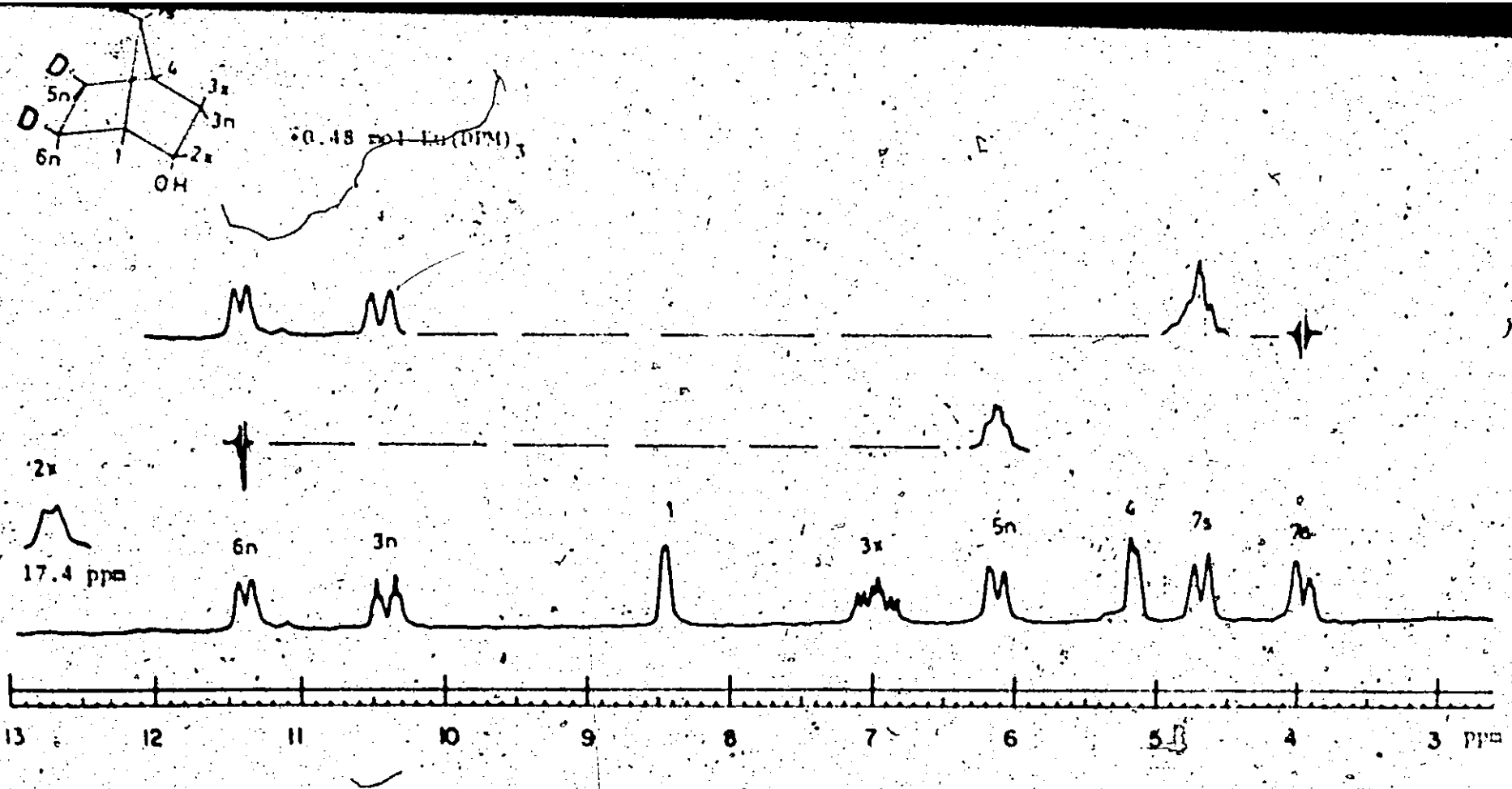


Fig. 2. Proton resonance spectrum of endo-2-norborneol-exo-5-exo-6-d_2 in the presence of 0.48 mol $Eu(DPM)_3$ (mol = molar ratio of Eu-complex to alcohol) in carbon tetrachloride recorded with 100 Mc Varian HA-100 Spectrometer. The top two spectra are double resonance experiments where the 6n and 7a signals have been saturated by irradiation.

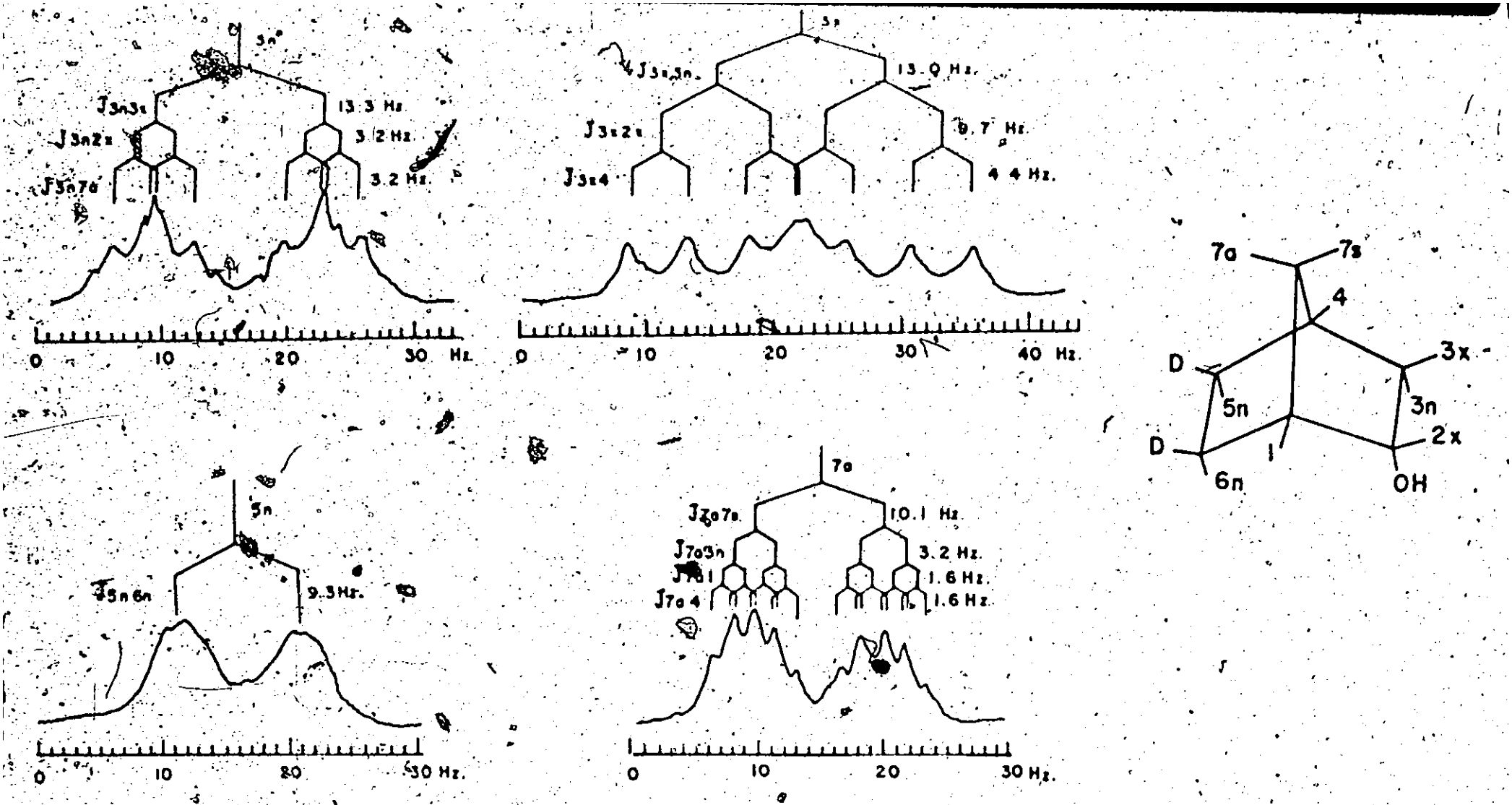


Fig. 3. Parts (3n, 3x, 5n and 7a signals) of the 100 Mc proton spectrum of endo-2-norbornol-exo-5-exo-6-d_2 in the presence of 0.5 mol Eu(DPM)$_3$ (mol = molar ratio of Eu-complex to alcohol) in carbon tetrachloride. The first order analysis of the large couplings of protons 3n, 3x, 5n and 7a is illustrated.

6-d_2 (Fig. 2) corroborates our assignment. Since Paasivirta did not clearly resolve the spectrum of endo-norborneol the crossover of the 6x and 4 signals (discussed later) was not observed and thus led to the erroneous assignment of 6x and 4 at 0.33 mol $Eu(DPM)_3$.

The chemical shift data for analyses at varying $Eu(DPM)_3$ concentrations are collected in Table 5 and plotted as chemical shift versus mole ratio of $Eu(DPM)_3$ to alcohol in Figure 4. The 7a and 5a protons have been omitted in Fig. 4 for the purposes of clarity. Figure 4 demonstrates the linearity of the chemical shift on metal ion concentration, in accord with earlier findings[139,145,154], and shows that shifts for all substrate protons are in the same direction, i.e., to lower field values.

The scattering of points in Fig. 4 arises because in all cases the samples were filtered through glass wool to remove suspended particles which tended to interfere with the recording of a spectrum. Invariably, this filtration process led to discrepancies between the weighed and actual amount of $Eu(DPM)_3$ in any one particular sample.

Rerunning a sample of alcohol and $Eu(DPM)_3$, after standing at room temperature for six days, showed no changes in the n.m.r. spectrum. This indicates that the europium samples are reasonably stable over a short period of time.

A crossover of signals 4 and 7s was detected when the molar ratio of $Eu(DPM)_3$ to alcohol exceeded 0.78 (Fig. 5). At low concentrations of $Eu(DPM)_3$ the 4 and 7s signals were not resolved. At intermediate concentrations of $Eu(DPM)_3$, the 4 and 7s protons were cleanly separated. As the $Eu(DPM)_3$ concentration was increased from a molar ratio of 0.60 to 0.69, the difference in chemical shift between the 4 and 7s proton decreased from

Table 5. Chemical shifts (δ, ppm) of the protons in endo-norborneol (in CCl_4) in the presence of $Eu(DPM)_3$ (mol = molar ratio of $Eu(DPM)_3$ to alcohol).

$Eu(DPM)_3$ mol	2x	6n	3n	1	3x	5n	6x	4	7s	5x	7a
0.00	4.10	1.60	0.80	2.15	1.85	1.25	1.35	2.08	1.30	1.35	1.20
0.20	9.46	5.72	4.70	4.70	3.90	3.28	2.90	3.32	•2.8-2.6•		2.30
0.25	10.78	6.68	5.60	5.30	4.40	3.75	3.30	3.62	•3.2-2.9•		2.60
0.32	13.08	8.20	7.17	6.30	5.28	4.55	4.17	4.15	3.63	3.63	3.08
0.33	13.32	8.50	7.50	6.60	5.50	4.74	4.32	4.12	3.76	3.70	3.24
0.48	17.41	11.38	10.40	8.6	6.98	6.24	D	5.18	4.70	D	3.98
0.48	17.08	11.20	10.24	8.67	7.30	6.44	5.62	5.62	5.12	5.00	4.46
0.58	19.78	12.76	11.80	9.50	7.82	6.82	5.84	5.64	5.28	5.02	4.46
0.59	20.97	13.40	12.50	10.08	8.30	7.20	6.20	5.88	5.58	5.22	4.56
0.60	21.18	13.46	12.62	10.14	8.36	7.22	6.18	5.92	5.64	5.25	4.70
0.63	23.67	14.93	14.16	11.26	9.30	8.00	6.80	6.40	6.28	5.74	5.20
0.68	23.75	15.10	14.40	11.40	9.40	8.04	6.90	6.52	6.34	5.80	5.28
0.69	24.23	15.47	14.75	11.78	9.80	8.64	7.36	6.98	6.80	6.30	5.72
0.78	-	16.84	16.24	12.92	10.70	9.18	7.90	7.46	7.46	6.70	6.20
0.83	28.1	17.38	16.82	13.25	10.90	9.20	D	7.40	7.50	D	6.20

These analyses were carried out on completely deuterated samples which were obtained from solvolysis of nortricyclyl and norbornenol substrates in deuterated media.

†These values were obtained from reference 144.

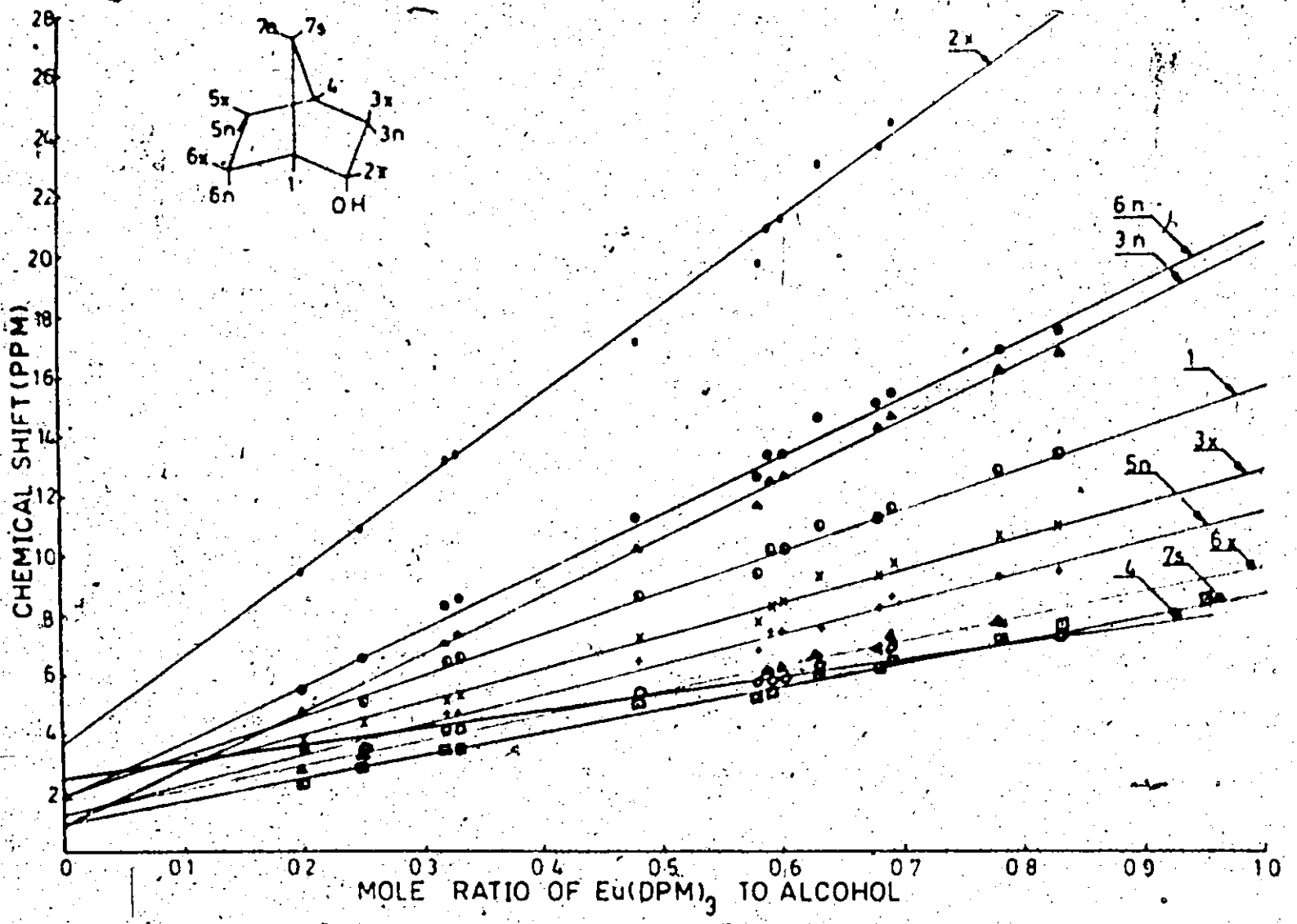


Fig. 4. Variation in the chemical shift for the different protons of endo-norborneol with increasing concentration of $Eu(DPM)_3$. The 5x and 7a protons have been omitted.

0.28 ppm to 0.18 ppm until finally at a molar ratio of 0.78 the 4 and 7s protons were superimposed at 7.46 ppm. The 4 and 7s signals had crossed over at an $Eu(DPM)_3$ to alcohol molar ratio of 0.83.

Figures 4 and 5 clearly show the crossover of the 4 and 6x protons which led Paasivirta[144] astray and indicate that care must be taken when assigning protons of the norbornyl skeleton in partially resolved spectra. The best signal separation is achieved in the spectrum of endo-norborneol, at a molar ratio of $Eu(DPM)_3$ to alcohol between 0.58 and 0.69.

Coupling Constants

Since a complete analysis of the coupling constants in endo-norborneol has not yet been reported, endo-2-norborneol-exo-5-exo-6-d_2 was studied in the presence of $Eu(DPM)_3$ (mol = 0.48) to provide additional support for the chemical shift assignments. The results are given in Table 6. These spin-spin coupling constants were obtained directly by first-order analysis of the multiplets for 3n, 3x, 5n and 7a as illustrated in Fig. 3.

The coupling constants of the norbornyl system obtained in the presence of $Eu(DPM)_3$ (Table 6) are very similar to the well-known characteristic couplings of the norbornane skeleton, obtained in the absence of $Eu(DPM)_3$[150,155]. This result is not surprising since Eaton et al.[156] have shown that contact shifts do not markedly affect the nuclear spin-spin coupling constants.

The values in Table 6 show that for norbornanes, the bridgehead proton is more strongly coupled to the exo proton (J_{3x4} = 4.4 cps) than to its endo counterpart ($J_{3n4} \simeq$ 0-1 cps and is not observed). J_{3n4} is expected to be close to zero because of the unfavourable dihedral angle (ca. 79°)[148, 151,154]. The dihedral angle between the 3x and 4 protons is about 44°[151],

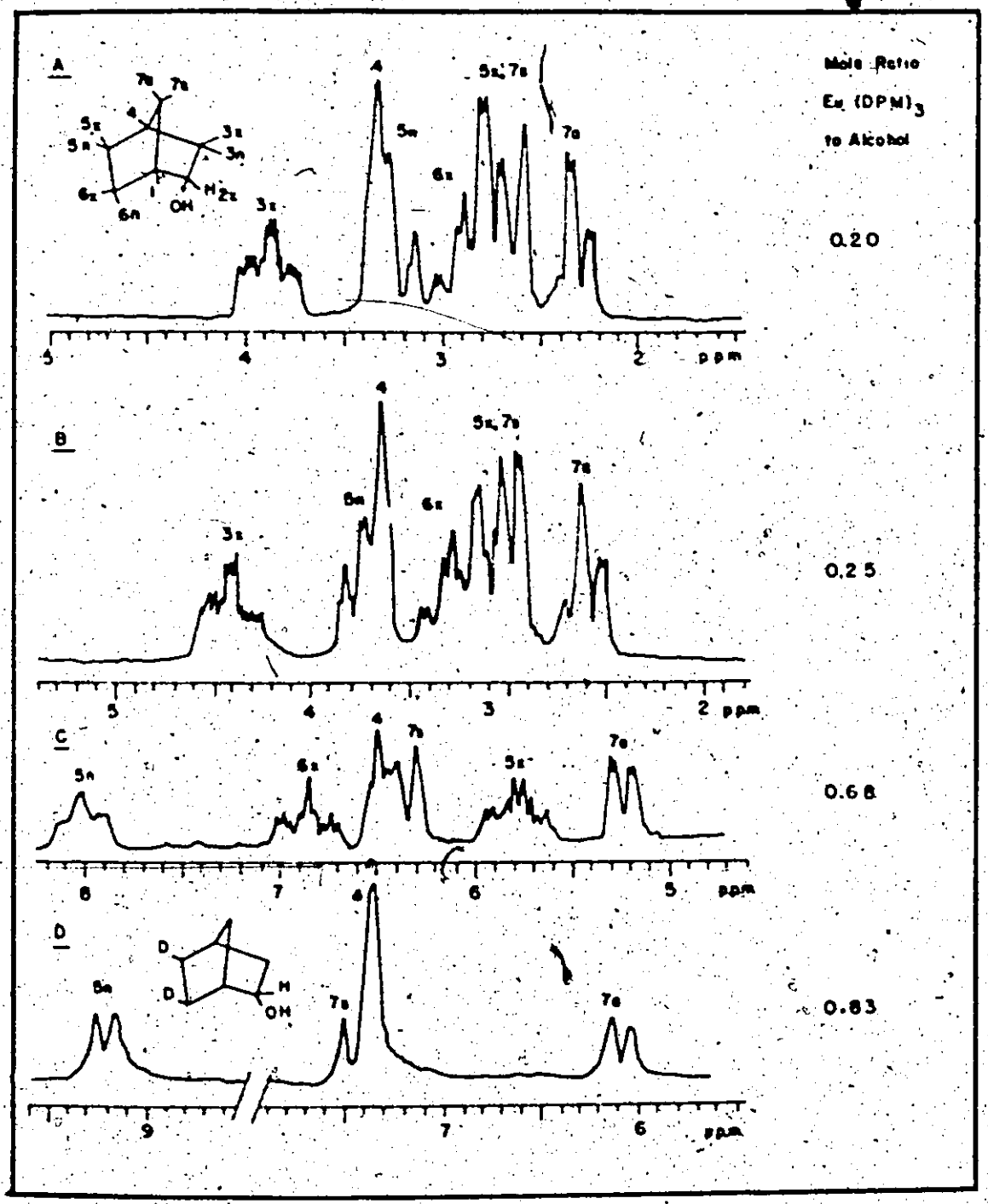


Fig. 5. Cross-over of proton 4 with 5n(B), 6x(C) and 7s(D) protons with increasing relative concentration of $Eu(DPM)_3$.

Table 6. Proton-Proton Coupling Constants (J, ±0.3 cps) in endo-Norborneol.

Protons	2x3x	2x3n	3x3n	3x4	3n7a	5n6n	5n7s	6n7s	7a1 or 7a4	7s1 or 7s4	7a7s
J	9.7	3.2	13.3 13.0	4.4	3.2	9.3	3.0	3.0	1.6	1.5	10.1

and according to Karplus[148] should give rise to a coupling constant of ca. 4-5 cps. The coupling between the bridgehead and bridge protons is 1.5 (7s1 or 7s4) and 1.6 cps (7a1 or 7a4) and also correlates with the Karplus equation[148] (dihedral angle 60°).

The usual[155] (3-4 cps) long-range W-coupling between the bridge and endo protons is also observed in our case (J_{5n7a} = 3.2 and J_{5n7s} = 3.0). The coupling between the exo-2 (exo-3) and exo-6 (exo-5) protons is not observed because of deuterium substitution. No W-coupling between the bridgehead protons is observed. This coupling is weak and has only been observed in a few cases[157].

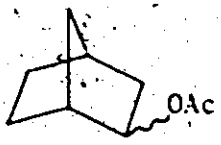
V. Hydration of Norbornene at 250°

The high temperature and dilute acid (HTDA) exchange conditions have been applied to the hydration of norbornene (53). In 10% v/v CH_3COOD-D_2O at 250°, 53 yields primarily a mixture (69:31) of deuterated exo- and endo-norborneol (56 and 57) which contains up to 9.5 atoms of deuterium per molecule. Norbornyl acetate (55) and the di-norbornyl ether (58), as a mixture of stereoisomers, are also formed. I.r., n.m.r., m.s. and elemental analysis data are consistent with structure 58. N.m.r. shows that the stereoisomeric mixture is composed of 70% exo and 30% endo linkages. The results of the hydration studies are listed in Table 7.

That the exchange is acid-catalyzed is shown by entries 4 and 6. A free radical mechanism is not likely because norbornene is stable in D_2O at 250° and the formation of $CH_3-C\overset{O}{\underset{O\cdot}{}}$ and H· is an improbable process. As shown by entries 4 and 5, strong acid lowers the yield of norborneols by forming intractable materials. Entries 2, 3, 4, 7 and 8 show that the exchange is rapid and essentially complete (89% exchange) in 4h, and that isotopic

53

54



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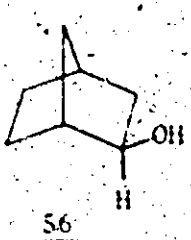

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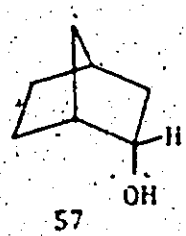

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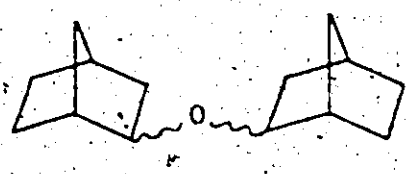

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dilution through exchange of the methyl group in CH_3CO_2D reduces the total deuterium incorporation. That this type of isotopic dilution occurs is confirmed by the isolation of norbornyl acetate containing d_{12}, d_{13} and d_{14} species.

Norbornene has also been reported to undergo perdeuteration in 44% DBr-D_2O at reflux for 20 h[82]. However, under these conditions (low temperature and strong acid), the yield is only 14% with 50% exchange in one cycle. Four cycles are needed for 99% exchange. Certainly the conditions described herein (high temperature and dilute acid) are superior for perdeuteration of the [2.2.1] system in terms of cost of isotope, percent yield and percent exchange.

$Eu(DPM)_3$ analysis as described previously was used to establish the deuterium distribution in an exo- and endo-norborneol mixture which was obtained by heating norbornene for 3 h at 250° in the presence of 10% v/v CH_3COOD-D_2O (entry 2 of Table 7). The mixture was oxidized* to norcamphor

*Control experiments show that exchange α to the carbonyl is not significant. N. H. Werstiuk and R. Taillefer, unpublished results.

Table 7: Data for Hydration of Norbornene at 250°

Entry[a]	Time (h)	Relative % Yield[b]							% Yield[c]	D/molecule[d]
		53	54	55	56	57	58	Other	56+57	in 56+57
1	1.5	63.2		7.2	22.9	5.7	-	1.0	21	2.20
2	3	25.0	7.0	8.0	48.5		6.0	5.5	41	5.90
3	4	8.1	9.2	9.1	42.8	19.3	6.8	4.7	36	9.80
4	15	2.8	3.1	7.2	57.4	26.0	1.3	2.2	69	9.55
5[e]	15	15.4	-	-	23.8	10.8	2.6	27.4	29	9.90
6[f]	60	99.0	-	-	-	-	-	1.0		
7[g]	120	1.2	-	9.2	56.2	20.9	7.4	5.1	80	10.05
8	528	0.7	0.6	7.8	23.1	10.2	4.7	53.0	10	9.85

[a] Typically a solution of 53 in 10% v/v CH_3COOD-D_2O was degassed and heated in a sealed tube at 250°.

[b] Determined by g.l.p.c. on 10 ft x 1/8 in 10% SE-30 and 10% Carbowax on Chromosorb-W columns.

[c] Determined by preparative g.l.p.c and corrected for collection losses (see Appendix A).

[d] Determined mass spectrometrically on the acetates at low voltage. The mass spectral data (uncorrected relative intensities) are listed in Table 6 of Appendix C.

[e] Run in 1% v/v HCl-D_2O.

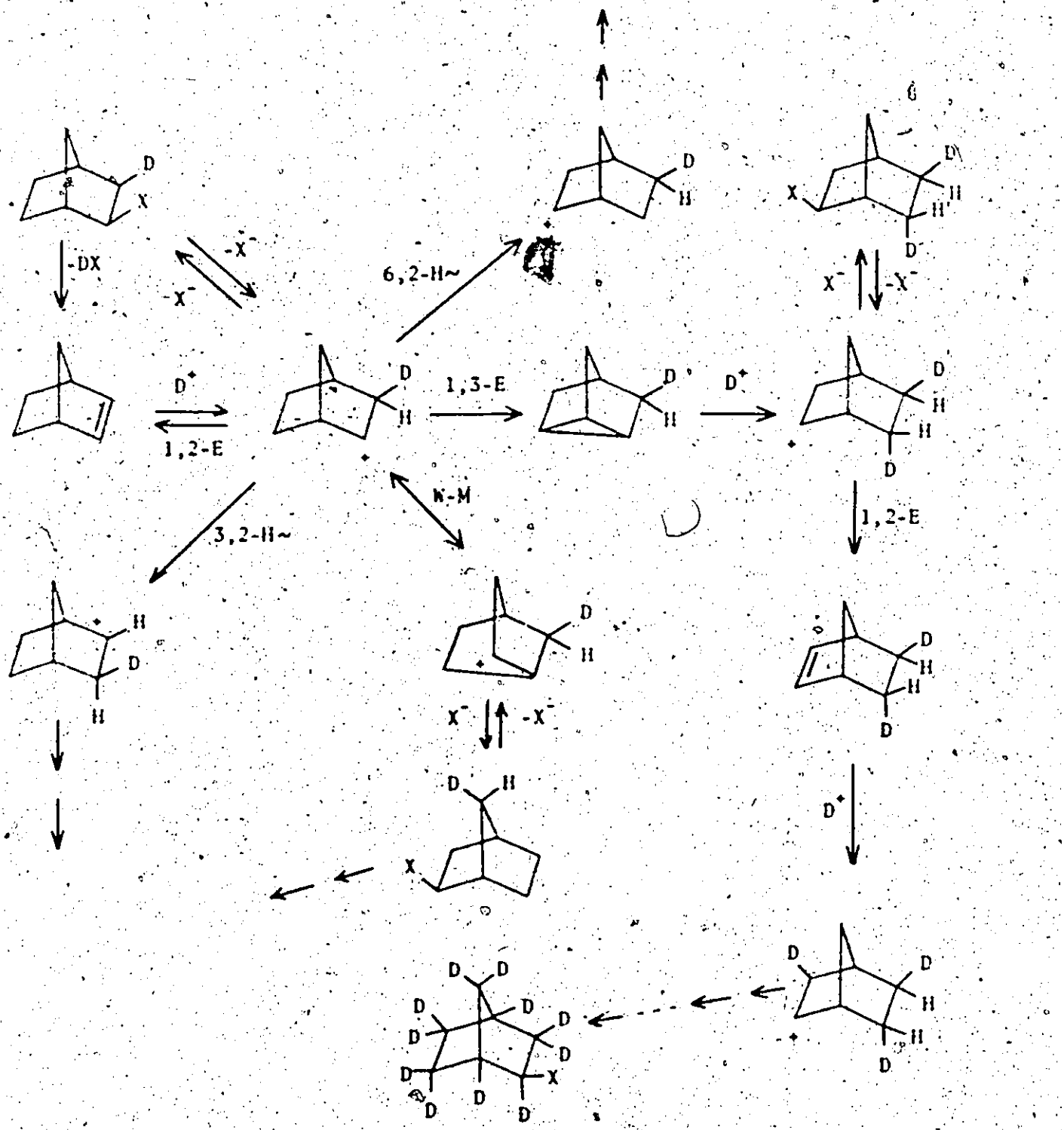
[f] Run in D_2O only.

[g] Run in 10% v/v CD_3COOD-D_2O.

with Brown's reagent and the ketone was reduced with lithium aluminum hydride to the deuterated endo-norborneol. $Eu(DPM)_3$ analysis at mol = 0.6 at 100 MHz in CCl_4 established the following deuterium distribution: 0.5 at C-1, 0.5 at C-3-exo, 0.5 at C-3-endo, 0.5 at C-4, 0.5 at C-5-exo, 0.5 at C-5-endo, 0.6 at C-6-exo, 0.6 at C-6-endo, 0.5 at C-7-syn and 0.5 at C-7-anti (± 0.05), respectively, a total of 5.2 deuterium atoms per molecule. The label at C-2 of the original norborneol mixture could not be determined directly by the $Eu(DPM)_3$ analysis because it was lost during the oxidation stage. However, a value of 0.7 deuterium atoms at C-2 was obtained indirectly from the difference in the deuterium content of the norborneol before oxidation (5.9 as determined by m.s.) and the endo-norborneol obtained from the reduction of the norcamphor (5.2 as determined by $Eu(DPM)_3$ integral analysis). The deuterium distribution in this partially-exchanged system shows that there is no preferential site of exchange and that all hydrogens are exchanged at the same rate in the unsubstituted norbornyl cation at 250°. This contrasts with the results obtained when norbornyl hydroxy-cations are generated. The hydroxy-cations undergo incomplete and preferential exchange at all positions, depending upon the initial substrate.

The temperature is a critical factor for perdeuteration. At -78 to 100°, the addition of deuterioprotic acids to norbornene yields exclusively exo-norbornyl derivatives which contain only one deuterium atom per molecule and which show little scrambling with the tag distributed between the exo-2- and syn-7- positions[158,159a,b]. In order to accomplish perdeuteration, addition-elimination must occur (Scheme I-1). The high temperature facilitates the important 1,2 and 1,3 elimination reactions, and establishes the reversible sequence leading to complete perdeuteration (Scheme II-26).

SCHEME II-26



D-11 species

Table 8. Data for Exchange of Norbornyl Substrates at 250°

Entry[a]	Substrate	Time (h)	Relative % Yield[b]							% Yield[c]	D/molecule[d]
			53	54	55	56	57	58	Other	56+57	in 56+57
1	54	15	-	-	5.0	93.5		-	1.5	42	9.80
2	55	15	0.8	0.5	39.2	37.3	16.7	-	5.5	51	10.25
3	56	15	0.7	1.3	8.0	61.0	28.2	0.4	0.4	79	9.80
4[e]	56+57[f]	4									10.45

[a]Typically a solution of substrate in 10% v/v CH_3COOD-D_2O was degassed and heated in a sealed tube.

[b]Determined by g.l.p.c. on 10 ft x 1/8 in 10% SE-30 and 10% Carbowax on Chromosorb-W columns.

[c]Determined by preparative g.l.p.c. and corrected for collection losses as described in Appendix A.

[d]Determined mass spectrometrically on the acetates at low voltage. Mass spectral data (uncorrected intensities) are given in Table 6 of Appendix C.

[e]Run in 10% v/v CD_3COOD-D_2O.

[f]The norborneol from entry 3 of Table 7 containing 9.80 D/molecule was used in this run.

The preceeding results indicate that complete exchange should be possible for any system that generates an unsubstituted 2-norbornyl cation. For example, nortricyclane (54) and 2-substituted norbornanes (e.g., 55, 56, 57, etc.), all of which produce a 2-norbornyl cation, should undergo perdeuteration under the reaction conditions described herein. The data for exchange of these substrates at 250° in 10% w/v CH_3COOD-D_2O is listed in Table 8.

Entries 1, 2 and 3 show that 54, 55 and 56 also tend to the same mixture of products as is obtained from norbornene. As shown by entries 1, 2 and 3, a high degree (~90%) of isotope incorporation occurs in only one cycle with reasonable yields (40-80%) of norborneol. Entry 4 shows that 2-3 cycles are required for exchange >95%.

Certainly, the hydrogen-deuterium exchange occurs by protonation-deprotonation and/or addition-elimination of acetic acid or water pathways in combination with 1,2-Wagner-Meerwein shifts, 6,2- and 3,2-hydrogen (deuterium) shifts, and 1,2- and 1,3-elimination of a proton (deuteron) (Scheme II-26).

VI. Solvolysis of exo-2-Phenyl-endo-2-Hydroxynorbornane

To extend the studies on the high temperature and dilute acid exchange conditions, exo-2-phenyl-endo-2-hydroxynorbornane (59) was examined under various reaction conditions. 59 was chosen not only because it was readily available (phenyl Grignard reaction on norcamphor), but because it had a convenient label (phenyl group) and it does not generate an hydroxy-cation which would lead to incomplete exchange via conversion to stable "sink" compounds. Table 9 lists the results of the study.

Table 9. Solvolysis of exo-2-Phenyl-endo-2-Hydroxynorbornane

Entry[a]	Conditions			Relative % Yield[b]		% Yield[c]	D/molecule[g]
	Solvent	Temp. (°C)	Time (h)	60	Other[d]	60	60
1	10% v/v HOAc-H_2O	295	51	85.8	14.2	11	
2	10% v/v DOAc-D_2O	295	51	93.0	7.0	11	3.80
3	H_2O	250	24	68.6	31.4		
4	D_2O	295	24	93.0	7.0	63[e]	4.40
5	4% v/v HCl-D_2O	295	24	-	100.0[f]	-	

[a]Typically, a solution of exo-2-phenyl-endo-2-hydroxynorbornane in solvent was degassed and heated in a sealed tube.

[b]Determined by g.l.p.c. on a 10 ft x 1/8 in 10% Carbowax on Chromosorb-W column.

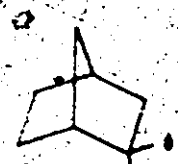
[c]Determined by micro distillation.

[d]Does not include starting material.

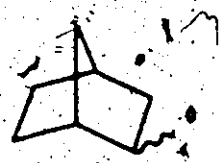
[e]Crude yield.

[f]Composed of at least 11 products.

[g]Determined mass spectrometrically on 60. The uncorrected intensities are given in Table 7 of Appendix C. N.m.r. established that all the deuterium was in the norbornyl system.



59 OH



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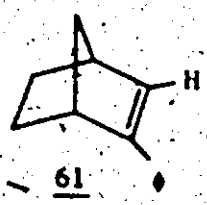

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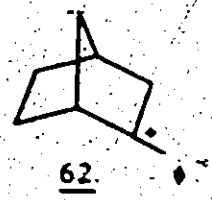

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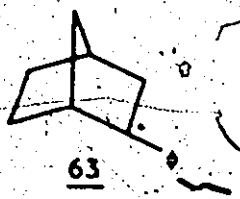


63

In this case, 2-phenylnorbornane (60)* was isolated, in low yields (11%), as the major product. Since the reduction occurs in both acid and water alone (entries 1 and 3), the reducing species probably is the norbornyl skeleton through an intermolecular hydride transfer process[72]. Thermal homolytic cleavage of the C—O bond to give a benzyl radical, 63, and subsequent radical exchange and reduction is possible but it is not an attractive alternative to a carbonium ion mechanism because (a) in order to explain the perdeuteration, a radical process would require D· and ·OD species, which are unfavourable relative to D· and ·OD and (b) Wagner-Meerwein shifts, 3,2- and 6,2-hydrogen shifts of the norbornyl skeleton are known to proceed via carbonium ion, not radical intermediates.

The low yield of 60 is due to polymerization via species such as 61 since g.l.p.c. analysis showed that 61 was a minor reaction product and styrene, which is similar to 61, is known to undergo extensive polymerization in dilute acid at 130°[73].

Again, as in other norbornyl systems, entry 5 shows the great susceptibility of the norbornyl skeleton to undergo decomposition in strong acid

*I.r., n.m.r., and m.s. data are consistent with structure 60.

media, such as dilute HCl, at high temperatures.

Mass spectral analysis showed that 60 contained 3.80 D atoms/molecule, consisting of d_0 to d_{11} species. Since n.m.r. integral analysis (4.0 D) showed that all the D was in the norbornyl skeleton and not the aromatic ring, all positions of the norbornyl skeleton must have been reached via a series of addition-elimination reactions in combination with (a) 1,2 and 1,3 eliminations, (b) 3,2- and 6,2-hydride shifts, and (c) Wagner-Meerwein shifts. Most likely the exchange occurs via eliminations which yield phenylnorbornene or phenylnortricyclane.

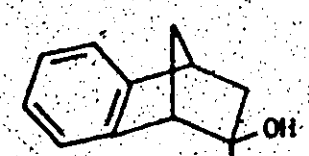
Superficially, it appears, as in the case of hydroxy substituted norbornenes and nortricyclanes, complete exchange of the norbornyl skeleton in 59 is prevented by the formation of a "sink" compound, 60, which is inert to further exchange.

Regardless of the mode of exchange and reduction, this interesting reaction was not explored any further because of low yields.

VII. Hydration of Benzonorbornadiene at 250°.

As a continuation of the studies on the hydration of olefins at 250° in 10% v/v HOAc-H_2O (10% v/v DOAc-D_2O) as a route to perdeuterio-materials, benzonorbornadiene (64) was studied. Complete perdeuteration of the norbornyl skeleton of the corresponding alcohol, 65 and 66, was expected since every position is readily accessible by a series of addition-elimination reactions in combination with a Wagner-Meerwein shift. The results of the study are shown in Table 10.

64



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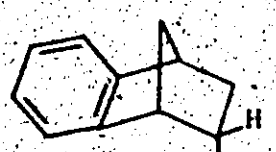

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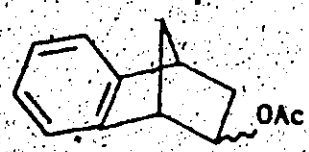

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Table 10. Hydration of Benzonorbornadiene at 250°

Entry[a]	Time (h)	Relative % Yield[b]					% Yield[c] of 65	D/molecule[d] of 65	Position (by nmr)
		64	65	66	67	Other			
1[e]	3	3.0	85.4	3.2	7.7	0.7	39		
2	3	6.9	74.6	11.7	6.1	0.7	35	1.20	
3[f]	12	0.1	64.2	34.2	0.8	0.7	-	2.95	2.0 aromatic 1.0 norbornyl
4	114	1.8	72.2	22.4	1.9	1.7	42	4.30	2.9 aromatic 1.2 norbornyl
5[g]	48	-	36.2	3.8	-	60	7		

[a] Typically, a solution of substrate in 10% v/v Cl_3COOD-D_2O was degassed and heated in a sealed tube.

[b] Determined by g.l.p.c. on a 10 ft x 1/8 in 10% Carbowax on Chromosorb-W column.

[c] Determined by preparative g.l.p.c. and uncorrected for collection losses (Appendix A).

[d] Determined by mass spectrometry. Table 7 of Appendix C gives the uncorrected intensities.

[e] Run in 10% v/v Cl_3COOH-H_2O.

[f] The benzonorbornenol from entry 2 containing 1.20 D/molecules was used in this run.

[g] Run in 10% v/v Cl_3COOD-1% v/v conc. HCl-D_2O.

Entries 2, 3 and 4 show that initial protonation of the norbornene double bond and subsequent quenching of the carbonium ion by D_2O introduces only one deuterium atom into the norbornyl skeleton. There is no further significant exchange in the norbornyl skeleton of benzonorbornenol. Although extended reaction times (114 h; entry 4) can result in some additional exchange (0.2 D) in the norbornyl skeleton, the rate of exchange in the aromatic ring is much faster than in the norbornyl system of 65:

The results establish that exchange with the undeuterated alcohols (65 and 66) and even the acetate (67) should lead to complete perdeuteration (after 3-4 cycles) of the aromatic ring only, with excellent recovery. Entry 5 shows that increased acidity leads to decomposition.

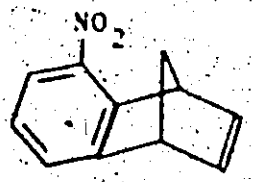
Since both benzene and exo-2-phenyl-endo-2-hydroxynorbornane do not undergo exchange of the aromatic nucleus in 10% v/v CH_3COOD-D_2O at 250° while m-xylene does (discussed in Section II-B-III), the exchange in the aromatic ring of benzonorbornenol occurs because the aromatic ring is activated to electrophilic attack by the alkyl groups and strain.

A significant aspect of our results is the high ring selectivity of the high temperature-dilute acid conditions for exchange of protons bound to an aromatic nucleus, activated by electron-releasing substituents. Thus 65 is converted to benzonorbornenol-d_4, not benzonorbornenol-d_{11}. In contrast, quenching of the organosodium derivative of benzonorbornadiene leads to 90% exchange of the C-2 and C-3 protons and 7.5% of each of the benzene protons.(160)

In summary, treatment of bicyclic compounds at temperatures of about 250° in the presence of dilute acid and deuterium oxide (HTDA) gives deuterated bicyclic compounds. The extent of deuteration at 250° depends on the acidity and the substituents. Although a dilute mineral acid, such

as HCl increases the rate and the degree of isotope incorporation, the large extent of decomposition makes the conditions of high acidity impractical. The use of weaker acids, such as CH_3COOD, is required to obtain maximum yields.

By appropriate manipulation of temperature, acidity and/or substituents, a large host of perdeuterated bicyclic compounds can be prepared. For example, by placing a substituent, such as $-NO_2$, which is deactivating towards electrophilic aromatic substitution, in benzonorbornadiene, 68, it should be possible to completely perdeuterate the norbornyl skeleton, rather than the aromatic ring.



68

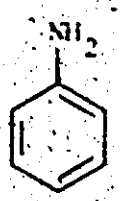
Our results have shown that both incomplete and complete exchange of the norbornyl skeleton are possible. In cases where partial exchange occurs and the detection of deuterium becomes difficult, it would be more beneficial to use more easily detectable tritium.

B. Exchange in Aromatic Systems

As a continuation of our studies of utilizing the high temperature and dilute acid procedure as a general method of perdeuteration of organic molecules, numerous aromatic systems were examined.

1. Aniline Hydrochloride

Although hydrogen exchange at 100° between aniline hydrochloride (70) and D_2O has been followed[161], only the amino and the ortho- and para-hydrogen atoms are exchanged. No exchange of the meta-hydrogen atoms has



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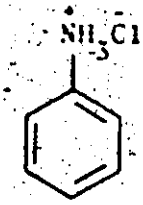

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been detected. It was our purpose to re-examine this reaction at temperatures above 400° to determine whether exchange of the meta-protons could be effected. The results of the study are summarized in Table 11.

The deuterium analyses were performed by n.m.r. on the free amine (aniline), using the back-exchanged amino protons as the internal standard of integration. The ortho-, meta- and para-signals were well resolved and readily assignable (Fig. 4, Appendix D). The amount of exchange is expressed in terms of % exchange, based on only the five nuclear aromatic positions. An acid-base extraction work-up (as described in the Experimental) was used to isolate and separate the aniline and phenol and to back-exchange the amino position.

Entry 1 shows that at 175° no appreciable exchange of the meta-positions occurs within 24 h (Fig. 6, Appendix D). On increasing the temperature up to 300° (entry 2) in an attempt to effect exchange of the meta-positions, it was observed that no aniline or aniline hydrochloride remained in the reaction mixture after 48 h. Only phenol and ammonium chloride were isolated. At this high temperature, substitution of the amino group is important. Even 275° and a considerably shorter reaction time (24 h, entry 3) lead to 31% of phenol. This high degree of conversion to phenol makes temperatures ≥ 275° impractical for the preparation of perdeuterated aniline.

• i.r., n.m.r., m.s. and m.p. data are consistent with this.

Table II. Deuterium Exchange in Aniline Hydrochloride in D_2O

Entry[a]	Conditions		D/molecule in aniline[b]	% Exchange[c]	Position[d]			% Yield	
	Temp. (°C)	Time (h)			o	m	p	Aniline	Phenol
1	175	24	2.85	57	1.90	0.0	0.95	86	-
2	300	48	-	-	-	-	-	0	e
3[f]	275	24	-	-	-	-	-	44	31
4	195	6	3.05	61	1.90	0.20	0.95	81	-
5	250	12	3.60	72	1.85	0.80	0.95	74	1
6	250	14	4.20	84	1.90	1.35	0.95	85	3
7	250	35	4.60	92	1.90	1.75	0.95	72	3
8	250	54	4.75	95	1.90	1.90	0.95	69	4
9[g]	250	48	4.15	83	1.75	1.55	0.85	82	e
10[h]	250	50	4.85	97	1.95	1.95	0.95	72[i]	e

[a] Typically, a solution of recrystallized substrate in water was degassed and heated in a sealed tube.

[b] Determined by n.m.r. using the back-exchanged amino group as an internal standard.

[c] Based only on the aromatic nucleus.

[d] o = ortho; m = meta; p = para

[e] Not determined.

[f] Run in H_2O.

[g] The amino protons had been back-exchanged with D_2O at room temperature prior to heating.

[h] The crude 70 obtained from entry 9 and containing 4.15 aromatic deuterons was used.

[i] Overall yield of large scale reaction of entries 9 and 10.

In order to define the exact conditions for the attainment of equilibrium at 250°, numerous exchange experiments were carried out, the results of which are summarized in entries 5 to 8. Complete equilibration is attained in 54 h at 250° with 95% exchange of a 0.75 M solution in only one cycle (Fig. 6, Appendix D), establishing the optimum exchange conditions (in terms of % exchange and yield). Interestingly back-exchange of the o- and p- positions occurs on a 15% Carbowax column at 175° during isolation of the aniline. Thus all deuterium analyses were performed on the crude aniline by n.m.r. integration.

Whereas large scale (ca. 20 g) preparations of deuterated aniline, using concentrated solutions (ca. 2.6 M, entries 9 and 10), require two or three cycles to achieve a high degree of isotope incorporation, small scale (ca. 1 g) preparations can be achieved in only one cycle using more dilute solutions (0.7 M, entry 8).

Presently aniline-d_5 is obtained via expensive base-or metal-catalyzed exchange procedures (KND_2-ND_3 at 0° and activated platinum in D_2O at 140° for 3 days respectively)[31]. Aniline-d_7 has also been prepared in an overall yield of 70% by nitration of benzene-d_6, followed by reduction of the nitrobenzene-d_5[162]. The HTDA method described herein is vastly superior to all other methods because of simplicity and cost and is certainly extendible to polynuclear aromatic amines. Careful control of conditions also allows for the preparation of perdeuterioaniline and perdeuteriophenol simultaneously from aniline hydrochloride.

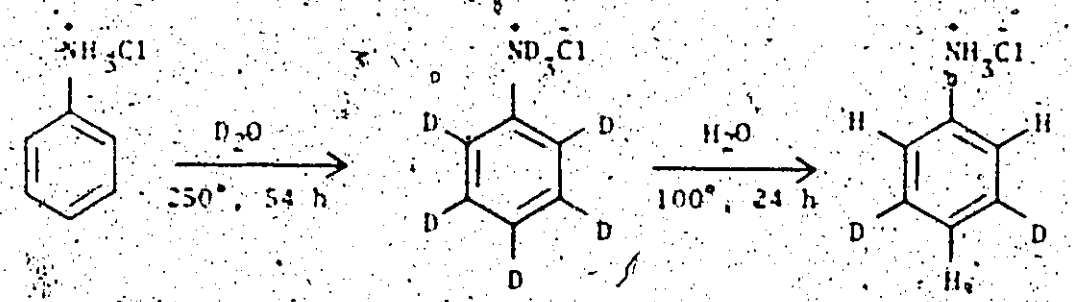
In a typical large-scale preparation of aniline-d_5 (entries 9 and 10), freshly recrystallized aniline hydrochloride (20.0 g, 0.15 mole, m.p. 196-9°) was first stirred with D_2O (50 ml) at room temperature for several hours in

order to avoid dilution of the deuterium pool by the amino protons. The D_2O was then distilled off under vacuum and recovered for use in the first cycle of subsequent exchanges. The amino exchanged aniline hydrochloride (20 g) was dissolved in fresh deuterium oxide (60 ml, 2.6 M) and sealed in a glass tube after being degassed three times via freeze-pump-thaw cycles. The tube was heated at 250° in a 2-liter Parr Pressure Apparatus containing H_2O to equalize the internal pressure. After 48 h, the D_2O and traces of phenol were distilled off under vacuum to leave a yellowish solid (16.4 g, 82%). N.m.r. integral analysis of an aliquot established the following deuterium distribution: 1.75, 1.55 and 0.85 at the ortho-, meta- and para-positions respectively (83% exchange). The crude aniline hydrochloride (16.4 g) was heated at 250° with another fresh batch of D_2O (60 ml). After 50 h, the D_2O was again reclaimed by vacuum distillation to leave a yellowish solid. This solid was dissolved in H_2O and then basified with concentrated NaOH and extracted with ether. This ether extract was washed with 10% HCl. The aqueous HCl phase, containing the anilinium salt, was basified with concentrated NaOH and extracted with ether. The ether extract was washed with water and dried. After removal of solvent, vacuum distillation yielded aniline-d_5 (10.25 g; 72% overall yield after two cycles, b.p. 43-4° (2mm Hg)). N.m.r. analysis showed that all the aromatic positions had been equilibrated with 97% exchange (entry 10).

With this new procedure, it is now a simple matter to prepare aniline-2,3,4,5,6-d_5 (71) or aniline-3,5-d_2 (72) as their anilinium salts (Scheme II-27A).

Whereas base-catalysis of aromatic amines leads to exchange at all positions of the ring, acid-catalysis leads to exchange predominantly in the

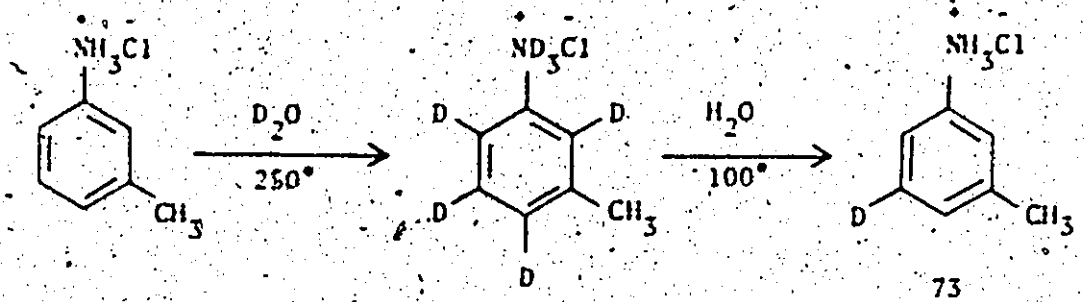
SCHEME II-27A



71 72

ortho- and para- positions or at all aromatic positions, depending upon the temperature. Thus by controlling the temperature, acid-catalysis can be used to prepare specifically meta- or ortho- and para- labelled amines. For instance, Scheme II-27B illustrates a very rapid and convenient way of synthesizing 3-methylaniline hydrochloride-5-d_1 (73). In contrast,

SCHEME II-27B

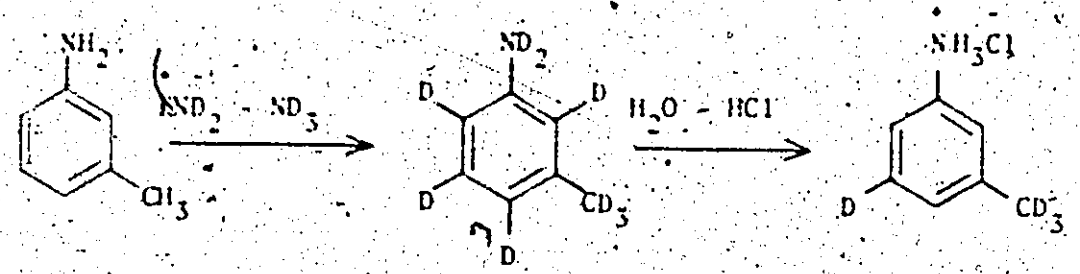


73

base-catalysis would be more complicated and expensive and would also lead to exchange of the methyl group (Scheme II-28).

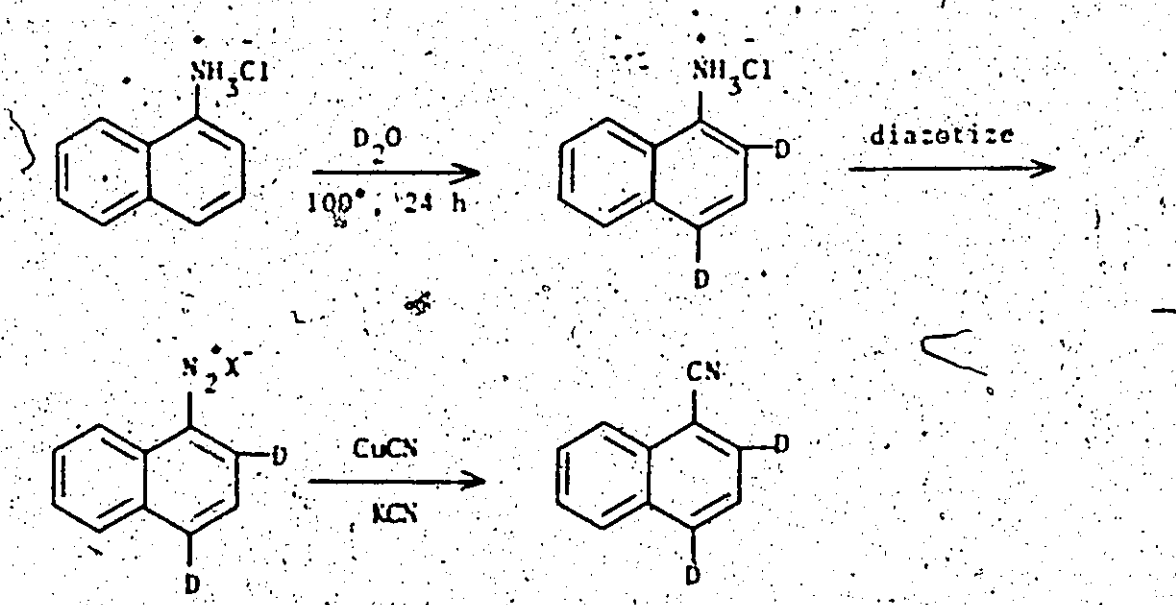
Ring substituted anilinium salts are very useful organic starting materials for preparing specifically and/or completely deuterated aromatics because the amino group can be diazotized and the resultant diazonium salt

SCHEME II-28



can then be converted to a large number of other compounds (Scheme II-29). Although there are conflicting reports about the loss of deuterium in the diazotization step, numerous authors have reported diazotization stages without alteration of the deuterium content. The great utility of anilinium salts for preparing specifically perdeuterated compounds is illustrated in the synthesis of 1-cyanonaphthalene-2,4-d_2 (74) as shown in Scheme II-30.[93]

SCHEME II-30[93]



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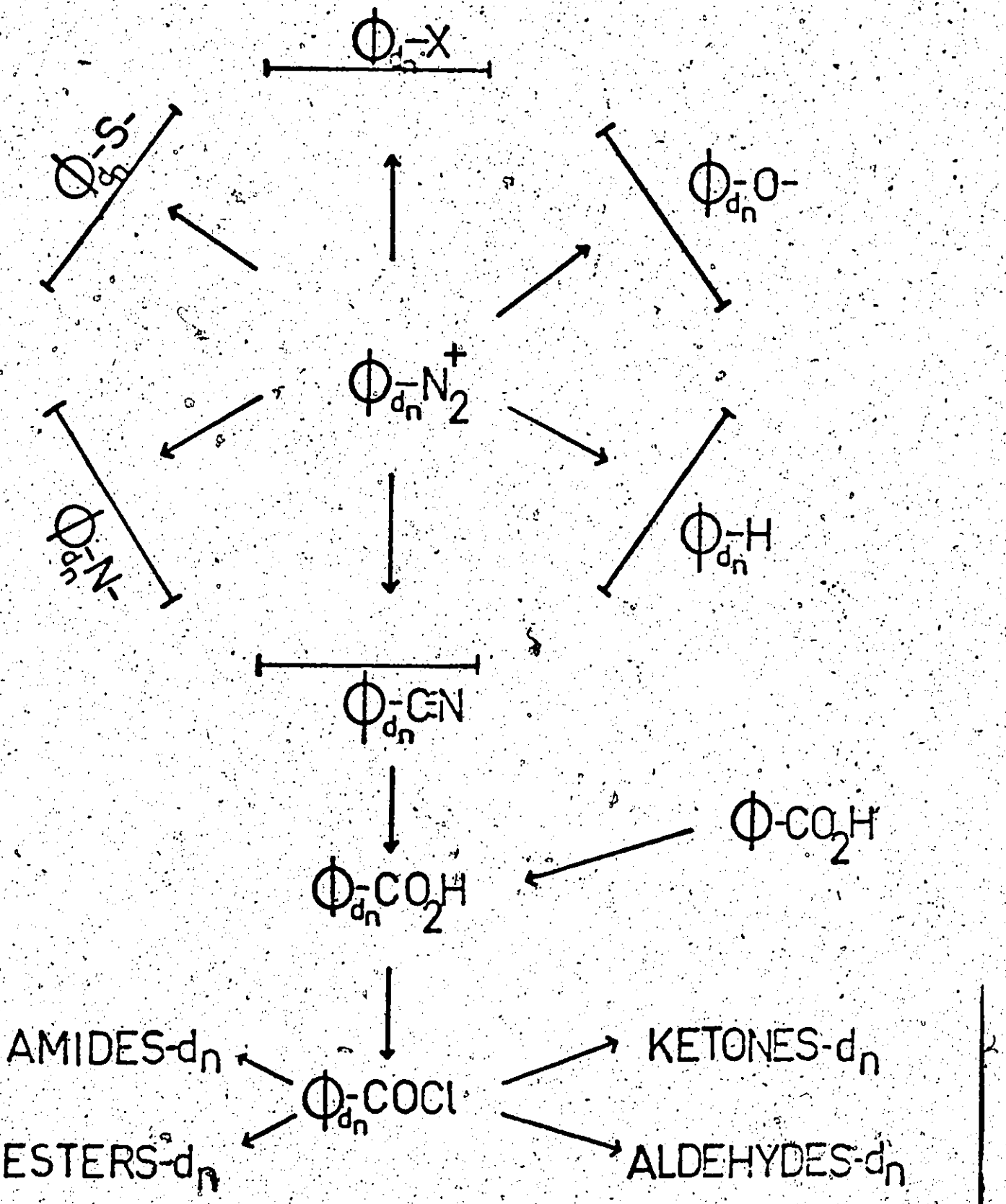
SCHEME II-29


Φ_{d_n}-X
Φ_{d_n}-S-
Φ_{d_n}-O-
Φ_{d_n}-N_2^+
Φ_{d_n}-N-
Φ_{d_n}-H
Φ_{d_n}-C≡N
Φ-CO_2H
Φ_{d_n}-CO_2H
AMIDES-d_n
KETONES-d_n
Φ_{d_n}-COCl
ESTERS-d_n
ALDEHYDES-d_n

An additional advantage of the high temperature exchange conditions is that certain aromatic amine hydrochlorides and polynuclear aromatic amines can readily be converted to deuterated phenols. For example at sufficiently high temperatures, say 275-300°, it should be possible to convert the o-, m- or p-toluidine hydrochlorides to the corresponding completely deuterated (aromatic protons) cresols!

Mechanism of Exchange

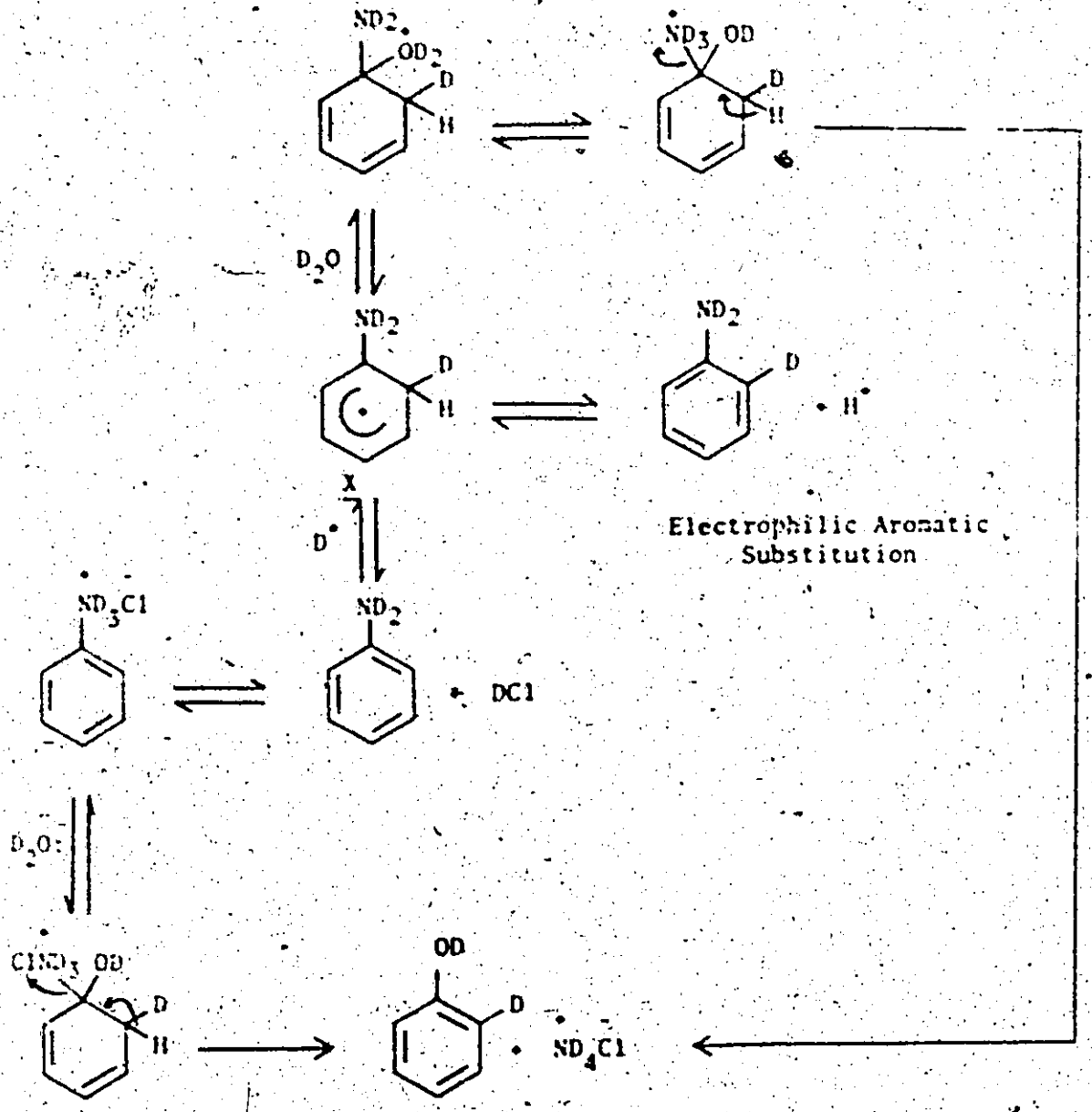
Ingold et al.[75] have shown that hydrogen-isotope exchange between acids (in the generalized sense of proton- or deuteron-donors) and the aromatic nucleus of benzene derivatives show all the characteristics of an ordinary aromatic electrophilic substitution process: it is facilitated or retarded, and therefore oriented, in just the same way as are other typical electrophilic aromatic substitutions such as nitration. In the reaction between aniline hydrochloride and heavy water, the interacting species can plausibly be assumed to be the aniline molecule and the deuteroxonium ion.*

The mechanism of exchange is illustrated in Scheme II-31. Acid-catalyzed exchange via the anilinium ion is energetically unfavourable (relative to exchange via the free amine) and coulombic charge interactions predict that exchange should occur fastest for the meta-position, than the ortho- and para-positions, contrary to our results. The fact that acid-catalyzed nucleophilic substitution does not compete with exchange up to 250° indicates that if exchange occurs via the free amine, deprotonation must compete with attack by D_2O on X.

On the basis of H_0 - rate correlations, it has been suggested that exchange proceeds by the rapid reversible formation of a D^+-aromatic π

* For the sake of brevity, the deuteroxonium ion, D_3O^+, will be represented as D^+.

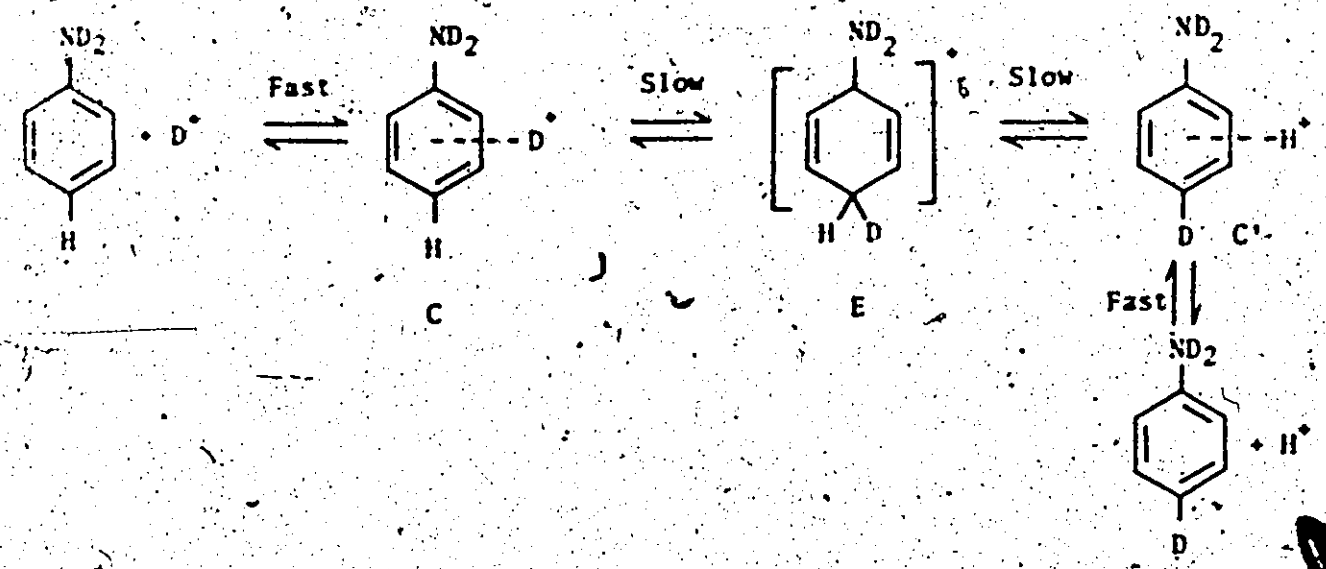
SCHEME II-31


ND2
OD2
D
H
ND3 OD
D2O
ND2
D
H
ND2
D
• H
X
D
Electrophilic Aromatic Substitution
ND3Cl
ND2
• DCl
D2O
ClND3 OD
D
H
OD
D
• ND4Cl
Nucleophilic Aromatic Substitution

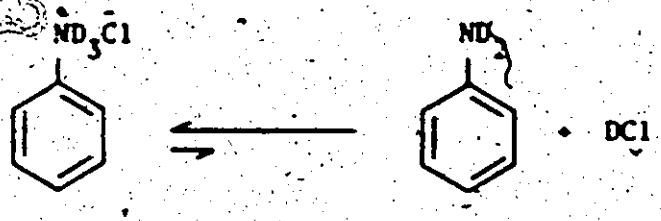
complex (C and C') which then undergoes a slower isomerization to a σ complex (E) as shown in Scheme II-32[163]. In view of the uncertainties that attend the use of the H_0 function, this evidence must be considered as weak, and, in fact, it has been shown that such a mechanism is not applicable to 1,3,5-trimethoxybenzene[164] and azulene[165]. These authors found that aromatic hydrogen exchange was subject to general acid catalysis, in agreement with the simple mechanism of Scheme I-3, and in disagreement with any mechanism involving a rate-limiting interconversion of isomeric π and σ complexes.

One drawback of utilizing high temperatures for the complete perdeuteration of aniline is the competing side reaction of solvolysis which leads to the irreversible formation of phenol (Scheme II-31). However, if the temperature is kept at 250° or slightly lower, the competing solvolysis reaction is very minor (ca. 4% in 54 h at 250°). This type of competing loss of substrate is not uncommon and also occurs during base-catalyzed exchange of such substrates as nitrobenzene[15e].

SCHEME II-32[163]



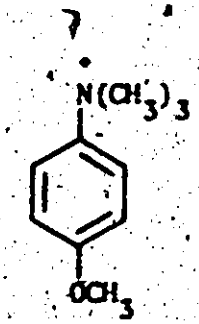
Since the rate and extent of exchange is a function of acidity and temperature, the complete perdeuteration (even meta-positions) of aniline could be attempted by using a more acidic reaction medium and a lower temperature. However, with increased acidities, the equilibrium described in Equation II-4 shifts more to the anilinium species and since exchange occurs via the free amine, there is a limiting effect of increasing the acidity in order to increase the rate and extent of exchange. That is,



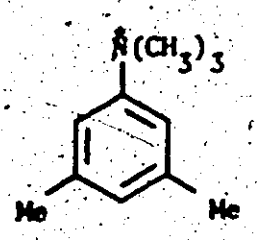
[II-4]

in the limiting case of high acidities, the rate of exchange will become independent of solvent acidity and further increases in the acid strength will in fact decrease the rate of exchange because of the low concentration of free amine. Thus exchange is facilitated under the conditions of high temperature and dilute acid.

Blackborow and Ridd[166] have shown that a methoxy and a dimethyl substituted trimethylanilinium ion, 75a and 75b respectively, undergo exchange, in 95% D_2SO_4 at 35°, via the anilinium ion and not the free amine. Thus exchange can occur via the anilinium ion in appropriately substituted substrates.



75a



75b

11. Phenol

Phenol (76) should also undergo exchange under the HTDA conditions. That is, like the NH_2 group, -OH should strongly accelerate deuteration of the benzene ring. Table 12 gives the results of our study.

76

Entries 3 and 4 show that temperatures >200° are required to facilitate the exchange of all five aromatic protons. Entry 1 shows that even at 260° aqueous acetic acid is not sufficiently acidic to cause exchange of the m-position (Fig. 9, Appendix D). A stronger acid, such as HCl, is required (entry 2) for total equilibration. For large scale preparations, the first cycle would be carried out in HCl-D_2O while in subsequent cycles DCl-D_2O would be used to ensure maximum isotope incorporation.

To our knowledge, this is the first case of complete perdeuteration of phenol via acid-catalysis. Phenol-2,4,6-d_3 and phenol-2,3,4,5,6-d_5 are prepared conventionally by base-catalyzed exchange using NaOD-D_2O at 100° for 96 h[167a] and $K^+ND_2^-$-ND_3[167b], respectively. Perdeuterated phenol has also been prepared by converting benzene-d_6 to aniline-d_5 which in turn is diazotized and hydrolyzed to phenol[168]. However, although the m-positions were fully deuterated, the o- and p-positions contained only 19% deuterium. Clearly, heating phenol in 1-4% v/v HCl-D_2O at 250° or aniline hydrochloride* in D_2O at 275-300° is a more convenient and economical one-

*The phenol obtained from entry 7 of Table 11 of the previous section contained 4.5 deuterium atoms (90% exchange) after the hydroxy hydrogen had been back-exchanged.

Table 12. Deuterium Exchange in Phenol

Entry	Conditions			D/molecule[b]	% Exchange	Position[c]		% Recovery
	Acid[a]	Temp. (°C)	Time (h)			o+p	m	
1	A	260	53	2.55	51	2.5	0.0	72[d]
2	B	260	53	3.90	78	equilibrated		-
3	C	200	48	3.90	78	2.7	1.3	95
4	C	175	72	3.05	61	2.7	0.2	-

[a] A = 10% v/v Cl_3COOD-D_2O; B = 10% v/v Cl_3COOD-1% v/v conc. HCl-D_2O; C = 4% v/v conc. HCl-D_2O.

[b] Determined by mass spectrometry after the O-D had been washed out. Mass spectral data (uncorrected intensities) are listed in Table 9 of Appendix C.

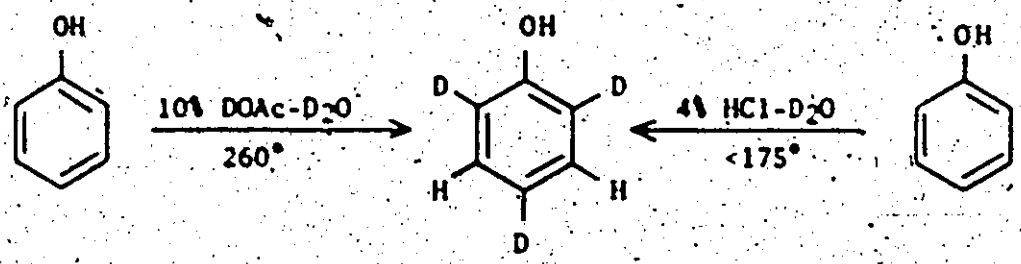
[c] Determined by n.m.r. integral analysis. o = ortho; p = para; m = meta.

[d] Preparative g.l.p.c. was used to determine this yield. The value is corrected for collection losses (see Appendix A).

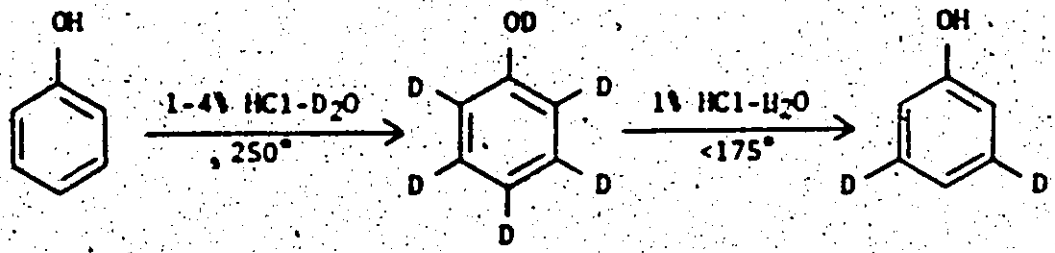
step method of synthesizing perdeuterated phenol.

As usual, the great differences in the reactivities of the aromatic nucleus can be used for the preparation of specifically labelled species. By controlling either the acidity, the temperature or both of them, specifically m- or o- and p-labelled phenol can be obtained (Schemes II-33 and 34). In

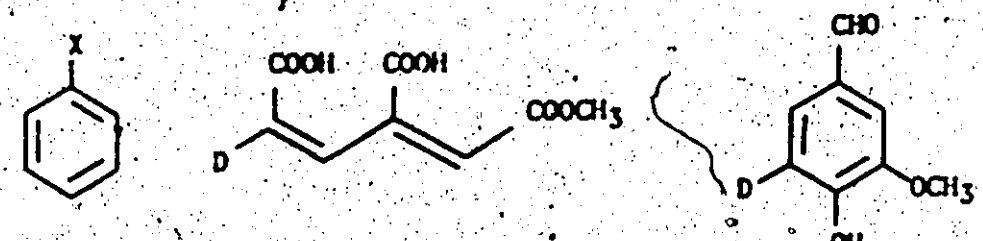
SCHEME II-33



SCHEME II-34



principle, this method can be applied to any benzene derivative 77, where X = NH_2, NR_2, OH, OCH_3(OR).

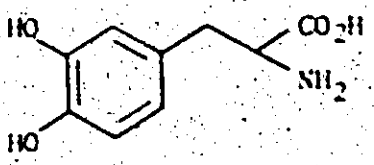


77 78 79

The ready availability of specifically deuterated phenols makes them particularly useful in the search for routes to compounds that are more difficult to obtain. For example, the increased oxidizability of phenols over other aromatic compounds has been utilized to develop a very convenient preparation of the monomethyl ester of 2-carboxy-cis-cis-muconate (78), deuterated in the position shown, by oxidation of the correspondingly deuterated vanillin (79)[169].

There has been considerable interest in the biosynthesis of complex phenolic compounds, especially phenolic alkaloids[170]. Quite often it has been necessary to synthesize radio-labelled phenols for testing as precursors of the natural substances. To compliment base-catalyzed exchange[171,180], it seems that exchange of the phenolic precursors in acidic tritiated water should provide a convenient and inexpensive labelling procedure--especially on a preparative scale. Low temperature-acid conditions (4.1 N TCl at 100°)[171] have been used successfully to completely tritiate the aromatic ring of 3,4-dihydroxyphenylalanine (80). Under similar conditions, tyrosine (81), which is less activated towards electrophilic substitution, only exchanges the 3,5 positions.* Thus high temperature-dilute acid conditions could be an effective method of completely tritiating or deuterating the aromatic ring of phenolic compounds, especially if the aromatic ring is not strongly activated towards electrophilic aromatic substitution (e.g., 81, 82, 83). The phenyl ring of phenylalanine (82) and 81 both of which occur in polypeptides can possibly be deuterium or tritium labelled in the polypeptide chain. This labelling is potentially very useful in n.m.r. studies because the n.m.r. spectra of proteins can be simplified by deuterating

*Under less vigorous conditions, CF_3COOD-D_2O at 25°, 81 does not undergo any exchange[173].



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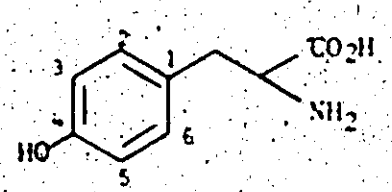

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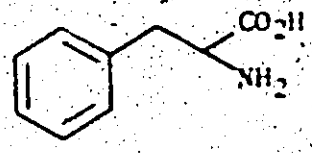

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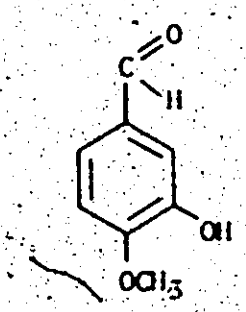


83

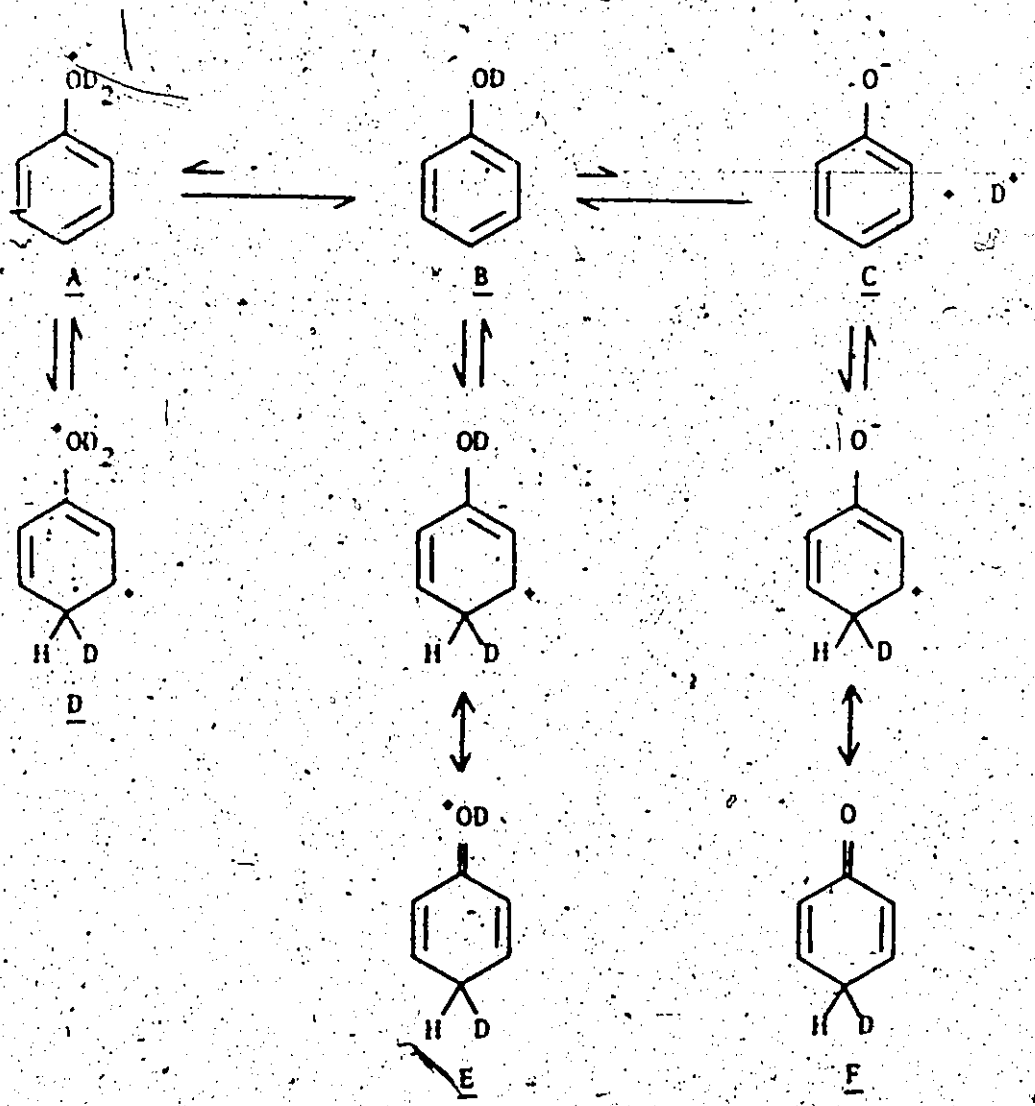
some amino acids in order to remove some of the many overlapping signals.

An additional advantage of the HTDA procedure is the likelihood of preparing ^{18}O labelled phenols since as in the anilime hydrochloride case, substitution probably occurs in this case as well.

Mechanism of Exchange

Although the phenyl protons of phenol are likely exchanged via an electrophilic aromatic substitution sequence (Scheme I-3), the nature of the exchanging species is unclear. Exchange could occur via the conjugate acid, the free phenol and/or the phenoxide ion, A, B and C, respectively, as shown in Scheme II-35. Exchange via the conjugate acid is unfavourable because of coulombic interaction in the intermediate (D), in which case exchange at the m-position should occur most readily, contrary to fact. Exchange via the phenoxide ion, containing the strongly electron-donating -O⁻ group should be most facile (compare D, E and F in Scheme II-35). However, in the presence of dilute acid, the concentration of C would be

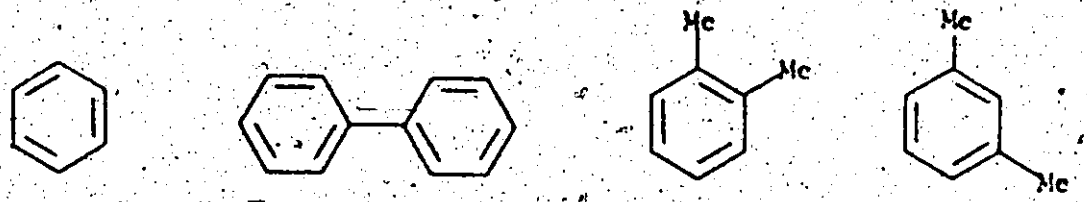
SCHEME II-35



so low that exchange should occur via the free phenol, although some exchange could occur via the phenoxide ion. This latter supposition is supported by the fact that acid-catalyzed deuterium exchange of free phenols is generally faster than that of the corresponding ethers[174]. The ether presumably exchanges slower than the phenol because the ether can not form a phenoxide ion.

III. Benzene, Biphenyl and o- and m-Xylene

To continue the HTDA exchange studies, aromatic nuclei less reactive than aniline and phenol were examined. The results of the exchange of benzene (84), biphenyl (85) and o- and m-xylene (86 and 87) are summarized in Table 13.



84 85 86 87

I.r., n.m.r. and g.l.p.c. data was used to establish the purity and identity of products (i.e., starting material) and in particular, to check for the isomerization of the xylenes[175]. Control experiments in undeuterated media showed that both o- and m-xylene were stable in aqueous acid at 250°; that is, isomerization did not occur. Although the retention times of the m- and p-xylene were identical and shorter than o-xylene on a 10 ft x 1/8 in 5% SE-30 column at 100°C, the identification of products was accomplished by i.r. (fingerprint region) and n.m.r. spectroscopy.

Although aqueous acetic acid is sufficiently acidic to effect slow exchange in dialkyl substituted benzenes (entry 11), benzene and biphenyl require increased acidities (entries 1 and 5). Entries 2, 3, 4, 6, 7, 8, 12, 13 and 14 show that a temperature of 250°C is required to facilitate exchange. Entries 2, 6, 9 and 12 show that at 250°C one cycle results in complete equilibration and maximum exchange as dictated by the deuterium pool. Entries 9 and 10 show that two cycles only, using DCl in the second cycle, are required to accomplish at least 98% exchange in 95-100% yield. Entries 12

Table 13. Exchange of Benzene and its Derivatives with Dilute Hydrochloric Acid in D_2O

Entry	Substrate	Conditions			D/molecule[d]	% Exchange[e]	Position of Deuterium	% Recovery
		Acid	Temp. (°C)	Time (h)				
1	84	a	250	60	0.00	0	-	-
2	84	b	250	48	5.25	88	-	98
3	84	b	200	48	1.25	21	-	98
4	84	b	175	72	0.35	6	-	98
5	85	a	250	48	0.00	0	-	-
6	85	b	250	48	9.40	94	-	98
7	85	b	200	48	4.05[f]	40	-	98
8	85	b	175	72	0.50	5	-	98
9	86	b	250	43	3.5	88	ring[h]	92
10	86[g]	c	250	42	3.90	98	3.9 ring. 0.1 methyl	100
11	87	a	250	48	0.95	24	ring	-
12	87	b	250	40	3.80	91	3.6 ring[h] 0.3 methyl	97
13	87	b	200	48	3.15	78	3.1 ring[h] 0.2 methyl	97
14	87	b	175	72	2.85	70	C-2,4,6 only	97

[a] a = 10% v/v CH_3COOD-D_2O; b = 4% v/v conc. HCl-D_2O; c = 4% v/v conc. DCl-D_2O.

[d] Determined by mass spectrometry. Mass spectral data (uncorrected intensities) for 84, 85, 86 and 87 are listed in Tables 8 and 10 of Appendix C.

....continued

[e]The % exchange is based only on exchange in the aromatic ring. For 86 and 87 the extent of exchange in the aromatic ring was determined by n.m.r. integral analysis. The total deuterium content determined by n.m.r. is slightly greater than that by mass spectrometry.

[f]Total equilibration at all ring positions did not occur. The m-positions contained considerably less deuterium than the o- and p-positions.

[g]The o-xylene used was obtained from entry 9.

[h]Total equilibration of all the ring positions had occurred.

[i]Total equilibration at all ring positions did not occur. The C-5 (meta to both methyls) position contained less deuterium than the other positions.

(Fig. 15, Appendix D) and 14 (Fig. 14, Appendix D) show that by controlling the temperature it is possible to achieve specific deuteration of the aromatic nucleus.

In a typical experiment, a mixture of o-xylene (23 g, entry 10) and 4% v/v conc. DCl-D_2O (70 ml) was sealed in each of two glass tubes (10 in x 2 in O.D.) after being degassed three times via freeze-pump-thaw cycles. The tubes were heated at 250° in a 2-litre Parr Pressure Apparatus, Model 4914 containing H_2O and o-xylene to equalize the internal pressure. After 42 h, the clear colourless o-xylene (46 g) layers were drawn off with the aid of a separatory funnel. The clear D_2O-DCl solution was retained for the first cycle of a subsequent exchange. The o-xylene obtained from this second cycle, contained 3.9 deuterium atoms in the aromatic nucleus and 0.1 deuterium atoms in the methyl groups as established by n.m.r. and mass spectrometric analyses.

The great utility of the HTDA method is its adaptability to large scale preparations, resulting in selective deuteration of the aromatic nucleus with excellent isotopic incorporation and essentially quantitative yields. An added attraction is the "work-up" of the reaction mixture. Aromatic hydrocarbons insoluble in aqueous HCl(DCl),** such as 84, 86 and 87, can be isolated neat with only the use of a separatory funnel. No solvents, etc., are needed! This is not the case for water soluable substrates, such

---

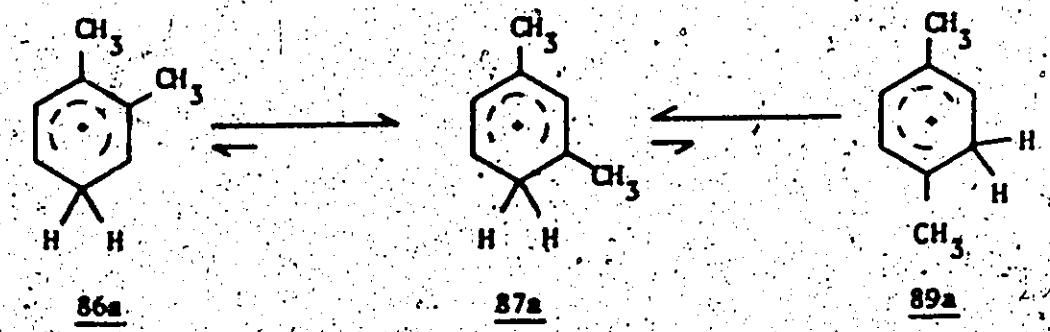
*In a trial large scale reaction of heating the o-xylene and 4% v/v DCl-D_2O directly in the 2-litre bomb fitted with a glass liner, the resultant o-xylene and aqueous layers were yellowish because the steel bomb was reactive to HCl. Large scale (>50 g) reactions should be carried out directly in a Hastelloy B bomb which is inert to HCl or, as has been described, in large sealed glass tubes.

**Experiments carried out in aqueous acetic acid were worked-up by neutralization and extraction because of the increased solubility of the organic substrate in the aqueous phase.

as aniline hydrochloride. Water insoluble solids, such as 85, can be isolated directly by suction filtration.

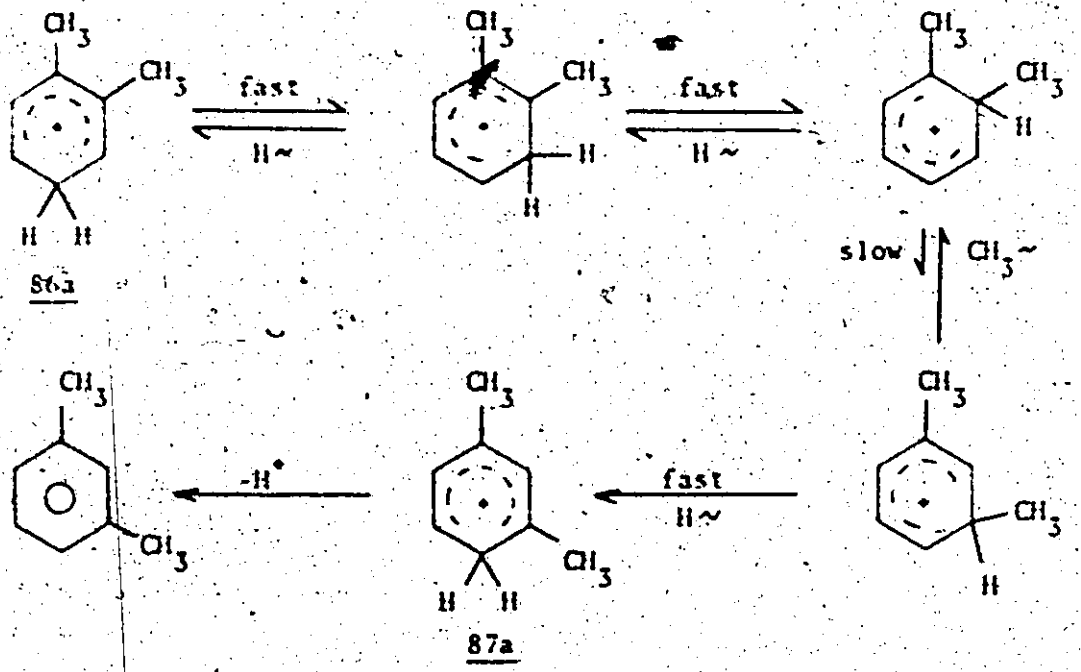
Since electrophilic hydrogen isotope exchange reactions occur via arenonium (or benzonium) ion intermediates[72], which are also intermediates in a wide variety of electrophilic substitution reactions and many acid-catalyzed reactions such as isomerization, transalkylation and dealkylation, it might be expected that some side reactions could occur under our exchange conditions. For instance, in highly acidic media such as HF + SbF_5 or HF + BF_3, the cations derived from o- and p-xylene isomerize to the more highly stabilized cation derived from m-xylene (Scheme II-36A). These isomerizations proceed by successive intramolecular 1,2-hydrogen and 1,2-methyl shifts, with the methyl shifts as the rate-determining step, as depicted for 86 in Scheme II-36B. Initial rapid reversible protonation at the ring carbon bearing the methyl substituent, followed by methyl migration, and subsequent loss of a proton has also been postulated[175]. The introduction of a methyl group at the reactive site decreases its basicity[72] and thus initial protonation of the methyl substituted carbon seems unfavourable relative to protonation of a hydrogen substituted carbon. Fortunately,

SCHEME II-36A



86a 87a 89a

SCHEME II-36B



86a

87a

no side reactions such as isomerization or solvolysis as in the case of aniline (hydrochloride) occur under the prescribed HTDA exchange conditions. This results in essentially quantitative yields of deuterated starting material.

For a given acidity, the rate of and hence extent of exchange depends upon and increases with increasing basicity of the substrate. For arenes, the basicity is expressed in terms of the total basicity constant, K_B, as defined by equations II-5 and 6.

$$Ar + HX \rightleftharpoons HAr^{+} + X^{-} \qquad [II\text{-}5]$$

$$K_B = \left(\frac{a_{HAr^{+}} a_{X^{-}}}{a_{Ar}}\right)\left(\frac{f_{+}^{2}}{f_{Ar}}\right) \qquad [II\text{-}6]$$

where K_B = basicity constant

m_{ArH^+} = molality of the arenonium ion

m_{X^-} = molality of the acid anion

m_{Ar} = molality of the unprotonated arene

f = activities.

Our results, in conjunction with K_B or pK_B values, can be used to predict whether an arene will undergo exchange in 4% v/v $HCl-D_2O$ at 250°. Since the unsubstituted arene, benzene, with a pK_B value of 9.2, undergoes complete exchange at 250°C in 4% v/v $HCl-D_2O$, any other arene which is as basic or more basic than benzene (i.e., $pK_B \leq 9.2$) should also undergo exchange. This indeed was found to be true with biphenyl, o- and m-xylene which have pK_B values of 5.5, 5.3 and 3.2, respectively.* Certainly unsubstituted polynuclear arenes such as triphenylene (92), naphthalene (93), chrysene (94), pyrene (95) and anthracene (96), methylbenzenes such as toluene (88), p-xylene (89), durene (90) and isodurene (91) and methyl-substituted polynuclear arenes such as 1-methylnapthalene (97), 2-methylnapthalene (98), 2-methylanthracene (99) and 9-methylanthracene (100), all of which are more basic than benzene (i.e., pK_B values < 9.2) (Table 14), will also undergo complete exchange of the aromatic nucleus in 4% v/v $HCl-D_2O$ at 250°C. Since ethyl, isopropyl, t-butyl groups have the same stabilizing effect as the methyl group, this exchange method can equally well be applied to these alkylbenzenes. Clearly, the generality of the high temperature-dilute acid exchange method has been well established, especially as applied to arenes.

The reactivities of arenes to acids can be predicted theoretically from simple Huckel or SCF calculations of localization energies[175]. These

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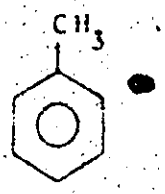
*Studies have shown that exchange also occurs in an arene such as benzoic acid which is less basic than benzene (i.e., $pK_B > 9.2$).



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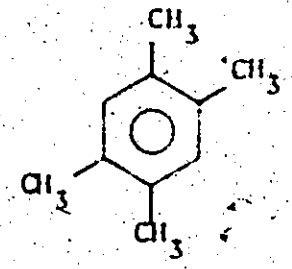

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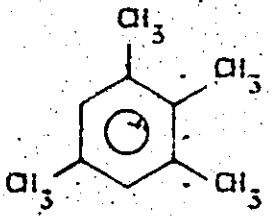

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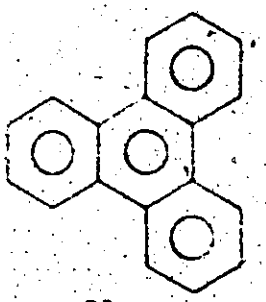

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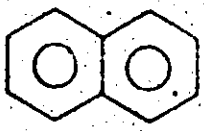

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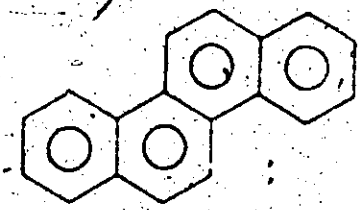

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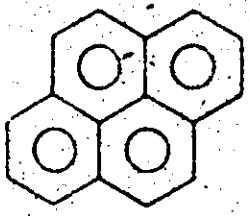

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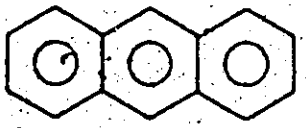

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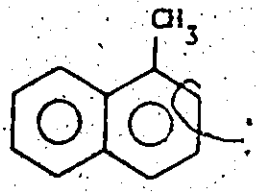

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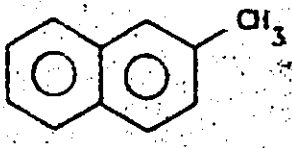

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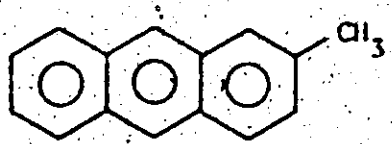

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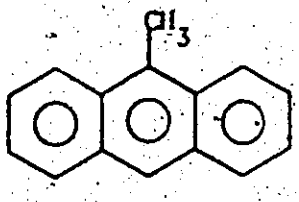


100

Table 44. Basicity Constants[72] of Some Arenes

Compound	pK_B
Benzene (84)	9.2
Toluene (88)	6.3
p-Xylene (89)	5.7
Durene (90)	2.2
Isodurene (91)	-0.1
Triphenylene (92)	4.6
Naphthalene (93)	4.0
Chrysene (94)	1.7
Pyrene (95)	-2.1
Anthracene (96)	-3.8
1-Methynaphthalene (97)	1.7
2-Methynaphthalene (98)	1.4
2-Methylanthracene (99)	-4.7
9-Methylanthracene (100)	-5.7

theoretical calculations, in addition to experimentally determined K_B values, can be used to predict whether acid-catalyzed exchange (deuterium or tritium) of the aromatic nucleus is feasible.

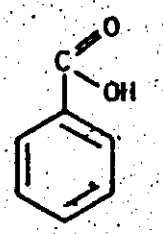
III. Benzoic Acid

In order to establish the complete generality of the high temperature and dilute acid conditions, benzoic acid (101) which is deactivated towards electrophilic aromatic substitution was examined. The results of the study are tabulated in Table 15.

Table 15. Exchange in Benzoic Acid in 4% v/v $HCl-D_2O$

Entry	Conditions		D/molecule[a]	% Exchange (Aromatic)
	Temp. (°C)	Time (h)		
1	175	72	0	0
2	250	65	3.4	72
3	275	75	4.7	94

[a]Determined by n.m.r. integral analysis, using the O-H as an internal standard. Recovered yields of benzoic acid were >95%.



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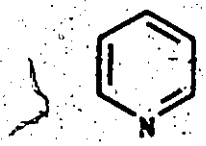
As usual, benzoic acid and 4% v/v $HCl-D_2O$ were degassed and heated in a sealed glass tube in the Parr Pressure Apparatus. After the appropriate reaction time and cooling, the white crystalline solid was collected by

suction filtration and dissolved in base. The acid was precipitated by the addition of dilute acid and the n.m.r. integral analysis was carried out using the O-H as an internal standard.

These results (entries 1, 2 and 3) show that conditions of high temperature (250-300°) and dilute acid can be used successfully to completely deuterate or tritiate deactivated aromatic nuclei and illustrate the great utility and generality of this method. It is not necessary to give an endless list of the effect of substituents on acid-catalyzed deuterium exchange but only to mention that exchange should occur in aromatic nuclei containing any combination of (activating and deactivating) substituents described herein.

V. Pyridine

In order to expand the HTDA exchange conditions to heterocyclics, pyridine (102) was examined under various reaction conditions. The results of the study are summarized in Table 16.



102

When pyridine and 4% v/v HCl-D_2O (degassed) were heated at 250° for 48 h in a sealed tube, a black reaction mixture was obtained (entry 1). After work-up, g.l.p.c. analysis established that the ether extract contained pyridine (95%*) and three unidentified products (5%). Preparative g.l.p.c. using a 15% Carbowax column established that the isolable yield of pyridine was 23%.

Mass spectral analysis showed that the pyridine contained 4.25

*Relative percentage.

deuterium atoms per molecule and established that 84% exchange had occurred in one cycle. N.m.r. integral analysis established that the 2, 3 and 4 positions had been equilibrated.

That a temperature of ca. 250° is required for complete perdeuteration of 102 is illustrated by entry 1 and the work of Zoltewicz and Smith[176] who showed that at 218° in D_2O-DCl, exchange occurs only at the 2,6-positions of 102. In addition entries 1, 2 and 3 clearly indicate that the acidity of the medium is also very important for complete exchange. That is, for complete perdeuteration of 102, 4% v/v HCl-D_2O must be used. By controlling the temperature and/or the acidity, and carrying out back-exchanges it is now possible to easily prepare specifically deuterated or tritiated pyridines.

Table 16. Deuterium Exchange of Pyridine in Dilute Acid

Entry	Conditions			Position of D[c]			% Exchange	Yield % 102
	Acid	Temp.(°C)	Time (h)	2,6	3,5	4		
1	a	250	48	1.7	1.7	0.8	84	25[d]
2	b	245	40	1.9	0.1	0.0	40	60[e]
3[f]	b	275	45	1.9	0.3	0.0	44	51[e]

[a] 4% v/v conc. HCl-D_2O.

[b] 1% v/v conc. HCl-D_2O.

[c] Determined by n.m.r. integral analysis using methanol as an internal standard.

[d] Isolable yield from preparative g.l.p.c.

[e] Determined by micro distillation of 102.

[f] The partially deuterated pyridine from entry 2 was used.

C. CONCLUSION

Our studies have shown that treatment of bicyclic, aromatic and heterocyclic compounds in the presence of dilute acid and deuterium oxide or with deuterium oxide alone in cases where the substrate can generate an acid in situ) at temperatures in excess of 200°C in suitable pressure equipment gives perdeuterated bicyclic, aromatic and heterocyclic compounds, respectively. In many cases complete perdeuteration is accomplished in two cycles with quantitative recovery of products. Moreover, by using appropriate acid and temperature conditions, selective deuteration is also possible in some cases.

The preceeding list of compounds that have undergone deuterium exchange establishes that many other related compounds will also undergo acid-catalyzed deuterium exchange under the high temperature-dilute acid conditions developed herein. Typical examples of systems that will probably undergo deuterium and/or tritium exchange are:

(i) Substituted aromatics such as p-xylene, toluene, t-butylbenzene, bromobenzene, chlorobenzene, methoxybenzene, etc.

(ii) Polynuclear aromatics such as anthracene, naphthalene, acenaphthylene, chrysene, coronene, phenanthrenene, etc.

(iii) Bicyclic compounds such as bicyclo[2.2.2]octane derivatives (alcohols, halides, acetates, etc.).

(iv) Heterocyclics such as furan, thiophene, pyridone, etc.

Although some bicyclic, aromatic and heterocyclic compounds are prone to decomposition due to extended reaction times, high temperatures and/or very acidic conditions, the high temperature-dilute acid exchange method described herein presents substantial advantages over other perdeuter-

ation methods (vide supra) because of

(1) cost;

(2) simplicity;

(3) selectivity;

(4) freedom from steric effects and side reactions;

(5) high degree of isotope incorporation;

(6) essentially quantitative yields; and

(7) adaptability to large scale preparations.

Although the present investigation was undertaken to establish a general deuteration method and only involves deuterium, the technique can be used equally well to introduce tritium into organic molecules.

CHAPTER III

EXPERIMENTAL

General

All melting points were determined on a Kofler hot-stage apparatus. The melting points are uncorrected and rounded off to the nearest 0.5 degree. Boiling points are uncorrected and refer to 760 mm of mercury unless otherwise stated.

Infrared spectra were recorded on either a Perkin Elmer 337 Infrared Spectrometer equipped with gratings or a Beckman IR-5 equipped with sodium chloride optics and prisms. Band positions are uncalibrated and expressed in reciprocal centimeters (cm^{-1}). The notation (No. 51, CS_2) indicates that the infrared spectrum No. 51 was taken in carbon disulfide.

Nuclear magnetic resonance spectra were recorded on Varian A-60, T-60 and HA-100 instruments with tetramethylsilane as the internal standard. Samples were dissolved in one of the following solvents: chloroform-d_1, carbon tetrachloride, methanol-d_4, dimethyl sulfoxide-d_6 and pyridine. Chemical shifts are reported as "δ" values (ppm downfield from the internal standard).

Mass spectra were obtained on a Hitachi-Perkin-Elmer RMU-6A spectrometer at 80 and 15 or 11 eV. The method of deuterium analyses is described in the Deuterium Assay by Mass Spectrometry section (Appendix B). Appendix C gives the uncorrected relative intensities of all isotopic samples.

Two gas chromatographic instruments with helium as the carrier gas were used: Varian Aerograph Model 204B dual column analytical gas chromato-

graph with hydrogen flame-ionization detectors and a Varian Aerograph Model A-90-P preparative gas chromatograph with a thermal conductivity detector. The following symbolism is used to describe gas chromatographic analyses:

I - Varian Model 204B Gas Chromatograph.

II - Varian Model A-90-P Gas Chromatograph.

10% C - a 10 ft x 1/8 inch 10% Carbowax 20 M on Chromosorb W column.

5% SE-30 - a 5 ft x 1/8 inch 5% SE-30 on Chromosorb W column.

15% C - a 15 ft x 3/8 inch 15% Carbowax 20 M on Chromosorb W column.

15% SE-30 - a 10 ft x 3/8 inch 15% SE-30 on Chromosorb W column.

20% SE-30 - a 5 ft x 3/8 inch 20% SE-30 on Chromosorb W column.

5% KOH - 10 ft x 0.375 inch 5% KOH + 20% Carbowax 20 M on 60/80 mesh Chromosorb W column.

For example, (No. 273, I, 10% C, 145°) describes an analysis, number 273, on a Varian Model 204B instrument with a 10% Carbowax column at a column temperature of 145°. Relative percent yields were obtained by tracing, cutting out and weighing peaks. Collection losses during preparative g.l.p.c. were determined by injecting aliquots of known concentration and by determining the collection efficiency as described in Appendix A. In many experiments the isolated and corrected yields are given.

All solutions were dried over anhydrous sodium sulfate or magnesium sulfate.

Pentane was stirred over 30% fuming sulfuric acid, washed with bicarbonate solution, dried and distilled. Pyridine was distilled from barium oxide.

All exchange reactions were carried out in either a Carius oven (Gallenkamp-Model 5815) or a 2000 ml (Monel) Pressure Reaction Apparatus (Parr-Model 4914).

For the latter case time = 0 was when the desired temperature was reached after the bomb was inserted in the oven and time = t was when the bomb was removed from the heater. For the reactions carried out in the Carius oven, t = 0 was that point when the glass tube was inserted into the heater. The thermocouple which was used to determine the temperature of the reaction (i.e., steel bomb or Carius oven) was checked and calibrated in a paraffin wax bath.

Microanalyses were carried out by Sprang Microanalytical Laboratory in Ann Arbor, Michigan, or by A. B. Gygli Microanalysis Laboratories Limited in Toronto, Ontario.

A. Norbornyl Systems

1. Solvolysis of Substituted Nortricyclanes and Norbornenes

(i) Solvolysis of Nortricyclanol (9c)

Acetic Acid-O-d

Acetic acid-O-d was prepared by heating equimolar quantities of acetic anhydride (freshly distilled) and deuterium oxide (99.8%, d_2) for 12 h on the steambath in a flask protected from atmospheric water with a drying tube.

Nortricyclanol

Nortricyclanol, m.p. 107-110° (lit. m.p. 108-110°)[177] was prepared from norbornadiene by the procedure of Meinwald et al.[177]

Solvolysis of Nortricyclanol

Nortricyclanol (15.5 g, 0.14 mole, m.p. 107-110°) and 10% v/v CH_3COOH-H_2O (40 ml) were introduced to a thick-walled glass tube. The solution was degassed three times, the tube was sealed and then heated for 4 h at 250° in a Carius oven. The reaction mixture was neutralized with solid sodium

bicarbonate, saturated with NaCl and extracted with ether (8 x 40 ml). The ether extract was dried and the solvent was removed on the rotatory evaporator to give a viscous mass. Analytical g.l.p.c. (No. 147, I, 5% SE-30, 165°) showed that the mixture was composed of 40% diols, 50% 2-(cyclopentene)acetaldehyde, 3-(cyclopentene)acetaldehyde, 3-(cyclohexene)carboxaldehyde and norcamphor, and 10% products of intermediate retention time (these included exo-5-, endo-5-, and anti-7-norbornenol). The viscous mass was washed with pentane (4 x 20 ml). G.l.p.c. analysis showed that the aldehydes and norcamphor were extracted preferentially and the viscous material which remained, solidified on standing. The aldehydes and norcamphor were isolated by preparative g.l.p.c. (No. 23, II, 15% C, 150°). After six injections, the temperature of the oven was increased to 215-220° to clean the column of the diols which interfered with the collection of the aldehydes and norcamphor. 2-(Cyclopentene)-acetaldehyde (11), 3-(cyclopentene)acetaldehyde (12): i.r., (No. 7, CCl_4), 3052 (>C=C<H), 2710 (H—C=O), 1730 (>C=O), 1612 (>C=C<) and 666 cm^{-1} (>C=C<H); n.m.r. (No. 4, CCl_4), δ 9.74 (m, 1 H, H—C=O), 5.67 (m, 2 H, H-C=C-H), 2.8-1.8 (m, 7H); m.s., (No. 12, 80 eV), M^+ at m/e 110 corresponds to $C_7H_{10}O$. 2,4-DNP; m.p. 120.5 - 122.5° after two recrystallizations from aqueous ethanol.

Anal: calc. for $C_{13}H_{14}N_4O_4$: C, 53.79; H, 4.86; N, 19.30. Found: C, 53.61; H, 4.83; N, 19.29.

3-(Cyclohexene)carboxaldehyde (13): i.r., (No. 6, CCl_4), 3024 (>C=C<H), 2700 (H—C=O), 1730 (>C=O), 1655 (>C=C<), 660 cm^{-1} (>C=C<H); n.m.r. (No. 2, CCl_4), δ 9.55 (s, 1 H, H—C=O), 5.68 (m, 2 H, H-C=C-H), 2.2-1.8 (m, 7 H). The i.r. and n.m.r. spectra were identical to those obtained from an authentic sample of 3-(cyclohexene)carboxaldehyde. M.s., (No: 13, 80 eV)

showed M^+ at m/e 110 corresponding to $C_7H_{10}O$. Norcamphor (14): m.p. 89-91° (lit. m.p. 90-91°)[131]; m.p. of 2,4-DNP 129-131° (lit. m.p. 130-131.5°)[178]; i.r. (No. 14, CS_2), 1735 (C=O), 1170 m, 1064 m, 938 m, 909 w, 849 w and 755 cm^{-1}; n.m.r., (No. 7, CCl_4), δ 2.70 (m, 1 H, C-1 bridgehead), 2.50 (m, 1 H, C-4 bridgehead), 2.1-1.5 (m, 8 H, norbornyl envelope). The i.r. and n.m.r. spectra were identical to those obtained from an authentic sample of norcamphor. M.s., (No. 11, 80 eV) showed M^+ at m/e 110 corresponding to $C_7H_{10}O$. No attempt was made to isolate the diol fractions.

Solvolysis of Nortricyclanol in Deuterated Medium

Nortricyclanol (12.1 g, 0.11 mole, m.p. 107-110°) and 10% v/v CH_3COOD-D_2O (35 ml) were introduced into a heavy walled glass tube. The solution was degassed three times, sealed under vacuum and heated in a Carius oven for 9.5 h at 250°. The dark brown mixture was neutralized with solid sodium bicarbonate, saturated with NaCl, extracted with pentane (10 x 50 ml) and then ether (5 x 50 ml). Gas chromatography of the pentane extract (No. 206, I, 10% C, 180°) showed that the aldehydes and norcamphor were extracted preferentially. In addition five minor components (5%) of retention time near norcamphor and ten components (10%) of retention time in the diol region were present. Gas chromatographic analysis of the ether extract on the same column showed ten components (90%) in the diol region, aldehydes, norcamphor, and five components in the region of norcamphor (total 10%). The pentane and ether extracts were decolorized with Norit, dried and concentrated by distillation through a 12 inch Vigreux column. The concentrated pentane and ether extracts were transferred quantitatively into 10 ml and 5 ml volumetrics, respectively, and made up to volume.

Injection of several aliquots (0.05 ml) of the pentane and ether ex-

traps through the 15 ft x 3/8 inch 15% Carbowax on Chromosorb W column (150°) established the yields of the acetaldehydes, 3-(cyclohexene)carboxaldehyde and norcamphor as 0.6 g (5%), 1.1 g (9%) and 3.2 g (27%) respectively. Correction for collection losses established the actual yields as 1.1 g (9%) of 2- and 3-(cyclopentene)acetaldehyde, 1.8 g (15%) of 3-(cyclohexene)carboxaldehyde, and 4.0 g (33%) of norcamphor (see Appendix A). No attempt was made to isolate materials of longer retention time. However, comparison of retention time data on a 10 ft x 1/8 inch 10% Carbowax on Chromosorb W column with authentic samples of syn- and anti-7-exo-2-norbornanediols indicated that the major components of the ether extract were the 2,7-norbornanediols.

The enolizable deuterium in the aldehydes was washed out by three injections of each material through a 5% KOH column (150-170°) as described in the norcamphor homoenolization experiment. The deuterated norcamphor (0.16 g) isolated from the pentane extract (sodium bisulfite extraction was used to remove the aldehydes) was washed three times at 25±3° for 24 h with 4-6 ml portions of a solution made up of methanol (20 ml), water (10 ml), and KOH (1.0 g). Each wash solution was worked up by the addition of water (5 ml) and extraction with pentane (1 x 10, 4 x 5 ml). In each case the pentane extract was concentrated by distillation through a 2 ft Vigreux column and the norcamphor was isolated by preparative g.l.p.c.

Deuterium assay mass spectrometrically at 11 eV (see Appendix B and Table 1 of Appendix C) on the samples from which the enolizable deuterium was washed out, established that (a) the 2- and 3-(cyclopentene)acetaldehyde mixture (No. 41) was composed of 2.7% d_5, 9.5% d_4, 23.5% d_3, 34.7 d_2, 24.7% d_1 and 4.2% d_0 species (2.15 atoms of deuterium); (b) 3-(cyclohexene)carbox-

aldehyde (No. 42) was composed of 3.0% d_5, 8.6% d_4, 18.8% d_3, 31.1% d_2, 32.7% d_1 and 4.9% d_0 species (2.00 atoms of deuterium); and (c) norcamphor (No. 47) was composed of 1.6% d_5, 5.4% d_4, 14.5% d_3, 28.8% d_2, 42.9% d_1 and 6.9% d_0 species (1.75 atoms of deuterium).

To determine the location of the deuterium, the deuterio-endo-norborneol (0.020 g, 1.70×10^{-4} mole), obtained from lithium aluminum hydride in ether reduction of the norcamphor, was subjected to n.m.r. area integral analysis in the presence of $Eu(DPM)_3$ (0.080 g, 1.13×10^{-4} mole) in CCl_4 (see Section II-A-IV). The analysis established the following deuterium distribution: (No. 117, CCl_4), 0.20 at C-1, 0.10 at C-4, 0.30 at C-5-exo, 0.45 at C-5-endo, 0.15 at C-6-exo, 0.20 at C-6-endo, 0.20 at C-7-syn and 0.15 at C-7-anti (1.75 atoms of deuterium).

A Check of the Deuterium Content in Nortricyclanol and the Norbornanediols

Nortricyclanol (2.3 g, 0.021 mole, m.p. 107-110°) and 10% v/v DOAc-D_2O (18 ml) were introduced into a thick-walled tube and sealed under vacuum after degassing three times. The tube was heated in the Carius oven at 250° for 30 min after which time the reaction mixture was neutralized with solid $NaHCO_3$ and extracted with pentane (3 x 20 ml) and ether (3 x 20 ml). Analytical g.l.p.c. (No. 228, 1, 10% C, temp. programming 165-220°) showed that the pentane extract contained the aldehydes, norcamphor and nortricyclanol (80%), four unidentified components (10%) and diols (10%). Gas chromatographic analysis of the ether extract on the same column showed predominantly diols (90%) as well as the aldehydes norcamphor, nortricyclanol and three minor unidentified peaks (10%). The nortricyclanol was isolated by preparative g.l.p.c from the concentrated pentane fraction and mass spectrometric deuterium assay (No. 57) showed 1.2% d_4, 2.2% d_3, 13.8% d_2,

85.8% d_1 and 15.0% d_0 species, a total of 1.00 atoms of deuterium per molecule (see Appendix C, Table 3).

The ether extract was concentrated by distillation to yield a two-phase liquid and solid mixture. The liquid phase was decanted and to the remaining solid was added pyridine (5 ml) and acetic anhydride (4 ml). The solution was stirred at 25±3° for 24 h and poured onto crushed ice (15 g). After the ice melted the solution was diluted to 65 ml with water and extracted with ether (4 x 15 ml). The ether extract was washed with 3% aqueous HCl (3 x 15 ml), water (2 x 15 ml) and dried. Analytical g.l.p.c. (No. 231-2, I, 10% C, 200°) showed four components (with increasing retention time) in the ratio of 1:1:1:2. Analytical g.l.p.c. of a mixture of syn-7-acetoxy-, anti-7-acetoxy-, exo-5-acetoxy-, endo-5-acetoxy-exo-2-norbornyl acetates obtained from Frinton Laboratories had identical retention times to the diacetates obtained from the nortricyclanol reaction and established that the diol portion of the nortricyclanol reaction was composed primarily of norbornanediols. The diacetate mixture was separated into three fractions by preparative g.l.p.c. (No. 41, II, 15% C, 190°). Peaks 3 and 4 separated by analytical g.l.p.c. were not resolved by preparative g.l.p.c. and were collected together. Deuterium assay mass spectrometrically at 11 eV (Appendix C, Table 3) using the M$^+$-43 (CH_3-C$\overset{O}{\leq}$) peaks because the molecular ion intensity was low gave the following data, peak 1: (No. 70, 11 eV), 14.4% d_2, 80.9% d_1 and 4.7% d_0 species; 1.10 d per molecule; n.m.r. (No. 69, CCl_4), τ 4.58 (doublet with fine structure, 1H, H-C-OAc), 4.20 (m, 1H, H-C-OAc), 2.48 (m, 1H, bridgehead C-H), 2.20 (m, 1H, bridgehead C-H), 1.96 (singlet, 6H, CH_3-C$\overset{O}{\leq}$O-), 1.90-0.90 (norbornyl envelope). Peak 2: (No. 60, 11 eV), 11.4% d_2, 85.9% d_1, 2.7% d_0; 1.10 d per molecule; n.m.r. (No. 70, CCl_4),

4.75 (m, 1H, H-C-OAc), 4.40 (m, 1H, H-C-OAc), 2.25 (m, 2H, bridgehead C-H), 1.96 (s, 6H, CH_3-C-), 1.90-0.90 (norbornyl envelope). Peak 3: (No. 59, 11 eV., 16.8% d_2, 77.4% d_1 and 5.8% d_0; 1.10 d per molecule; n.m.r.: (No. 65, CCl_4), δ 4.45 (m, 2H, H-C-OAc), 2.18 (m, 2H, bridgehead C-H), 1.96 (s, 6H, CH_3-C-O-), 1.90-0.90 (norbornyl envelope).

(ii) Solvolysis of syn-7-Hydroxy-exo-2-Norborneol in Deuterated Medium

syn-7-Hydroxy-exo-2-Norborneol (18a)

A combined procedure of Walborsky[179] and Paasivirta[180] was used in the synthesis of syn-7-hydroxy-exo-2-norborneol. Hydrogen peroxide (Fisher, 30%, 40 ml) was added slowly to a stirred solution of norbornene (Aldrich Chem. Co., 20 g, 0.21 mole) dissolved in ether (200 ml) and 88% formic acid. After the initial exothermic reaction subsided, the reaction mixture was stirred overnight. The solution was concentrated by vacuum distillation. The dark brown residue was saponified by slowly adding alcoholic sodium hydroxide (20 g NaOH, 48 ml methanol, 2 ml water) and then stirring overnight. The solution was diluted with water (25 ml) and extracted with ether (5 x 25 ml). The brown ether extract was partially decolourized with Norit, dried over anhydrous $MgSO_4$, concentrated on the rotatory evaporator and pumped to dryness on the vacuum line. The yellowish residue was recrystallized several times from ether-petroleum ether to yield the norbornanediol (6.76 g, 40%, m.p. 180-186°, lit. m.p. 179-181°[179]). The diol was further purified by grinding the solid into a fine powder with a mortar and pestle, by extracting it with warm carbon disulfide and by recrystallizing the carbon disulfide fraction from ether-petroleum ether (m.p. 180-181.5°, lit. m.p. 179-181°[179]): n.m.r. (No. 94, pyridine), δ 4.10 (m, 1H, C-2-anti), 3.96 (doublet with fine structure, 1H, C-2-endo), 2.20 (m, 2H, bridgehead C-H),

0.82-2.16 (norbornyl envelope).

Solvolysis in Deuterated Medium

syn 7-Hydroxy-exo-2-norborneol (0.34 g, 2.5×10^{-3} mole, m.p. 180-181.5°) was heated with 10% v/v DOAc-D_2O (6 ml) in a sealed tube for 97.5 h at 250°. Work-up in the usual manner and analytical g.l.p.c. analysis (No. 36, I, 10% C, 110°) showed 2- and 3-(cyclopentene)acetaldehyde (18%), 3-(cyclohexene)carboxaldehyde (21%), norcamphor (59%) and three other components (2%). The enolizable deuterium in norcamphor was washed out by injecting it through a basic preparative g.l.p.c. column (No. 76, II, 5% 10M, 175°)(0.040 g, 15%; corrected yield 40%). Deuterium assay mass spectrometrically (No. 114, 15 eV) showed that norcamphor was composed of 2.6% d_5, 6.3% d_4, 12.4% d_3, 20.4% d_2, 28.1 d_1 and 29.2% d_0 species, a total of 1.50 atoms of deuterium (see Appendix C, Table 2). The norcamphor was reduced to deuterated endo-norborneol with lithium aluminum hydride in ether and subjected to n.m.r. area integral analysis in the presence of $Eu(DPM)_3$. The analysis established the following deuterium distribution (rounded to 0.05 d): (No. 168, 169, CCl_4), 0.20 d at C-1, 0.15 d at C-4, 0.20 d at C-5-exo, 0.25 d at C-5-endo, 0.25 d at C-6-exo 0.20 d at C-6-endo, 0.15 d at C-7-anti and 0.20 d at C-7-syn (1.60 atoms of deuterium).

(iii) Solvolysis of anti-7-Norbornenol in Deuterated Medium

anti-7-Norbornenol (15)

A modified Story[181] procedure was used for the synthesis of anti-7-norbornenol. 7-Norbornadienyl acetate (Frinton Laboratories, 4.0 g, 0.026 mole) was added dropwise to a stirred solution of lithium aluminum hydride (1.7 g, 0.038 mole) in anhydrous ether (80 ml) under a nitrogen atmosphere. After being stirred at room temperature for 0.5 h, the reaction

mixture was quenched with wet sodium sulfate. The resultant white granular salt was filtered off by suction. The ethereal filtrate was washed with saturated sodium bicarbonate (2 x 10 ml), water (2 x 10 ml), saturated sodium chloride and dried over anhydrous $MgSO_4$. The ether extract was concentrated by distillation through a 12 inch Vigreux column to give crude alcohol (2.5 g, 85%). The anti-7-norbornenol was recrystallized with difficulty from pentane (1.1 g, 34%, m.p. 115-117°; lit. m.p. 117-118°[181]); i.r. (No. 19, CCl_4), 3300-3650 (broad O-H), 3055 ($>C=C<^{H}$), 1620 ($>C=C<$), 1072 (broad C-O), 700 cm^{-1} ($>C=C<^{H}$); n.m.r. (No. 10, CCl_4), τ 5.96 (t, 2H, $^{H}>C=C<^{H}$), 3.48 (m, 2H, C-7-syn), 2.49 (br, 2H, bridgehead C-H), 1.8-0.9 (norbornyl envelope).

Solvolysis in Deuterated Medium

anti-7-Norbornenol (0.32 g, 2.85×10^{-3} mole, m.p. 115-117°) was heated at 250° with 10% v/v DOAc-D_2O (6 ml) for 9.5 h and worked-up in the usual manner. Analytical g.l.p.c. (No. 361, I, 10% C, 110°) showed 2- and 3-(cyclopentene)acetaldehyde (3%), 3-(cyclohexene)carboxaldehyde (14%) and norcamphor (71%) as well as 12% of four other components which were not norbornanediols. The deuterated norcamphor was isolated by preparative g.l.p.c. (No. 77, 79, II, 15% C, 175°) (0.072 g, 23%, a correct yield of 63%) and reduced with lithium aluminum hydride. N.m.r.-Eu(DPM)$_3$ analysis (No. 166, CCl_4) of the deuterio-endo-norborneol established the following deuterium distribution (rounded to 0.05 d): 0.35 at C-1, 0.30 at C-4, 0.35 at C-5-exo, 0.40 at C-5-endo, 0.25 at C-6-exo, 0.35 at C-6-endo, 0.50 at C-7-syn and 0.25 at C-7-anti (2.75 atoms of deuterium).

(iv) Solvolysis of endo-5-Norbornenol in Deuterated Medium

endo-5-Norbornenol (10b) (Aldrich Chem. Co., 0.45 g, 4.10×10^{-3} mole) purified by preparative g.l.p.c. (No. 75, II, 15% C, 170°) was heated

in 10% v/v DOAc-D_2O (7 ml) as described previously. Work-up and g.l.p.c. analysis showed 2- and 3-(cyclopentene)acetaldehyde (12%), 3-(cyclohexene)-carboxaldehyde (15%), norcamphor (67%) and 6% of five other components which were not diols. Preparative g.l.p.c. (No. 78, II, 15% C, 175°) isolation gave 0.090 g of deuterio-norcamphor (19%, corrected yield 52%). N.m.r.-$Eu(DPM)_3$ analysis (No. 170, CCl_4) of the endo-norborneol obtained by lithium aluminum hydride reduction established the following deuterium distribution: 0.35 at C-1, 0.20 at C-4, 0.20 at C-5-exo, 0.45 at C-5-endo, 0.30 at C-6-exo, 0.45 at C-6-endo, 0.25 at C-7-anti and 0.25 at C-7-syn (2.45 atoms of deuterium).

(x) Solvolysis of exo-2,3-Epoxynorbornane in Deuterated Medium

Exo-2,3-Epoxynorbornane (19)

Norbornene (Aldrich-Chem. Co., 27.6 g, 0.294 mole) was added slowly to a cold chloroform solution (900 ml) containing peroxybenzoic acid[182] (46.5 g, 0.337 mole) and the resulting solution was stored in a refrigerator for 6 days. The chloroform solution was washed with 5% NaOH (6 x 150 ml), water (2 x 150 ml), and dried over anhydrous $MgSO_4$. After removal of the chloroform by distillation, there was obtained a forerun (4.59 g, b.p. 142-156°) which was discarded and the product (10.8 g, 33%, b.p. 156-158°) which solidified in the receiver flask and which was subsequently recrystallized from hexane (m.p. 119-124°, lit. m.p. 121-125°[183]); i.r. (No. 85, CCl_4), 850 cm^{-1} characteristic of 1,2-epoxides; n.m.r. (No. 132, CCl_4), δ 2.88 (s, 2H, C-2-endo and C-3-endo), 2.36 (bs, 2H, bridgehead C-H), 1.80-1.10 (norbornyl envelope).

Solvolysis in Deuterated Medium

exo-2,3-Epoxynorbornane (0.60 g, 5.5×10^{-3} mole, m.p. 119-124°) was heated in 10% v/v DOAc-D_2O (7 ml) as previously described. Work-up and

g.l.p.c. analysis (No. 361, 1, 10% C, 110°) showed 2- and 3-(cyclopentene)-acetaldehyde (3%), 3-(cyclohexene)carboxaldehyde (10%), norcamphor (69%), and three other components (18%) which were not diols. Preparative g.l.p.c. analysis established an isolable yield of 0.22 g (36%) and a corrected yield of 0.37 g (62%) for the deuterio-norcamphor. The enolizable deuterium in the norcamphor was washed out with three washings of a KOH-MeOH-H_2O solution as described in the "Solvolysis of Nortricyclanol in Deuterated Medium" section. Deuterium assay mass spectrometrically (No. 110, 15 eV) established that norcamphor was composed of 1.5% d_7, 3.2% d_6, 6.0% d_5, 9.6% d_4, 14.3% d_3, 19.5% d_2, 23.4% d_1 and 22.5% d_0 species, a total of 2.05 atoms of deuterium (see Appendix C, Table 21). The endo-norborneol obtained by lithium aluminum hydride reduction of norcamphor was subjected to $Eu(DPM)_3$ analysis (No. 167, CCl_4) which established a distribution of 0.30 d at C-1, 0.25 d at C-4, 0.35 d at C-5-exo, 0.35 d at C-5-endo, 0.20 d at C-6-exo, 0.25 d at C-6-endo, 0.25 d at C-7-syn and 0.20 d at C-7-anti (2.15 atoms of deuterium).

(vi) Solvolysis of Nortricyclyl Halides

Nortricyclyl Chloride (9b)

Nortricyclyl chloride (b.p. 48-50°, 10 mm) was prepared by the chlorination of norbornene as described by Roberts et al.[178]

Solvolysis in Water

Nortricyclyl chloride (0.88 g, 6.8×10^{-3} mole, b.p. 48-50° at 10 mm) and water (20 ml) were introduced into a clean heavy-walled glass tube. The solution was degassed three times, sealed under vacuum and heated in a Carius oven for 1.5 h at 250°. The dark reaction mixture was neutralized with sodium bicarbonate, saturated with sodium chloride and extracted with ether (4 x 20 ml). The extract was decolorized with Norit, dried and concentrated by dis-

tillation through a 12 inch Vigreux column and made up to volume in a 2 ml volumetric flask. Injection and collection of aliquots (0.1 ml) on the 15 ft x 3/8 inch 15% Carbowax on Chromosorb W column (155°) established that the isolable and corrected yields of norcamphor were 29% and 35%, respectively (see g.l.p.c. collection loss determination as described in Appendix A). Only minor amounts, <5%, of the aldehydes and diols (7 components) could be detected by analytical g.l.p.c. (No. 170-2, I, 10% C, temp. programming 165-220°).

Solvolysis in Deuterated Medium

Solvolysis of nortricyclyl chloride (2.4 g, 18.7 x 10^{-3} mole, b.p. 48-50° at 10 mm) in 10% v/v CH_3COOD-D_2O (15 ml) for 4 h at 250° and usual work-up showed norcamphor (93%) and two other components (7%). Preparative g.l.p.c. (No. 71, II, 15% C, 120°) gave 0.3 g (15%) of deuterated norcamphor which when corrected for collection losses established the actual yield at 30%. The enolizable deuterium was removed by three washings with a methanol-water-potassium hydroxide solution as described in the nortricyclanol solvolysis experiment. Mass spectrometric deuterium assay (No. 107, 15 eV, Table 1 of Appendix C) established the norcamphor as a composite of 3.9% d_8, 9.4% d_7, 12.3% d_6, 13.5% d_5, 13.9% d_4, 15.5% d_3, 15.2% d_2, 13.0% d_1 and 3.1% d_0 species (3.75 atoms of deuterium).

To determine the location of the deuterium, the deuterated endo-norborneol (0.020 g, 1.70 x 10^{-4} mole), obtained from the lithium aluminum hydride in ether reduction of deuterated norcamphor (after the enolizable deuterium was washed out), was subjected to n.m.r. integral analysis (No. 160, CCl_4) in the presence of $Eu(DPM)_3$ (0.85 g, 1.21 x 10^{-4} mole). The analysis established the following deuterium distribution: 0.40 d C-1, 0.30

d C-4, 0.55 d C-5-exo, 0.55 d C-5-endo, 0.55 d C-6-exo, 0.50 d C-6-endo, 0.60 d C-7-syn and 0.25 d C-7-anti (3.70 atoms of deuterium per molecule).

Nortricyclyl Bromide in Deuterated Medium

Nortricyclyl bromide (9a) (1.8 g, 9.8 x 10^{-3} mole) was heated in 10% v/v CH_3COOD-D_2O (15 ml) for 4 h at 250°. Work up in the usual manner showed norcamphor (>90%) and one other product (<10%). Preparative g.l.p.c. (No. 70, 11, 15% C, 140°) gave 0.2 g (13%) of deuterated norcamphor (correction for collection losses established the yield at 32%). After the enolizable deuterium was washed out by treatment with a methanol-water-potassium hydroxide solution, mass spectrometric deuterium assay (No. 108, 15 eV, Table 1 of Appendix C) established the following distribution: 2.6% d_8, 5.6% d_7, 7.8% d_6, 10.6% d_5, 13.6% d_4, 16.6% d_3, 18.9% d_2, 18.8% d_1 and 5.6% d_0 species (3.20 atoms of deuterium).

The position of the deuterium was determined via the deuterated endo-norborneol (0.020 g, 1.70 x 10^{-4} mole) using the $Eu(DPM)_3$ (0.080 g, 1.13 x 10^{-4} mole) method (No. 161, 165, CCl_4). The analysis established the following deuterium distribution (rounded to 0.05 d): 0.40 d C-1, 0.35 d C-4, 0.50 d C-5-exo, 0.50 d C-5-endo, 0.30 d C-6-exo, 0.40 d C-6-endo, 0.30 d C-7-syn, and 0.30 d C-7-anti (3.05 atoms of deuterium per molecule).

(vii) Assay of 2- and 3-(Cyclopentene)acetaldehyde Mixtures

(a) Solvolytic Assay

$LiAlH_4$ Reduction of (Cyclopentene)acetaldehydes from Nortricyclanol Reaction

The mixture of 2- and 3-(cyclopentene)acetaldehydes (0.13 g, 1.2 x 10^{-3} mole) isolated by preparative g.l.p.c. (as described previously in the "Solvolysis of Nortricyclanol" section) was dissolved in ether (70 ml) and reduced with lithium aluminum hydride (0.023 g, 0.6 x 10^{-3} mole). After a 3 h reflux, 10% NaOH

(0.5 ml) and water (0.2 ml) were added dropwise carefully to the cooled reaction flask. The gelatinous precipitate was filtered off and the ethereal filtrate was washed with saturated sodium bicarbonate (2 x 5 ml), water (1 x 5 ml), saturated aqueous sodium chloride and dried. The mixture of (cyclopentene)ethanols (0.071 g, 57%) >99% pure as shown by analytical g.l.p.c. (No. 186, I, 10% C, 155°) was isolated by preparative g.l.p.c. (No. 25, II, 15% C, 170°).

Preparation of (Cyclopentene)ethanol Nosylates

The mixture of (cyclopentene)ethanols obtained via solvolysis of nortricyclanol (0.071 g, 0.63×10^{-3} mole) was dissolved in dry pyridine (2.5 ml) and the solution was cooled in an ice-salt bath for 30 min. To the cold magnetically stirred solution was added freshly recrystallized (petroleum ether, b.p. 60-100°) p-nitro-benzenesulfonyl chloride (Baker Chem. Co., 0.14 g, 0.64×10^{-3} mole, m.p. 77-79°). After stirring for 45 min at 0 to -10° the reaction mixture was poured into a solution made up of 20 ml of ice-water and 3.5 ml of concentrated hydrochloric acid. The solid was collected on a sintered glass disc, washed with ice-cold 3% aqueous hydrochloric acid and several 10 ml portions of water and dried under vacuum at room temperature. The nosylate (0.13 g, 71%) had a m.p. of 64-67° (lit. m.p. 65-67°[184]).

Preparation of 2- and 3-(Cyclopentene)acetaldehyde. The CAN Oxidation of exo-Norborneol

Exo-norborneol (Aldrich Chem. Co., 5.0 g, 44.6×10^{-3} mole) was oxidized with ceric ammonium nitrate (48.9 g, 89.2×10^{-3} mole) according to the procedure of Trahanovsky[109]. After 30 min at 50°, the reaction mixture was cooled, diluted with water (150 ml) and extracted with pentane

(3 x 100 ml). The pentane extract was washed with saturated aqueous sodium bicarbonate (2 x 50 ml), water (2 x 50 ml), saturated aqueous sodium chloride (2 x 50 ml) and dried. Analytical g.l.p.c. analysis (No. 187, I, 10% C, 165°) showed that the aldehydes comprised 90% of the products. Control experiments showed that pentane extraction separated the aldehydes from the nitro-compound also produced in oxidation. The pentane was removed on the rotatory evaporation to give 5.0 g of crude product (61%). Some of the aldehyde was purified by preparative g.l.p.c. for spectroscopic analysis: i.r. (No. 54, CS_2), 3052 ($>C=C<^{H}$), 2710 ($H-C<^{O}$), 1730 ($>C=O$), 910, 718 and 666 cm^{-1} ($>C=C<^{H}$); n.m.r. (No. 42, CCl_4), δ 9.68 (m, 1H, $H-C<^{O}$), 5.67 (m, 2H, $^{H}>C=C<^{H}$), 2.8-1.8 (m, 7H).

Preparation of (Cyclopentene)ethanol Nosylates from CAN Oxidation of exo-Norborneol

The (cyclopentene)acetaldehyde mixture (3.0 g, 0.027 mole) obtained from the CAN oxidation of exo-norborneol was dissolved in ether (60 ml) and added slowly to a stirred solution of lithium aluminum hydride (0.55 g, 0.014 mole) in ether (200 ml). After refluxing for 3 h, usual work-up gave crude (cyclopentene)ethanols (2.8 g, 87%). From this, 0.28 g of a 2- and 3-(cyclopentene)ethanol mixture was isolated by preparative g.l.p.c. (No. 24, II, 15% C, 170°).

The mixture of (cyclopentene)ethanols (0.28 g, 2.5×10^{-3} mole) was converted to the mixture of nosylates (0.62 g, 84%, m.p. 66-68°) as described previously.

Acetolysis of Mixture of Nosylates Prepared from Aldehydes Obtained from CAN Oxidation of exo-Norborneol

The nosylate mixture (0.23 g, 0.78×10^{-3} mole, m.p. 66-68°) was

dissolved in anhydrous acetic acid (13 ml) which contained anhydrous sodium acetate (0.065 g, 0.79 x 10^{-3} mole). After heating at 100±2° in a constant temperature oil bath for 13 h, the solution was cooled, diluted with water (25 ml) and extracted with pentane (3 x 40 ml). The combined pentane extracts were washed with saturated sodium bicarbonate (3 x 15 ml), water (2 x 15 ml), and saturated brine solution (1 x 20 ml) and then dried over anhydrous $MgSO_4$. Removal of the pentane gave a colourless oil (0.11 g, 93%). Analytical g.l.p.c. (tracing and weighing peaks) (No. 191, I, 10% C, 125°) showed 58% of exo-norbornyl acetate and 42% of 2-(cyclopentene)ethyl acetate after comparison of retention times to those of authentic samples. Thus the (cyclopentene)acetaldehyde mixture from the CAN oxidation of exo-norborneol consisted of 58% of 3-(cyclopentene)acetaldehyde and 42% of 2-(cyclopentene)-acetaldehyde.

Acetolysis of Mixture of Nosylates Prepared from Aldehydes Obtained from Nortricyclanol Reaction

The mixture of nosylates (0.073 g, 0.24 x 10^{-3} mole, m.p. 64-67°) obtained previously was dissolved in anhydrous acetic acid (6 ml) containing 0.021 g of anhydrous sodium acetate and the solution was heated for 13 h at 100±2°. Work-up in the usual manner gave a pentane solution of acetates. Removal of the pentane gave 0.034 g (89%) of an oil which when analyzed (No. 192, I, 10% C, 125°) under the conditions employed previously showed 85% of norbornyl acetate, 14% of 2-(cyclopentene)ethyl acetate and 1% of an unknown acetate. Thus the (cyclopentene)acetaldehyde mixture from the solvolysis of nortricyclanol consisted of 85% of 3-(cyclopentene)acetaldehyde, 14% of 2-(cyclopentene)acetaldehyde and 1% of an unknown.

(b) I.r. Fingerprint Region Assay

Lithium Aluminum Hydride Reduction of 2-(Cyclopentene)acetic acid

2-(Cyclopentene)acetic acid (Aldrich Chem. Co., 8.2 g, 0.065 mole) in ether (50 ml) was added dropwise to a solution of lithium aluminum hydride (2.0 g, 0.052 mole) in ether (150 ml) and then refluxed for 12 h. Work-up, as described previously, yielded 2-(cyclopentene)ethanol (7.3 g, 95%): i.r. (No. 28, neat), 3340 (O-H), 3050 ($\rangle C{=}C\langle^{H}$), 1060 (C-O), 910, 718 cm^{-1} ($\rangle C{=}C\langle^{H}$); n.m.r. (No. 30, $CDCl_3$), δ 5.64 (bs, 2H, $^{H}\rangle C{=}C\langle^{H}$), 3.60 (t, 2H, $-CH_2-OH$), 2.84-1.40 (unresolved, 2H).

Silver Carbonate on Celite Oxidation of 2-(Cyclopentene)ethanol

A ten-fold excess of silver carbonate on celite (38 g, 66.2×10^{-3} mole) prepared by the method of Fetizon[185] was suspended in benzene (250 ml) and refluxed, collecting any residual water with a Dean-Stark apparatus. After all the water was removed, 2-(cyclopentene)ethanol (0.74 g, 6.62×10^{-3} mole) in benzene (75 ml) was added dropwise. After refluxing for an additional 16 h, the hot reaction mixture was filtered through a fine porosity fritted funnel which contained a thin layer of purified celite. The filtrate was concentrated on the rotary evaporator and the 2-(cyclopentene)acetaldehyde (0.60 g, 32%) was collected by preparative g.l.p.c. (No. 69, II, 15% C, 115°). 2,4-DNP: m.p. 98-99.5° after three recrystallizations from methanol (lit. m.p. 98-99°[186]; 100-101°[122a]); i.r. (No. 108, CS_2), 3052 ($\rangle C{=}C\langle^{H}$), 2710 ($H-C\langle^{O}$), 1730 ($\rangle C{=}O$), 910, 718 cm^{-1} ($\rangle C{=}C\langle^{H}$); n.m.r. (No. 153 and 154, CCl_4), δ 9.74 (t, 1H, $H-C\langle^{O}$), 5.67 (m, 2H, $^{H}\rangle C{=}C\langle^{H}$), 3.10 (bm, 1H), 2.40-2.1 (m, 5H), 1.50-1.25 (m, 1H); m.s. (No. 100, 80 eV), M^+ at m/e 110 corresponds to $C_7H_{10}O$.

I.r. Fingerprint Region Assay of 2- and 3-(Cyclopentene)acetaldehyde Mixtures

The i.r. fingerprint region (CS_2) of the 2- and 3-(cyclopentene)-acetaldehyde mixtures obtained from CAN oxidation of exo-norborneol (Fig. 2,

Appendix D) and solvolysis of nortricyclanol (Fig. 1, Appendix D) showed a peak at 910 and an unresolved broad doublet with maxima at 718 and 666 cm^{-1}. The i.r. fingerprint region of 2-(cyclopentene)acetaldehyde (Fig. 3, Appendix D) prepared by Ag_2CO_3 oxidation of 2-(cyclopentene)ethanol showed bands at 910 and 718. Analysis (tracing, cutting and weighing) showed that the 910 peak was 16% and 6% of the area of the 718-666 doublet for the aldehyde mixtures obtained from the CAS oxidation and the nortricyclanol reactions, respectively. Therefore, to obtain the amount of 2-(cyclopentene)acetaldehyde in a mixture of 2- and 3-(cyclopentene)acetaldehyde to within ±2-3%, the 910 peak area percentage is multiplied by 2.6 (16 x 2.6 = 41.6; 6 x 2.6 = 15.6). Application of the analysis to pure 2-(cyclopentene)-acetaldehyde (Fig. 3, Appendix D) showed that the 910 peak area x 2.6 was within 2% of the 718 peak area, establishing the validity of the method.

(viii) Control Experiments

Treatment of 3-(Cyclohexene)carboxaldehyde under Solvolysis Conditions

3-(Cyclohexene)carboxaldehyde (Aldrich Chem. Co., 0.46 g, 4.2×10^{-3} mole) and 10% v/v CH_3COOD-D_2O (11 ml) were sealed under vacuum in a thick-walled glass tube after degassing as described previously. The solution was heated in the Carius oven for 1.5 h at 250° and worked up in the usual manner. Gas chromatographic analysis (No. 106, I, 10% C, temp. programming 170-220°), showed by comparison with authentic samples that norcamphor and the (cyclopentene)acetaldehydes were not formed. Four minor components (<10%), one of retention lower than 3-(cyclohexene)carboxaldehyde and three of longer retention time were present. After the enolizable deuterium was washed out by three injections through the 5% KOH + 20% Carbowax on Chromosorb W column (160°), mass spectrometric analysis (No. 29, 30, 15 eV) showed

that no deuterium was incorporated into 3-(cyclohexene)carboxaldehyde.

Treatment of 3-(Cyclohexene)carboxaldehyde in 15% v/v DOAc-D_2O -1% HCl

3-(Cyclohexene)carboxaldehyde (Aldrich Chem. Co., 0.48 g, 4.4 x 10^{-3} mole) 15% v/v DOAc-D_2O (15 ml) and concentrated hydrochloric acid (0.4 ml) were introduced into a sealed tube, degassed three times and sealed under vacuum. The tube was heated at 250° in a Carius oven for 1.5 h and worked up as described previously. Gas chromatographic analysis (No. 163, 1, 10% C, temp. programming 180-230°) showed twelve components, and only a trace (<2%) of 3-(cyclohexene)carboxaldehyde. Norcamphor comprised approximately 15% of the mixture.

Treatment of 2-(Cyclopentene)acetaldehyde under Solvolysis Conditions

2-(Cyclopentene)acetaldehyde (0.58 g, 5.28 x 10^{-3} mole) and 10% v/v CH_3COOD-D_2O (12 ml) were sealed in a thick-walled glass tube. The tube was heated in a Carius oven for 1.5 h at 250° and worked up in the usual manner. Gas chromatographic analysis (No. 552, 1, 10% C, 115°) showed that only starting material was present. After the enolizable deuterium was washed out by four injections through the 5% KOH • 20% Carbowax on Chromosorb W column (155°), mass spectrometric analysis (No. 106, 15 eV) showed that deuterium was not incorporated into 2-(cyclopentene)acetaldehyde. I.r. analysis (No. 111, CS_2) showed that isomerization to 3-(cyclopentene)acetaldehyde did not occur.

Check for Acid-catalyzed Homoenolization

Run 1: Norcamphor (Aldrich Chem. Co., 0.5 g, 4.5 x 10^{-3} mole), 15% v/v DOAc-D_2O (10 ml) and concentrated HCl (0.37 ml) were introduced into a thick-walled tube and sealed under vacuum after three degassings. The solution was heated at 260° for 1.5 h, worked up in the usual manner and

made up to volume in a 4 ml volumetric flask. The norcamphor (42%) (corrected yield 73%) was isolated by preparative g.l.p.c. by injecting aliquots (0.1 ml) through the 5% KOH • 20% Carbowax column (150°). Deuterium assay mass spectrometrically (No. 16, 17 and 19, 15 eV, Table 4 of Appendix C) after one, two and three injections of the same sample gave the following results: one injection, 7.1% d_2, 58.4% d_1, 34.5% d_0 (0.75 atoms of deuterium); two injections, 1.8% d_2, 24.8% d_1, 73.4% d_0 (0.30 atoms of deuterium); three injections, 0.8% d_2, 4.4% d_1, 94.8% d_0 (0.05 atoms of deuterium) species. This established that deuterium is not incorporated into norcamphor via acid catalyzed homoenolization and that the 5% KOH column removes at least 95% of the enolizable deuterium from norcamphor after three injections.

Run 2: Camphenilone (0.19 g, 1.4×10^{-3} mole), 15% v/v DOAc-D_2O (10 ml) and concentrated HCl (0.13 ml) were introduced into a thick-walled glass tube and sealed under vacuum after degassing. The mixture was heated at 250° for 3 h and worked up as described previously. Mass spectrometric deuterium assay (No. 20, 15 eV) on the camphenilone (0.07 g, 39%) isolated by preparative g.l.p.c. (No. 23, II, 5% KOH, 145°) showed 98% d_0 and 2% d_1 species.

A duplicate of Run 2 with camphenilone (0.18 g, 1.3×10^{-3} mole), 15% v/v DOAc-D_2O (10 ml) and concentrated HCl (0.11 ml) that was heated for 18 h at 275° was worked up and analyzed by analytical g.l.p.c. (No. 57, I, 5% SE-30, 110°). Less than 5% of the camphenilone remained. There were three major components (80%) of retention time shorter than camphenilone as well as four other minor components (20%).

Run 3: Two sealed tubes, one containing 0.21 g of camphenilone and 2 ml of 10% v/v CF_3COOD-D_2O and the other 0.28 g in 2 ml of 10% v/v CF_3COOD-D_2O were prepared and heated at 205° for 17 h and 120 h, respectively. After

work-up, deuterium assay (No. 28 and 31, 15 eV) on samples isolated by preparative g.l.p.c. (No. 7, II, 10% C, 185°) showed that in both cases no deuterium had been incorporated into the camphenilone.

II. Hydration of Norbornadiene (21) at 250°

(a) Hydration in 10% v/v CH_3COOH-H_2O

Norbornadiene (Aldrich Chem. Co., 0.50 g, 5.4×10^{-3} mole) and 10% v/v HOAc-H_2O (8 ml) were placed in a glass tube (12 in x 0.5 in), degassed by the freeze-pump-thaw method and sealed under vacuum. After being heated at 250° for 5 h in a Carius oven, the reaction mixture was diluted with water (4 ml), neutralized with solid sodium bicarbonate, saturated with sodium chloride and extracted with ether (4 x 10 ml). The combined ether extracts were dried over anhydrous magnesium sulphate and concentrated by distillation through a 12 inch Vigreux column. Analytical g.l.p.c. (No. 214, I, 10% C, temp. programming 155-220°) showed that the mixture was composed of 14% of a mixture of the 2- and 3-(cyclopentene)acetaldehydes, 17% 3-(cyclohexene)-carboxaldehyde, 52% norcamphor, 14% norbornanediols and 3% of other products. The aldehydes and norcamphor were isolated by preparative g.l.p.c. on a 15 ft x 3/8 in 15% Carbowax on Chromosorb W column (150°) for identification purposes. 2- and 3-(cyclopentene)acetaldehyde: i.r. (No. 72, CS_2), 3052 ($\rangle C-C^{H}$), 2710 ($H-C^{=O}$), 1730 ($C=O$), 916, 718 and 666 cm^{-1} ($C=C^{H}$); n.m.r. (No. 77,78,80, CCl_4), δ 9.74 (m, 1H, $H-C^{=O}$), 5.67 (m, 2H, $^{H}\rangle C=C^{H}\langle$), 2.8-1.8 (m, 7H).

Comparison of the olefinic n.m.r. protons of 2- and 3-(cyclopentene)-acetaldehyde with those obtained from the nortricyclanol solvolysis (No. 3, CCl_4) and the CAN oxidation of exo-norborneol (No. 41, CCl_4) showed that the 2- and 3-(cyclopentene)acetaldehyde ratio was approximately 15:85.

Using the i.r. fingerprint region assay method of determining the amount of 2-(cyclopentene)acetaldehyde in a mixture of 2- and 3-(cyclopentene)acetalde-

hyde as described in the nortricyclanol solvolysis, it was established that there was ca. 15% of 2-(cyclopentene)acetaldehyde. Thus as in the nortricyclanol solvolysis, the ratio of 2- and 3-(cyclopentene)acetaldehyde was 15:85. 3-(Cyclohexene)carboxaldehyde: i.r., (No. 73, CS_2), 3024 ($\rangle C=C\langle^{H}$), 2700 ($H-C\langle^{O}$), 1730 ($\rangle C=O$), 1655 ($\rangle C=C\langle$), 660 cm^{-1} ($\rangle C=C\langle^{H}$); n.m.r., (No. 79, CCl_4), δ 9.55 (s, 1H, $H-C\langle^{O}$), 5.68 (m, 2H, $^{H}\rangle C=C\langle^{H}$), 2.2-1.8 (m, 7H). The i.r. and n.m.r. spectra were identical to those obtained from an authentic sample of 3-(cyclohexene)carboxaldehyde. Norcamphor: m.p. 88-90° (lit. m.p. 90-91°[131]); i.r. (No. 122, CS_2), 1735 ($\rangle C=O$), 1170 m, 1064 m, 938 m, 909 w, 849 w and 755 cm^{-1}; n.m.r. (No. 171, CCl_4), δ 2.70 (m, 1H, C-1 bridgehead), 2.50 (m, 1H, C-4 bridgehead), 2.1-1.5 (m, 8H). The i.r. and n.m.r. spectra were identical to those from an authentic sample of norcamphor.

(ii) Hydration in Deuterated Medium

Norbornadiene (Aldrich Chem. Co., 13.5 g, 0.146 mole) and 10% v/v CH_3COOD-D_2O (35 ml) were introduced into a thick-walled glass tube. The solution was degassed three times, sealed and heated for 9.5 h at 250° in a Carius oven. The dark brown reaction mixture was neutralized with solid sodium bicarbonate, saturated with sodium chloride and extracted with ether (5 x 20 ml). The combined ether extracts were decolorized with Norit, dried with anhydrous $MgSO_4$ and concentrated by distillation through a 12 inch Vigreux column. Analytical g.l.p.c. (No. 220, I, 10% C, 170-230°) showed 14% 2- and 3-(cyclopentene)acetaldehyde, 17% 3-(cyclohexene)carboxaldehyde, 54% norcamphor, 14% norbornanediols and 1% of other products. The concentrated ether extract was quantitatively transferred into a 25 ml volumetric flask and made up to volume. Preparative g.l.p.c. (No.38,II,15%C,185°) established the yields of the acetaldehydes, 3-(cyclohexene)carboxaldehyde and norcamphor as 0.6 g (4%), 0.9 g (7%) and 3.5 g (26%), respectively. Correction for collection losses (see Appendix A) established the actual yields as 0.1 g (8%) of 2- and 3-

(cyclopentene)acetaldehyde, 1.8 g (13%) of 3-(cyclohexene)carboxaldehyde and 4.4 g (33%) of norcamphor.

The enolizable deuterium in the aldehydes was washed out by three injections of each material through a 5% KOH column (170°) as described in the norcamphor monoenolization experiment. The deuterated norcamphor (isolated by preprative g.l.p.c. when collecting the aldehydes) was washed 3 times with a MeOH-H_2O-KOH solution as described in nortricyclanol solvolysis experiment.

Deuterium assay mass spectrometrically on the samples from which the enolizable deuterium was washed out (Table 5 of Appendix C) established that (a) the 2- and 3-(cyclopentene)acetaldehyde mixture (No.62,11 eV) was composed of 4.2% d_5, 13.8% d_4, 30.4% d_3, 36.3% d_2 and 14.3% d_1 species (2.55 atoms of deuterium); (b) 3-(cyclohexene)carboxaldehyde (No. 54, 11 eV) was composed of 1.7% d_6, 5.2% d_5, 13.8% d_4, 28.0% d_3, 38.7% d_2, 8.7% d_1 and 3.9% d_0 species (2.60 atoms of deuterium); and (c) norcamphor (No. 51, 11 eV) was composed of 1.5% d_6, 3.8% d_5, 10.1% d_4, 23.7% d_3, 44.1% d_2, 13.4% d_1 and 3.4% d_0 species (2.40 atoms of deuterium).

A control experiment[199] has shown that the enolizable deuterium in the aldehydes can be washed out by passing the sample through a 5% wt/wt KOH-Alumina column. However, column chromatography is not an efficient method for washing out the enolizable deuterium in norcamphor.

(iii) Large-scale Hydration-Synthesis of Norcamphor

A mixture of norbornadiene (Aldrich Chem. Co., 125 g, 1.35 mole) and 10% v/v HOAc-H_2O (500 ml) was heated for 18 h at 250° in a steel bomb. The resultant mixture consisted of a black organic layer and a yellow aqueous layer. This mixture was neutralized with solid sodium bicarbonate, saturated with sodium chloride and extracted with ether (5 x 200 ml). The combined ether extracts were washed with a saturated sodium bisulfite solution (5 x 150 ml) (to remove the aldehydes). The ether extract was then dried with anhydrous Na_2SO_4 and concentrated

by distillation through a 12 inch Vigreux column. Analytical g.l.p.c. analysis (No. 36', I, 10% C, 120°) showed 1% of 2- and 3-(cyclopentene)acetaldehyde, 6% of 3-(cyclohexene)carboxaldehyde, 92% of norcamphor and 1% of another product. The concentrated ether extract was vacuum distilled through a 15 inch vacuum jacketed Vigreux column to yield norcamphor (34 g, 23%, b.p. 40-50° (4 mm)). Analytical g.l.p.c. analysis showed 87% of norcamphor and 13% of 12 other products. I.r. and n.m.r. spectra of a sample isolated by preparative g.l.p.c. were identical to an authentic sample of norcamphor; m.p. 88-90° (lit. m.p. 88-91°[131]).

(iv) Treatment with H_2O at 250°

Norbornadiene (0.82 g, 8.8×10^{-3} mole) and water (6 ml) were placed in a glass tube, degassed three times by the freeze-pump-thaw method and sealed under vacuum. After heating at 250° for 10 h in a Carius oven the reaction mixture, containing some white solid material, was extracted with ether (5 x 8 ml). The combined ether extracts were dried and concentrated by distillation through a 12-inch Vigreux column. The white solid was only slightly soluble in ether and precipitated out in the concentrated ether extract. Analytical g.l.p.c. (No. 233 (234), I, 5% SE-30 (10% C), 115° (120°)) of the ether extract showed only the presence of norbornadiene and no aldehydes, norcamphor or diols.

III. Solvolysis of Hydroxy Tosylates and Brosylates

(i) exo-2-Hydroxy-syn and anti-7-Tosyloxynorbornane (35); Synthesis (Scheme II-7)

Gassman et al.[187] have shown that the solvolysis of exo-2-syn-7-ditosyloxynorbornane in refluxing 60% aqueous dioxane for 37 h yields a 75:25 mixture of syn- and anti-hydroxytosylate. In a trial run, our results have shown that when the ditosylate is solvolyzed in refluxing 75% aqueous acetone for 6 days, a 50:50 mixture of syn- and anti-hydroxytosylate results. Apparently the 6,2-hydride shift competes with solvent capture and attempts to prepare pure syn- or anti-hydroxytosylate from the solvolysis of the exo-

2-syn- or anti-7-ditosyloxynorbornanes respectively would be futile. Column chromatographic separation of the syn- and anti- isomers have also proven unsuccessful because of reactions occurring on the column during elution. Hence a large scale preparation of exo-2-hydroxy-syn- and anti-7-tosyloxynorbornane can be achieved from the solvolysis of exo-2-syn-7-ditosyloxynorbornane containing 6-10% of exo-2-anti-7-ditosyloxynorbornane.

exo-2-syn-7-Dihydroxynorbornane

The title compound was prepared as described in the solvolysis of substituted nortricyclanes and norbornenes. However, in this case, the diol was not repurified by carbon disulfide extraction and crystallization and hence it contained 6-10% of the anti-isomer.

exo-2-syn-7-Ditosyloxynorbornane

exo-2-syn-7-Dihydroxynorbornane (6.46 g, 5.1 x 10^{-2} mole, m.p. 180-186°) and freshly recrystallized tosyl chloride (21.2 g, 0.11 mole, m.p. 67-8°) were dissolved in dry pyridine (120 ml). After 6 days in the refrigerator, the reaction mixture was poured into a separatory funnel containing ice-water (600 ml) and extracted with chloroform (4 x 80 ml). The combined extracts were washed with dilute HCl (3 x 60 ml), saturated sodium bicarbonate (2 x 60 ml), water (1 x 60 ml) and dried over anhydrous magnesium sulphate. The dried extract was concentrated on the rotatory evaporator and pumped to dryness on the vacuum pump to yield a slightly coloured solid. This solid was recrystallized twice from hot methanol to yield exo-2-syn-7-ditosyloxynorbornane containing 6-10% of the anti-isomer (11.2 g, 51%, m.p. 114-115°, lit. m.p. of pure syn-isomer 121.5-121.6°[187]); n.m.r. (No. 144, $CDCl_3$), δ 7.9-7.3 (m, 8H, aromatic protons), 4.80 (m, 2H, C-2-exo and C-7-syn with 6-10% C-7-anti), 2.48 (s, 6H, $-CH_3$), 2.40-1.0

(norbornyl envelope); i.r. (No. 105, $CDCl_3$), 2950 (≥C-H), 1600 (aryl C=C), 1190 (-SO_2-O-) and 865 cm^{-1} (aryl C-H).

Mixture of exo-2-Hydroxy-syn- and anti-7-Tosyloxynorbornane

The solvolysis of exo-2-syn-7-ditosyloxynorbornane (8.93 g, 0.020 mole, m.p. 114-115°) was carried out in refluxing 75% v/v aqueous acetone (200 ml) containing an excess of powdered calcium carbonate (2.2 g, 0.02 mole). After refluxing for two weeks, the reaction was diluted with water (50 ml) and extracted with carbon tetrachloride (5 x 40 ml). The combined extracts were dried over anhydrous magnesium sulphate and concentrated on the rotatory evaporator. The remaining residue which was pumped on overnight yielded a viscous oil (5.17 g, 89%). Initial attempts to recrystallize the oil from ether-petroleum ether failed. After allowing the oil to stand in the refrigerator for two weeks, a white oily solid was formed. This oily solid was washed with petroleum ether (30-60°) and after four recrystallizations, yielded white plates (m.p. 79.5-81°): n.m.r. (No. 163, CCl_4); δ 7.6 (quartet with fine structure, 4H, aromatic protons), 4.78 (s, 0.22H, C-7-syn), 4.50 (s, 0.78H, C-7-anti), 3.80 (bm, 1H, C-1), 2.48 (s, 3H, $-CH_3$), 2.3-1.0 (norbornyl envelope); i.r., (No. 117, CCl_4), 3600 (-O-H), 2955 (≥C-H), 1600 (aryl C=C), 1190 (doublet, -SO_2-O-), 1095 (C-O), and 865 cm^{-1} (aryl C-H). As indicated above, the n.m.r. showed that the ratio of syn- and anti-tosyloxynorbornane was 78:22.

Anal: calc. for $C_{14}H_{18}SO_4$: C, 59.55; H, 6.43; found: C, 59.67; H, 6.57.

Solvolysis of a 78:22 Mixture of exo-2-Hydroxy-syn- and anti-7-Tosyloxynorbornane In buffered 10% v/v HOAc-H_2O at 95°

The mixture of syn- and anti-hydroxytosylate (0.11 g, 0.400 x 10^{-3}

mole, m.p. 79.5-81°) was introduced into a glass ampoule (3 in x 0.15 in) containing 10% v/v HOAc-H_2O (2 ml) buffered with 0.1M NaOAc. This mixture was degassed three times by the freeze-pump-thaw method and sealed under vacuum. When the sample reached room temperature, it was placed into a constant temperature oil bath at 95±1°C. After seven days, a yellowish oil gobule was observed in the bottom of the ampoule. The cooled solvolysis mixture was poured into ice-water (4 ml), neutralized with solid sodium bicarbonate and then extracted with petroleum ether (3 x 15 ml) and ether (3 x 10 ml) respectively. Both extracts were separately dried and concentrated by distilling the solvent through a glass helicies column (12 in). Both extracts were quantitatively transferred onto separate watch glasses and allowed to evaporate to dryness. The petroleum ether extract yielded a liquid, 2-(cyclopentene)acetaldehyde (0.036 g, 90%) while the ether extract yielded a semi-solid (0.003 g). G.l.p.c. analysis (No. 353, I, 10% C, 110°) of the petroleum ether extract showed only 2-(cyclopentene)acetaldehyde (>99%) while the ether extract indicated more than 95% of 2-(cyclopentene)-acetaldehyde and less than 5% of 3-(cyclohexene)carboxaldehyde, norcamphor and two other unidentified products.

The 3-(cyclohexene)carboxaldehyde, norcamphor and two other products from the ether extract probably arose from traces of unreacted hydroxy tosylate which reacted on the g.l.p.c. (see stability of 35 on g.l.p.c. injector block and/or column as described in the following section). Comparison of the i.r. fingerprint region (No. 113, CS_2) of the petroleum ether extract with that of an authentic sample of 2-(cyclopentene)acetaldehyde (No. 108, CS_2) clearly showed that the product was pure 2-(cyclopentene)-acetaldehyde (see Section III-A-1(vii), i.r. fingerprint region assay of 2-

and 3-(cyclopentene)acetaldehyde mixtures).

Stability on g.l.p.c. Injector Block and/or Column

The hydroxy tosylate, 35, was dissolved in acetone and injected in the g.l.p.c. (No. 353, I, 10% C, column temp. 110°, injector and detector temperature 235°). The gas chromatogram showed predominantly 2- and 3-(cyclopentene)acetaldehyde, 3-(cyclohexene)carboxaldehyde and norcamphor. In addition to these sink compounds, there were five other products. Although the relative % of products varied from one injector to another, the sink compounds were always the major products.

(ii) exo-6-Hydroxy-endo-2-Brosyloxynorbornane (36)

Synthesis (Scheme II-13)

Preparation of Aluminum t-Butoxide[188]

Aluminum foil*(64 g, 2.37 mole), t-butanol (254 ml, 2.7 mole), and aluminum i-propoxide (Eastern Chem. Co., 7 g) were placed in a 2 litre flask, fitted with a condenser and a drying tube. The mixture was heated to boiling on the steam bath and then mercuric chloride (0.4 g) was added. The mixture was then stirred vigorously, and then heated on the steam bath for 1.5 hours. t-Butanol (309 ml, 3.3 mole) and benzene (200 ml, previously distilled from lithium aluminum hydride) were then added. After heating for a few minutes on the steam bath, the reaction flask was set aside for 2 hours. It was then refluxed on the steam bath for 19 hours.

The benzene and the unreacted t-butanol were then removed by distillation, getting the last traces with the aspirator pump. Dry ether (1 litre, previously distilled from lithium aluminum hydride) was added, and the aluminum t-butoxide was dissolved by refluxing over the steam bath for a few minutes. After cooling, wet ether (35 ml) was added. After standing

for 1.5 hours, the mixture was centrifuged for 30 minutes at 1700 r.p.m. Wet ether was added again, and after standing for 2 hours, the mixture was centrifuged again. Evaporation of solvent gave 292 g (60%) of a grayish solid.

Dehydronorcamphor

Dehydronorborneol (Aldrich Chem. Co., 20 g, 0.182 mole) and p-benzoquinone (Baker Chem. Co., 101 g, 0.94 mole) were dissolved in benzene (2.6 l); 0.8 l of the benzene was distilled from the reaction mixture. After cooling, aluminum t-butoxide (34.6 g, 0.14 mole) dissolved in benzene (300 ml, distilled from lithium aluminum hydride) was added to the mechanically stirred solution over a period of several hours. After stirring for six days at room temperature, the reaction was quenched by adding water (10 ml). The solution was warmed on a steam bath, filtered through a coarse glass porcelain filter, washed several times with sodium hydroxide (5%) until clear and finally with water (1 x 50 ml). After drying, the solution was distilled through a vacuum jacketed Vigreux column using biphenyl (3 g) as a chaser to yield dehydronorcamphor (13.8 g, 70%, b.p. 97-98° (91 mm)): n.m.r. (No. 128, CCl_4), δ 6.50 (m, 1H, $>C=C<^{H}$), 6.10 (m, 1H, $>C=C<^{H}$), 3.20 (m, 1H, C-1 bridgehead), 2.88 (m; 1H, C-4 bridgehead), and 2.1-1.7 (norbornyl envelope); i.r. (No. 83, CS_2), 3055 ($>C=C<^{H}$), 1740 ($>C=O$), and 708 cm^{-1} ($^{H}>C=C<^{H}$).

Dehydronorcamphor Ethyleneketal

Dehydronorcamphor ethyleneketal was prepared according to the method of Heinwald and Cadoff[189]. Dehydronorcamphor (13.5 g, 0.125 mole) was dissolved in benzene (200 ml, distilled from LAH) and freshly distilled ethylene glycol (150 ml) containing p-toluenesulfonic acid (0.65 g). The mixture was refluxed for 16 h, using a water separator (Dean-Stark) to

collect the water. After cooling the reaction mixture and diluting with water, the benzene solution was washed with 10% aqueous sodium bicarbonate (2 x 50 ml) and with water (1 x 80 ml). After drying, most of the benzene was distilled through a Vigreux column to yield a benzene solution of the ketal (17.0 g, 90%, as determined by n.m.r.): n.m.r. (No. 129, CCl_4), δ 6.15 (m, 2H, $\rangle C{=}C\langle^{H}_{H}$), 3.76 (s, 4H, ketal), 2.80 (broad m, 1H, C-1 bridgehead), 2.58 (broad m, 1H, C-4 bridgehead), 1.84-1.40 (norbornyl envelope); i.r. (No. 84, CS_2), 3055 ($\rangle C{=}C\langle^{H}_{H}$); no $\rangle C{=}O$ absorption around 1750 cm^{-1}.

Preparation of Perbenzoic Acid[182]

Sodium peroxide (24 g, 0.31 mole) was slowly added to ice-cold water (405 ml) such that the temperature did not reach 10°. The suspended solids were then filtered through a fine porosity fritted glass funnel, keeping the filtrate in an ice bath to keep cool. The filtrate was then place in a 3-liter beaker which was kept in an ice-water bath. To the magnetically stirred solution ethanol (95%, 540 ml) was added, followed by a solution of $MgSO_4 \cdot 7H_2O$ (1.5 g, in 20 ml of water), in a manner such that the temperature did not reach 10°. Benzoyl chloride (34.8 ml, 0.30 mole) was then added dropwise over a period of 45 minutes, so that the temperature remained below 8°. After filtration through a coarse porosity fritted glass funnel, the solution was slowly acidified with sulfuric acid (20%), so as to keep the temperature below 10°. The solution was then extracted 5 times with benzene using a total volume of 0.5 l. The benzene was dried ($MgSO_4$) and was stored in the refrigerator. Yield: 25 g (65%), as determined by iodimetric titration.

exo-2,3-Epoxy-5-Ethylenedioxynorbornane

Dehydronorcamphor ethyleneketal (17.0 g, 0.112 mole) was added to a

solution of perbenzoic acid (25 g) in benzene (500 ml). The mixture was stored in the refrigerator (ca. 5°) for four days, then washed with 5% NaOH (3 x 100 ml) until basic, water (3 x 100 ml), and saturated brine solution (1 x 100 ml). After drying, distillation yielded the epoxyketal (17.6 g, 93%, b.p. 103-107° (8 mm), lit. b.p. 53° (0.25 mm)[189]): n.m.r. (No. 130, CCl_4), δ 3.80 (s, 4H, ketal), 3.18 (s, 2H, C-2- and C-3-endo), 2.38 (m, 2H, bridgehead protons), 1.80-1.1 (norbornyl envelope); i.r. (No. 125, CS_2), 3030 (C-H of epoxide ring), 1190, 1085 and 1042 (C-O) and 852 cm^{-1} (C-O-C of epoxide ring).

exo-6-Hydroxy-2-Ethylenedioxynorbornane.

The previously obtained epoxyketal (17.6 g, 0.105 mole) was added to a slurry of lithium aluminum hydride (4.0 g, 0.10 mole) in N-ethylmorpholine (150 ml, freshly distilled from LAH). The mixture was heated with magnetic stirring for six days at 110°-15°. After cooling in ice, the reaction was quenched with 10% sodium hydroxide (5 ml) and water (5 ml). Filtration of the inorganic salts, followed by vacuum distillation through a 4 inch vacuum jacketed Vigreux column gave the desired alcohol (8.17 g, 46%, b.p. 70-72° (0.1 mm), lit. b.p. 70-72° (0.1 mm)[189]): n.m.r. (No. 133, CCl_4), δ 4.22 (doublet with fine structure, 1H, C-2-endo), 3.80 (s, 4H, ketal), 2.38-1.22 (norbornyl envelope); i.r. (No. 86, CS_2), 3600-3500 (O-H), 1190, 1078, 1042 and 955 cm^{-1}.

exo-6-Hydroxy-Norboran-2-one

Concentrated hydrochloric acid (60 drops) was added to the hydroxy ketal (9.01 g, 5.3 x 10^{-2} mole) in water (300 ml). The solution was stirred at room-temperature for forty-five minutes, saturated with ammonium chloride and extracted thoroughly with ether. The combined ether extracts were dried

and concentrated on the rotatory evaporator to yield a viscous oil (5.70 g, 84%). Recrystallization from ether-petroleum ether afforded a sticky crystalline solid (m.p. 108-112°, lit. m.p. 102-113°[189]): n.m.r. (No. 134, CCl_4): δ 4.30 (m, 1H), 4.0 (m, 1H), 2.78 (s, 1H, bridgehead proton), 2.56 (s, 1H, bridgehead proton), 2.08-1.62 (norbornyl envelope); i.r. (No. 150, CCl_4), 3500 (O-H), 1740 (C=O), 1068 cm^{-1} (C-O). A p-toluenesulfonate ester was recrystallized three times from ether-petroleum ether; m.p. 67-69°, lit. m.p. 68-69°[189]. The corresponding p-bromobenzenesulfonate was crystallized from cyclohexane; m.p. 91-94°, lit. m.p. 93-94°[189]

exo-6-Pyranylether-Norbornan-2-one

A mixture of hydroxy ketone (1.02 g, 8.1 x 10^{-3} mole), dihydropyran (1.03, 12.2 x 10^{-3} mole) and concentrated hydrochloric acid (1 drop) was stirred for four hours at room temperature. The resultant mixture was taken up in ether, washed with 10% NaOH (3 x 15 ml), water (1 x 15 ml) and dried. Removal of the solvent on the rotatory evaporator and pumping on the vacuum line yielded crude product (1.55 g, 91%): n.m.r. (No. 177, CCl_4), δ 4.62 (m, 1H), 3.81 (m, 2H), 2.8 (m, 1H), 2.2-1.5 (norbornyl envelope and pyranyl ether protons); i.r. (No. 132, neat), 1740 (C=O), 1125 cm^{-1} (C-O).

exo-6-Pyranylether-endo-2-Hydroxynorbornane

The previously prepared exo-6-pyranylether-norborman-2-one (1.54 g, 7.3 x 10^{-3} mole) was reacted with LAH (0.152 g, 4 x 10^{-3} mole) in refluxing ether (50 ml) for 5 h. The usual work-up gave 1.24 g (80%) of crude product: n.m.r. (No. 178, CCl_4), δ 4.72 (m, 1H), 4.18-3.43 (m, 4H), 2.2-1.5 (norbornyl envelope and pyranyl ether protons); i.r. (No. 133, neat), 3400 (O-H), 1025 cm^{-1} (C-O).

exo-6-Pyranylether-endo-2-Brosyloxynorbornane

The hydroxy pyranylether (1.20 g, 5.68 x 10^{-3} mole) and recrystallized

brosyl chloride (1.48 g, 5.8 x 10^{-3} mole, m.p. 76-8°) in dry pyridine (40 ml) were stored in the refrigerator at 0°C for six days. The resultant reaction mixture was quenched with ice-water (60 ml) and extracted with ether (3 x 25 ml). The combined ether extracts were washed with dilute HCl (4 x 15 ml), saturated sodium bicarbonate (1 x 15 ml) and dried over anhydrous magnesium sulphate. The ether was removed on the rotatory evaporator and pumped to dryness on the vacuum line to yield crude pyranyl-ether brosylate (1.63 g, 67%): n.m.r. (No. 179, CCl_4), δ 7.6 (broad m, 4H, aryl), 4.2-3.4 (m, 4H), 2.3-1.4 (norbornyl envelope and pyranyl ether protons); i.r. (No. 134, CCl_4), 1586 (aryl C=C), 1185 cm^{-1} (doublet, $-SO_2-O-$). Attempts to recrystallize the ether brosylate from methanol and ether-petroleum ether failed, and consequently the crude product was used in the following hydrolysis.

exo-6-Hydroxy-endo-2-Brosyloxynorbornane (36)

The pyranylether brosylate (1.42 g, 3.30 x 10^{-3} mole) was dissolved in 2% wt/v oxalic acid-70% v/v aqueous methanol (50 ml) and stirred at room temperature. After 2.5 h, addition of water (20 ml) turned the clear reaction mixture milky. This solution was extracted with ether (3 x 20 ml). The combined ether extracts were washed with saturated sodium bicarbonate (1 x 10 ml), water (2 x 10 ml), saturated sodium chloride (1 x 10 ml) and dried over anhydrous magnesium sulphate. The ether was removed on the rotatory evaporator to yield an oil. On adding carbon disulfide (2 ml) to this oil, white crystals slowly appeared. These crystals were rinsed twice more with carbon disulfide, pumped on the vacuum line for 20 minutes, and finally recrystallized thrice from ether-pentane to afford an analytical sample of white fluffy crystals (0.36 g, 31%, m.p. 113-115°): n.m.r. (No.

187, $CDCl_3$), δ 7.60 (s, 4H, aryl), 4.78 (m, 1H, C-6-exo), 4.38 (d, C-2-endo), 2.51-1.1 (norbornyl envelope); i.r. (No. 152, $CDCl_3$), 3600 (O-H), 3065 (aryl C-H), 1586 (aryl C=C), 1185 (d, $-SO_2-O-$), 1090 (-C-O), and 960 cm^{-1} (aryl C-H).

Anal: calcd. for $C_{13}H_{15}SO_4Br$: C, 44.97, H, 4.35; found: C, 45.08, H, 4.39.

endo-6-Hydroxy-exo-2-Tosyloxynorbornane (42)

Via $LiAlH_4$ (Scheme II-14)

The p-toluenesulfonate ester of exo-6-hydroxy-norborman-2-one (0.09 g, 0.34×10^{-3} mole, m.p. 67-69°, lit. m.p. 68-69°[189]) prepared in the usual manner and recrystallized three times from ether-petroleum ether was dissolved in anhydrous ether (35 ml) and then cooled to 0° in an ice-water bath. On addition of $LiAlH_4$ (0.004 g, 0.13×10^{-3} mole), the mixture was stirred for 1.5 h at 0° and then quenched with 10% aq. NaOH. After the gelatinous precipitate was filtered off, the ether layer was dried and concentrated on the rotatory evaporator. Final traces of ether were removed on the vacuum line to give a viscous oil: i.r. (No. 102, CCl_4), 3610 and 3450 (O-H), 1595 (C=C), 1355 and 1185 cm^{-1} ($-SO_2-O-$) with no C=O band; n.m.r. (No. 146 and 147, CCl_4), δ 7.8-7.2 (quartet, aromatic, 7 units/H), 5.64 (s, $\overset{H}{\underset{}{>}}C=C\overset{H}{\underset{}{<}}$, 4.5 units/H), 5.2 (b.m., C-2-endo), 4.25 (m, hydroxy tosylate), 3.65 (triplet, $-CH_2-O-$), 2.4 (s, $-CH_3$), 2.35-1.4 (norbornyl envelope and remainder of 3-(cyclopentene)ethanol). Parts (δ at 5.64 and 3.65) of this n.m.r. were very similar to the n.m.r. (No. 31, CCl_4) of the 2-(cyclopentene)ethanol. N.m.r. integral analysis of the aromatic and olefinic protons established that 3-(cyclopentene)ethanol (40%) and the hydroxy tosylate (60%) were present. Attempts to purify the hydroxy tosylate by pumping off

the ethanol derivative on the vacuum line and subsequent recrystallization from pentane; ether and ether-petroleum ether failed.

The ratio of the fragmentation product (2-(cyclopentene)ethanol) and hydroxy tosylate varied, depending upon the reaction conditions. Reductions carried out at room temperature contained more of the ethanol derivative.

Via $NaBH_4$ (Scheme II-16)

An ice-cooled solution of $NaBH_4$ (0.056 g, 1.5×10^{-3} mole), water (3 ml) and 10% aq. NaOH (1 drop) was added dropwise with stirring over a period of 10 minutes to a methanolic (12 ml) solution of exo-6-tosyloxy-norborman-2-one[11] (0.85 g, 3.0×10^{-3} mole, m.p. 67-69°) maintained at 0°. After stirring for an additional 20 minutes at 0°, the reaction mixture was quenched by the addition of dilute H_2SO_4 (20 ml) and extracted successively with petroleum ether (3 x 40 ml), carbon disulfide (3 x 40 ml) and ether (3 x 40 ml). Each extract was washed with saturated bicarbonate (1 x 20 ml), water (3 x 20 ml) and dried. After concentration of the extracts on the rotatory evaporator and pumping on the vacuum line a viscous oil was obtained from the petroleum ether (0.028 g), carbon disulfide (0.376 g) and ether (0.050 g) extracts. The petroleum ether extract was discarded. The i.r. and n.m.r. spectra of the CS_2 and ether extracts were similar. The absence of a C=O band in the i.r. indicated that the reaction was complete: i.r. (No. 129, CS_2), 3600-3400 (O-H), 1355 and 1185 cm^{-1} ($-SO_2-O-$); n.m.r. (No. 196, CCl_4), δ 7.75-7.2 (quartet, 4H, aromatic), 5.1 (b.m., 1H, C-2-endo), 4.2 (b.m., 1H, C-2-exo), 3.3 (s, 1H, O-H), 2.4 (s, 3H, $-CH_3$), 2.35-1.2 (norbornyl envelope). Although the i.r. and in particular the n.m.r. spectrum indicated that the major product was the hydroxy tosylate, attempts to purify it by recrystallization from ether-petroleum ether failed. Similar

results were obtained from the reduction of the exo-6-brosyloxynorbornan-2-one (m.p. 91-94°, lit. m.p. 93-94°[189]).

Solvolysis of exo-6-Hydroxy-endo-2-Brosyloxynorbornane

In buffered 10% v/v HOAc-H_2O at 95°

The hydroxy brosylate (0.12 g, 0.343 x 10^{-3} mole, m.p. 113-115°) was introduced into a glass ampoule (3 in x 0.5 in) containing 10% v/v HOAc-H_2O (2 ml) buffered with 0.1 M NaOAc. The mixture was degassed three times, sealed under vacuum and placed in a constant temperature oil bath at 95±1°C. After 13 days, the cooled brownish solvolysis mixture was poured into ice-water (2 ml), neutralized with solid sodium bicarbonate and extracted with pentane (6 x 10 ml) and then with ether (4 x 10 ml). Both extracts were dried separately and concentrated by distillation through a glass helicies column (12 in). Both extracts were quantitatively transferred onto tared watch glasses and allowed to evaporate to dryness. The pentane extract yielded a pungent smelling liquid, 3-(cyclopentene)acetaldehyde (0.028 g, 74%) whereas the ether extract yielded a CS_2 insoluble white solid (0.016 g). G.l.p.c. analysis (No. 390, I, 10% C, 115°) of the pentane extract showed 3-(cyclopentene)acetaldehyde (94%), 3-(cyclohexene)carboxaldehyde (3%) and one unidentified product (3%) while the ether extract indicated 51% of 3-(cyclopentene)acetaldehyde and 49% of nine other unidentified products whose retention times were lower than the norbornanediols. An i.r., (No. 172, CS_2), of the pentane extract showed that the product was 3-(cyclopentene)acetaldehyde: 3052 ($\rangle C{=}C\langle^{H}$), 2710 ($H{-}C\langle^{O}$), 1730 ($\rangle C{=}O$), 666 cm^{-1} ($\rangle C{=}C\langle^{H}$) (see section on i.r. fingerprint region assay of 2- and 3-(cyclopentene)acetaldehyde mixtures).

Stability on g.l.p.c. Injector Block and/or Column

Pure exo-6-hydroxy-endo-2-brosyloxynorbornane was dissolved in acetone

and injected in the g.l.p.c. (No. 384,385,386, I, 10% C, 115°, injector and detector temperature 225°). The gas chromatogram showed only one peak, having the same retention time as 2-(cyclopentene)acetaldehyde and 3-(cyclopentene)acetaldehyde. From the solvolysis results, one can infer that this peak was probably due to the Δ^3 isomer. No 3-(cyclohexene)-carboxaldehyde or norcamphor could be detected.

Similar results were obtained, when a crude sample of endo-6-hydroxy-exo-2-tosyloxynorbornane was passed through the g.l.p.c.

(iii) cis-exo-3-Hydroxy-2-Tosyloxynorbornane (37)

Synthesis (Scheme II-23)

cis-exo-2,3-Dihydroxynorbornane

A combined procedure of Kwart[190] and Bartlett[191] was used for the preparation of cis-exo-2,3-dihydroxynorbornane (37). Potassium permanganate (47 g, 0.297 mole) in water (100 ml) and acetone (1 litre) was added with stirring over the course of an hour to a dry ice-acetone cooled solution of norbornene (Aldrich Chem. Co., 24.5 g, 0.260 mole, m.p. 45-47°) and acetone (50 ml). After the addition of the permanganate solution, the reaction was gradually allowed to warm to room temperature and then filtered. The reddish-brown filtrate was saturated with carbon dioxide and the precipitated potassium carbonate was removed by filtration. The solution was decolorized with Norit and then the acetone was removed by distillation. The residue was dissolved in ether, dried over anhydrous sodium sulphate and stripped in vacuo. This residue was crystallized from ether-pentane and then vacuum sublimed (115-120° at 30 mm) to yield white plates (6.90 g, 21%, m.p. 115-140°, lit. m.p. 140°[190]). These crystals were further purified by recrystallizing twice from ether (2.91 g, 8.8%, m.p. 135-140°,

lit. m.p. 140°[190]): n.m.r. (No. 83, pyridine), δ 3.80 (d, 2H, C-2-endo, C-3-endo), 2.28 (b.s., 2H, bridgehead C-H), 2.05 (m, 1H, C-7-syn), 1.6-0.9 (norbornyl envelope). The yield and purity can perhaps be increased by using a salt-ice bath as suggested by Walborsky and Loncrini[179] rather than the dry-ice acetone bath.

cis-exo-3-Hydroxy-2-Tosyloxynorbornane

Crude cis-exo-3-hydroxy-2-tosyloxynorbornane (1.0 g, 20%, m.p. 45-50°) was prepared by the reaction of cis-exo-2,3-dihydroxynorbornane (2.4 g, 1.88 x 10^{-3} mole, m.p. 135-140°) and freshly recrystallized tosyl chloride (3.9 g, 2.06 x 10^{-3} mole) according to the method of Lambert and Holcomb[192]. The crude hydroxy ester was recrystallized numerous times from boiling hexane (0.95 g, 17%, m.p. 53-56°): n.m.r. (No. 121, CCl_4), δ 7.9-7.3 (quartet, 4H, aromatic), 4.38 (d, 1H C-3-endo), 3.7 (m,1H,C-2-endo), 2.5 (sharp s, 3H,-CH_3), 2.22-1.0 (norbornyl envelope).

Solvolysis of cis-exo-3-Hydroxy-2-Tosyloxynorbornane in buffered 10% v/v HOAc-H_2O At 95°

The hydroxy tosylate (0.121 g, 0.426 x 10^{-3} mole, m.p. 53-56°) was introduced into a glass ampoule (3 in x 0.5 in) containing 10% v/v HOAc-H_2O (2 ml) buffered with 0.1 M NaOAc. The mixture was degassed three times by the freeze-pump-thaw method and sealed under vacuum. When the sample reached room temperature, it was placed in a constant temperature oil bath at 95±1°C. After 7 days, the ampoule was removed, cooled and opened. The solvolysis mixture was poured into ice-water (2 ml), neutralized with solid sodium bicarbonate and extracted with ether (3 x 10 ml). The combined ether extracts were dried over anhydrous magnesium sulphate and concentrated by distilling the ether through a glass helicies column (12 in). The concentrated ether extract was transferred onto a watch glass and allowed to

evaporate to dryness to yield a semi-solid (0.049 g, 88% of norbornanediols). G.l.p.c. analysis of this semi-solid (No. 356, I, 10% C, 165-180°) showed traces of norcamphor (<1%) (no cyclopentenyl or cyclohexenyl aldehydes), syn- and anti-3-hydroxy-exo-2-norborneol (24% and 37%) and eight other products (38%) with retention times in the region of norbornanediols.

At 250°

As described above, the hydroxy tosylate (0.033 g) was solvolyzed in 10% v/v HOAc-H_2O (5 ml) buffered with 0.1 M NaOAc for 1 hour at 250°C in a Carius oven. Usual work up and g.l.p.c. analysis (No. 309, I, 10% C, 125°) showed 2- and 3-(cyclopentene)acetaldehyde (8%), 3-(cyclohexene)carboxaldehyde (12%), norcamphor (25%) and four other products (55%) with retention times in the region of norbornanediols.

Stability on g.l.p.c. Injector Block and/or Column

The hydroxy tosylate, 37, was dissolved in acetone and injected in the g.l.p.c. (No. 386, I, 10% C, column temp. 115°, injector and detector temp. 220°). The gas chromatogram indicated 2- and 3-(cyclopentene)acetaldehyde, 3-(cyclohexene)carboxaldehyde and norcamphor in the ratio of about 1:2:4 respectively. In addition to these aldehydes and norcamphor, there were also three other minor unidentified products whose relative percent changed from one injection to another.

IV. N.m.r. Spectra Analysis of endo-Norborneol in the Presence of the Chemical Shift Reagent, $Eu(DPM)_3$

Weighed quantities of tris(dipivalomethanato)europium, $Eu(DPM)_3$ [Stohler Isotope Chemicals], and endo-norborneol were placed in a 2 dram sample vial containing CCl_4 (0.5 ml), shaken vigorously for five minutes

and filtered through glass wool. Spectra were run on the Varian HA-100 instrument with tetramethyl silane as the internal standard.

Initially, the spectra (No. 99, 100 and 102) of several samples containing different relative amounts of $Eu(DPM)_3$ were recorded. $Eu(DPM)_3$ was added to small aliquots until all the n.m.r. signals of endo-norborneol were cleanly resolved (first order). The signals of endo-norborneol were assigned by a combination of first order analysis of the splitting patterns, double resonance experiments and by using endo-2-norborneol -exo-5-exo-6-d_2. N.m.r. integral analysis of partially deuterated endo-2-norborneol (Section II-A-I, "Solvolysis of Substituted Nortricyclanes and Norbornenes" and Section II-A-V, "Hydration of Norbornene at 250") was carried out by using the exo-2 and/or endo-3 and exo-3 protons (in the cases where the enolizable deuterium in norcamphor had been washed out prior to reduction with lithium aluminum hydride) as internal standards.

V. Hydration of Norbornene (53) at 250°

(i) Hydration in 10% v/v CH_3COOH-H_2O

Norbornene (Aldrich Chem. Co., 5.14 g, 5.46×10^{-2} mole, m.p. 45-7°) and 10% v/v HOAc-H_2O (25 ml) were introduced into a glass tube, degassed three times by the freeze-pump-thaw method and sealed under vacuum. After heating at 250° for 60 h in a Carius oven, the two phase reaction mixture was diluted with water (30 ml), neutralized with solid sodium bicarbonate, saturated with sodium chloride and extracted with ether (4 x 40 ml). The combined ether extracts were dried over anhydrous $MgSO_4$ and concentrated by slow distillation through a 15 inch glass helicies column. Analytical g.l.p.c. (No. 261-2, I, 10% C, temp. programming 110-155°) showed that the reaction mixture consisted of 2% norbornene, 4% nortricyclane, 8% exo- and

endo-norbornyl acetate, 28% exo-norborneol, 11% endo-norborneol and 47% di-norbornyl ether. The concentrated ether extract was quantitatively transferred into a 10 ml volumetric and made up to volume. Preparative g.l.p.c. (No. 58, 1', 45% C, 175°) established the yields of exo- and endo-norbornyl acetate, exo- and endo-norborneol and di-norbornyl ether as 0.36 g (4%), 1.76 g (29%) and 2.0 g (18%) respectively. Correction for collection losses, as shown in Appendix A, established the yield of norborneol as 2.05 g (33%). exo- and endo-Norbornyl acetate: i.r. (No. 79, neat), 1738 (C=O), 1018 and 1072 cm^{-1} (C-O stretch); n.m.r. (No. 111, 112, CCl_4), δ 4.72 (m, 0.13 H, C-2-exo), 4.50 (b.d., 0.87H, C-2-endo), 2.24 (b.s., 2H, bridgehead C-H), 1.92 (s, 3H, $-O-\overset{O}{\overset{\|}{C}}-CH_3$), 1.74-1.05 (norbornyl envelope, 8H); m.s. (No. 84, 15 eV), M^+ at m/e 154 corresponding to $C_9H_{14}O_2$. The i.r., n.m.r. and m.s. spectra were identical to those of an authentic sample of exo-norbornyl acetate. N.m.r. integration of the C-2-exo- and endo-protons showed that the exo:endo ratio of norbornyl acetates was 87:13. exo- and endo-Norborneol: m.p. 127-130° (lit. m.p. of exo-isomer 127-128°[193]; i.r. (No. 32, CS_2), 3600 (free-OH), 3350 (H bonded-OH), 1118, 1110 (d, C-H), 1082 (C-O stretch), 1032, 1022 (d, C-H), 1000 (C-O stretch), 916, 832, 806 cm^{-1} (C-H); n.m.r. No. 33, $CDCl_3$), δ 4.05 (m, 0.25H, C-2-exo), 3.74 (b.d., 0.75H, C-2-endo), 2.18 (m, 2H, bridgehead C-H), 1.7-0.9 (8H, norbornyl envelope); m.s. (No. 37, 15 eV) M^+ at m/e 112 corresponded to $C_7H_{12}O$; M^+ of the acetalated alcohol showed an m/e 154 corresponding to $C_9H_{14}O_2$. By comparison of the i.r. finger-print region of pure exo- and endo-norborneol with the norborneol from the reaction (1118 and 1010 doublet, 1032 and 1022 doublet, and 806 cm^{-1} singlet) it can be concluded that the norborneol from the hydration of norbornene consisted mostly of the exo-isomer. This fact is verified by n.m.r. integration

of the C-2-exo- and endo-protons. Di-norbornyl ether (a glassy solid): m.p. 51-53° (after three injections through g.l.p.c. column); i.r. (No. 80, CCl_4), 1095 (C-O), 1248, 1176, 1152, 1026, 862, and 693 cm^{-1} (C-H); n.m.r. (No. 110, CCl_4), δ 3.76 (b.m., 0.55H, C-2-exo), 3.32 (m, 1.45H, C-2-endo), 2.22 (b.s., 4H, bridgehead C-H) and 1.76-0.94 (norbornyl envelope, 16H); m.s. (No. 84, 15 eV), M^+ at m/e 206 corresponds to $C_{14}H_{22}O$.

Anal: calcd. for $C_{14}H_{22}O$: C, 81.50, H, 10.75; found: C, 81.79, H, 10.86.

N.m.r. area integration of the C-2-exo- and endo-H of di-norbornyl ether showed that the stereoisomeric mixture was composed of 70% exo and 30% endo linkages.

(ii) Hydration in Deuterated Medium

Norbornene (Aldrich Chem. Co., 0.52 g, 5.56×10^{-3} mole) and 10% v/v CD_3COOD-D_2O (8 ml) were sealed in a glass tube (7 in x 1/2 in) as previously described. After heating at 250° for 120 h, a milky aqueous layer and a pale yellow organic layer were formed. After the usual work-up, analytical g.l.p.c. (No. 250, I, 10% C, temp. programming 125-140°) showed that the reaction mixture consisted of 1.2% norbornene, 9.2% exo- and endo-norbornyl acetate, 56.2% exo-norborneol, 20.9% endo-norborneol, 7.4% di-norbornyl ether and 5.1% of two other products. The concentrated ether extract was quantitatively transferred into a 1 ml volumetric flask and made up to volume. As illustrated in Appendix A, preparative g.l.p.c. (No. 50, II, 15% C, 155°) established the yield of exo- and endo-norborneol as 0.40 g (69%): corrected for collection losses 0.46 g (80%).

Since mass spectrometric deuterium assay on the norbornyl acetate is more accurate than analysis on the norborneol, due to the large M-1 and M-2

peaks associated with the latter, the norborneol was converted to the acetate by the following procedure. The norborneol (0.23 g, 2.05×10^{-3} mole) isolated by preparative g.l.p.c. was dissolved in pyridine (8 ml) and acetic anhydride (6 ml) and stirred at room temperature for 24 h. The mixture was added to crushed ice (15 ml). After the ice had melted, the solution was diluted with water (80 ml) and extracted with ether (3 x 20 ml). The ether extract was washed with dilute HCl (3 x 10 ml) and water (2 x 10 ml), dried over anhydrous $MgSO_4$ and concentrated by the rotatory evaporator. Mass spectrometric deuterium assay (No. 80, 15 eV, Table 6 of Appendix C) on the exo- and endo-norbornyl acetate showed 44.0% d_{11}, 36.5% d_{10}, 14.2% d_9 and 5.5% d_8 species, a total of 10.05 atoms of deuterium per molecule.

(iii) Incomplete Exchange in Deuterated Medium

Norbornene (Aldrich Chem. Co., 1.26 g, 1.34×10^{-2} mole) and 10% v/v CH_3COOD-D_2O (20 ml) in a degassed sealed tube were heated at 250° for 3 h in a steel bomb. After the usual work up, analytical g.l.p.c. (No. 285, I, 10% C, temp. programming 85-125°) showed 25% norbornene, 7% nortricyclane, 8% exo- and endo-norbornyl acetate, 48.5% exo- and endo-norborneol, 6% di-norbornyl ether and 5.5% of four other products. The concentrated ether extract was quantitatively transferred into a volumetric flask (2 ml). Preparative g.l.p.c. (No. 63, II, 15% C, 125°) established the yield of norborneol as 0.53 g (35%): corrected for collection losses 0.61 g (41%). Some of the alcohol collected by preparative g.l.p.c. was converted to the acetate with pyridine and acetic anhydride as previously described. Mass spectrometric deuterium assay (No. 93, 15 eV, Table 6 of Appendix C) on the exo- and endo-norbornyl acetate showed 4.3% d_{11}, 11.7% d_{10}, 13.3% d_9, 11.1% d_8, 8.7% d_7, 8.0% d_6, 6.1% d_5, 5.9% d_4, 7.1% d_3, 9.2% d_2, 12.7% d_1 and 2.0% d_0, a total

of 5.90 atoms of deuterium per molecule.

The remainder of the alcohol isolated by preparative g.l.p.c. was oxidized by Jones reagent according to the following procedure. exo- and endo-Norborneol (0.31 g, 2.76 x 10^{-3} mole), ether (10 ml) and a chromic acid solution (3 ml, prepared from 5 g $Na_2Cr_2O_7 \cdot 2H_2O$ and 3.75 ml concentrated H_2SO_4 which is then diluted to 25 ml) were added together and stirred overnight. The ether layer was separated and the aqueous phase was extracted with ether (2 x 5 ml). The combined ether extracts were washed with saturated sodium bicarbonate (3 x 5 ml), water (1 x 5 ml), and dried over anhydrous $MgSO_4$. The ether was removed slowly by distillation through a 12 inch glass helicies packed column to yield norcamphor (0.22 g, 2.0 x 10^{-3} moles, 72%). To determine the location of the deuterium, the deuterated endo-norborneol (0.024 g, 2.0 x 10^{-4} mole) obtained from the lithium aluminum hydride in ether reduction of norcamphor, was subjected to n.m.r. area integral analysis in the presence of $Eu(DPM)_3$ (0.098 g, 1.39 x 10^{-4} mole) in CCl_4 as described in Section II-A-IV. The analysis established the following deuterium distribution (rounded to 0.1 d): (No. 119, CCl_4), 0.5 at C-1, 0.5 at C-3-exo, 0.5 at C-3-endo, 0.5 at C-4, 0.5 at C-5-exo, 0.5 at C-5-endo, 0.6 at C-6-exo, 0.6 at C-6-endo, 0.5 at C-7-syn and 0.5 at C-7-anti (5.2 atoms of deuterium). Since the original exo- and endo-norborneol contained 5.9 atoms of deuterium and the endo-norborneol obtained from the oxidation and reduction sequence contained 5.2 atoms of deuterium, the original exo-and endo-norborneol must have contained approximately 0.6-0.7 d at the C-2 position which was lost during the oxidation stage.

(iv) Hydration of Nortricyclane in Deuterated Medium

Norcamphor Tosylhydrazone

Concentrated hydrochloric acid (3 ml) was added to tosylhydrazine (Aldrich Chem. Co., 24 g, 0.129 mole, m.p. 110°) and norcamphor (Aldrich Chem. Co., 14.4 g, 0.131 mole, m.p. 90-92°) dissolved in 95% ethanol (300 ml). The mixture was refluxed for 6.5 h and poured into water (1000 ml). The resultant precipitate was collected and recrystallized from 95% ethanol to give norcamphor tosylhydrazone (20.8 g, 58%, m.p. 205-208°, lit., m.p. 206.5-208°[194]); i.r. (No. 77, $CHCl_3$), 3300, 3200 (N-H), 1660 (C-N), 1160 (S-O).

Nortricyclane (54).

Norcamphor tosylhydrazone (18.7 g, 6.7 x 10^{-2} mole, m.p. 205-208°) was added to purified diglyme (250 ml) in a three-neck flask equipped with a stoppered condenser and a nitrogen inlet and outlet. Freshly prepared sodium methoxide (30.2 g, 0.56 mole) was added and the reaction mixture was heated to reflux (140-150°). As nitrogen vented through the solution, the product was carried through a water wash, a KOH pellet drying system, and collected in a small flask and "U" tube cooled in dry ice. Analytical g.l.p.c. (No. 259, I, 5% SE-30, 105°) showed 99% nortricyclane and 1% norbornene.

Hydration of Nortricyclane

Nortricyclane (0.15 g, 1.60 x 10^{-3} mole) and 10% v/v DOAc-D_2O (8 ml) were introduced into a glass tube (8 in x 1/2 in), degassed three times by the freeze-pump-thaw method and sealed under vacuum. After heating at 250° for 15 h in a Carius oven, the two phase reaction mixture was diluted with water (8 ml), neutralized with solid sodium bicarbonate, saturated with sodium chloride and extracted with ether (4 x 15 ml). The combined ether extracts were dried over anhydrous $MgSO_4$ and concentrated by slow distilla-

tion through a 15 inch glass helicies packed column. Analytical g.l.p.c. (No. 265, 269, I, 10% C, temp. programming 85-155°) showed 5% exo- and endo-norbornyl acetate and 95% exo- and endo-norborneol. The concentrated ether extract was quantitatively transferred into a 1 ml volumetric flask and made up to volume. Preparative g.l.p.c. (No. 60, II, 15% C, 180°) established the yield of norborneol as 0.064 g (36%): corrected for collection losses (see Appendix A) 0.075 g (42%). As previously described, the alcohol was converted to the norbornyl acetate which was subjected to mass spectrometric deuterium assay: (No. 94, 15 eV, Table 6 of Appendix C) 37.1% d_{11}, 35.5% d_{10}, 14.8% d_9, 4.3% d_8, 1.3% d_7 and 7.0% d_6 species, a total of 9.80 atoms of deuterium per molecule.

(v) Solvolysis of exo-Norborneol in Deuterated Medium

As described in the hydration of nortricyclane experiment, exo-norborneol (0.7 g, 6.28 x 10^{-3} mole) and 10% v/v DOAc-D_2O were heated at 250° for 15 h. Analytical g.l.p.c. (No. 267, 290, I, 10% C, temp. programming 80-155°) showed 0.7% norbornene, 1.3% nortricyclane, 8.0% exo- and endo-norbornyl acetate, 61.0% exo-norborneol, 28.2% endo-norborneol, 0.4% di-norbornyl ether and 0.4% of another product. The concentrated ether extract was quantitatively transferred into a 2 ml volumetric flask and made up to volume. Preparative g.l.p.c. (No. 60, II, 15% C, 180°) established the yield of norborneol as 0.48 g (67%): corrected for collection losses (Appendix A) 0.56 g (79%). Mass spectrometric deuterium assay (No. 97, 15 eV, Table 6 of Appendix C) on the acetylated alcohol showed 27.4% d_{11}, 38.7% d_{10}, 23.2% d_9, 8.5% d_8 and 2.2% d_7 species, a total of 9.80 atoms of deuterium per molecule.

(vi) Solvolysis of endo-Norbornyl Acetate in Deuterated Medium

As described elsewhere, norcamphor was reduced to predominantly endo-norborneol with lithium aluminum hydride in ether. The endo-alcohol was then acetylated to endo-norbornyl acetate with pyridine and acetic anhydride.

As described in the hydration of nortricyclane experiment, endo-norbornyl acetate (0.55 g, 3.59×10^{-3} mole) was heated at 250° for 15 h. Analytical g.l.p.c. (No. 289, I, 10% C, 95°) showed 0.8% norbornene, 0.5% nortricyclane, 39.2% exo- and endo-norbornyl acetate, 37.3% exo-norborneol, 16.7% endo-norborneol and 5.5% of two other products. The concentrated ether extract was quantitatively transferred into a 5 ml volumetric flask and made up to volume. Preparative g.l.p.c. established the yield of norborneol as 0.18 g (45%): corrected for collection losses 0.20 g (51%). Mass spectrometric deuterium assay (No. 95, 15 eV) on the norbornyl acetate isolated from the reaction mixture contained predominantly d_{14}, d_{13} and d_{12} species, indicating that the acetate methyl group was also being exchanged under the reaction conditions. Thus to get an accurate analysis on the deuterium incorporation into the norbornyl skeleton, mass spectrometric deuterium assay must be done on the acetylated alcohol. As before, the exo- and endo-norborneol was converted to the norbornyl acetate and mass spectrometric deuterium assay (No. 98, 15 eV, Table 6 of Appendix C) on this acetylated alcohol showed 39.6% d_{11}, 38.5% d_{10}, 17.2% d_9 and 4.7% d_8 species, a total of 10.25 atoms of deuterium per molecule.

VI. Solvolysis of exo-2-Phenyl-endo-2-Hydroxynorbornane (59)

exo-2-Phenyl-endo-2-Hydroxynorbornane (59)

Magnesium turnings (3.36 g, 0.14 mole) washed with ether and dried in an oven were placed in a warm, dry 3-neck round bottom flask fitted

with a condenser and a $CaCl_2$ drying tube. After cooling, anhydrous ether (20 ml) and distilled bromobenzene (22.8 g, 0.145 mole) were added to the magnesium. After the reaction was initiated, an additional 50 ml of dry ether was added. When all the magnesium had disappeared, norcamphor (Aldrich Chem. Co., 13.88 g, 0.126 mole) in ether (25 ml) was added to the Grignard reagent over a 10-minute period. After refluxing for 3 h and cooling, aqueous ammonium chloride was added to the reaction mixture. The ether extract was washed with water (2 x 25 ml), 5% KOH (2 x 25 ml) and steam-distilled through a wide bore condenser to remove any norcamphor and bromobenzene. The residue was extracted with ether, dried and vacuum distilled to give a water white distillate (16.17 g, 71.3%, b.p. 154-155° at 10 mm) which solidified on standing to give white crystals. G.l.p.c. analysis showed that it contained <5% of 2-phenyl-2-norbornene and >95% exo-2-phenyl-endo-2-hydroxynorbornane: n.m.r. (No. 211, CCl_4), δ 7.2 (m, 5H, aromatic) and 2.7-1.4 (11H, norbornyl envelope).

Solvolysis of exo-2-Phenyl-endo-2-Hydroxynorbornane in 10% v/v HOAc-H_2O at 295°

exo-2-Phenyl-endo-2-hydroxynorbornane (1.31 g, 6.96×10^{-3} mole) and 10% v/v HOAc-H_2O (4 ml) were introduced into a glass tube. After degassing the sample three times, it was sealed and heated at 295° for 51 h in the steel bomb. The resultant black reaction mixture was worked up in the usual manner. Analytical g.l.p.c. (No. 405, I, 10% C, 180°) showed that the reaction mixture was composed of 4 unidentified components (14.2%) and 2-phenylnorbornane (85.8%). The 2-phenylnorbornane(60) was isolated by preparative g.l.p.c. (No. 95, II, 10% C, 175°) for characterization: i.r. (No. 186, CS_2), 3020 (aryl-H), 2950 (saturated C-H), 760, 735, 718 and 698 cm^{-1} (aryl-H); n.m.r. (No. 216A and B, CCl_4), δ 7.14 (m, 5H, aryl), 3.2

(m, 1H, C-2), 2.35 (m, 2H, bridgehead C-H), and 2.1-1.2 (8H, norbornyl envelope); m.s. (No. 135, 80 eV), M^+ at m/e 172 corresponds to $C_{13}H_{16}$.

The concentrated ether extract was then vacuum distilled through a 6 inch Vigreux column to yield 60 as a colourless liquid (0.126 g, 11%, b.p. 60-63° at 5 mm).

Solvolysis of exo-2-Phenyl-endo-2-Hydroxynorbornane in 10% v/v CH_3COOD-D_2O at 295°

As in the preceeding experiment, exo-2-phenyl-endo-2-hydroxynorbornane (0.79 g, 4.2×10^{-3} mole) was treated with 10% v/v CH_3COOD-D_2O for 51 h. Analytical g.l.p.c. (No. 405, I, 10% C, 180°) showed that the reaction mixture was composed of six unidentified components (7.0%) and 2-phenylnorbornane (93.0%).

Deuterium assay mass spectrometrically (No. 137, 15 eV, Table 7 of Appendix C) established that the 2-phenylnorbornane was composed of 1.0% d_{11}, 2.2% d_{10}, 3.6% d_9, 5.1% d_8, 6.9% d_7, 8.4% d_6, 9.0% d_5, 10.27% d_4, 12.9% d_3, 16.3% d_2, 15.6% d_1 and 8.8% d_0 species (3.80 atoms of deuterium per molecule). N.m.r. area integration analysis indicated that 4.0 deuterium atoms were incorporated into the norbornyl skeleton and that no deuterium had been incorporated into the aromatic ring.

VII. Hydration of Benzonorbornadiene (65) at 250°

Benzonorbornadiene (65)

Benzonorbornadiene was prepared by the method of Wittig and Knauss[195]. A solution (15 ml) of 2-bromofluorobenzene (Aldrich Chem. Co., 13 g, 75×10^{-3} mole) and freshly distilled cyclopentadiene (4.9 g, 75×10^{-3} mole) in dry tetrahydrofuran (45 ml) was placed in a 3-neck round bottom flask equipped

with a magnetic stirrer, nitrogen inlet, a pressure equilibrated dropping funnel and a reflux condenser fitted with a $CaCl_2$ drying tube. The system was flushed with nitrogen after which magnesium turnings (2 g, 83 x 10^{-3} mole) were added to the stirred solution. The remainder of the bromofluorobenzene and cyclopentadiene solution (30 ml) was added under a slow flow rate of nitrogen. After 40 minutes when most of the magnesium had reacted, the solvent was removed by vacuum distillation. The residue, diluted with ether (50 ml), was washed with a saturated ammonium chloride solution (4 x 25 ml), dried with anhydrous $MgSO_4$ and distilled through a Vigreux column to give a major fraction (7 g, 66%, b.p. 82-83° at 12 mm) >99% pure as established by gas chromatographic analysis: n.m.r. (No. 205, CCl_4), δ 6.62-7.18 (m, 6H, 4 aromatic and 2 olefinic), 3.78 (m, 2H, bridgehead C-H), 2.22 (m, 2H, C-7).

(i) Hydration in 10% v/v HOAc-H_2O

Benzonorbornadiene (0.50 g, 3.5 x 10^{-3} mole, b.p. 82-83° at 12 mm) and 10% v/v CH_3COOH-H_2O (3 ml) were introduced into a glass tube (11 in x 0.5 in). The sample was degassed three times by the freeze-pump-thaw method, sealed, and heated at 250° for 3 h in a Parr Pressure Reaction Apparatus. The slightly yellowish reaction mixture was diluted with water (3 ml), neutralized with solid sodium bicarbonate, saturated with NaCl and extracted with ether (4 x 20 ml). The ether extract was dried, concentrated on the rotatory evaporator and quantitatively transferred into a 2 ml volumetric flask. Analytical g.l.p.c. (No. 392,393,396, I, 5% SE-30, 125°) showed that the mixture was composed of benzonorbornadiene (3.0%), endo-benzonorbornenol (3.2%), exo-benzonorbornenol (85.4%), benzonorbornenyl acetate (7.7%) and an unknown (0.7%). The products were isolated by preparative g.l.p.c. (No. 87, II, 5% SE-30, 195°) for characterization. exo-Benzonorbornenol: m.p. 72-74°

(lit. m.p. 74-75°[196]); i.r. (No. 176, CCl_4), 3620 (O-H), 3030 (aryl-H), 1070 and 1050 (C-O), 862 (C-H), and 730 cm^{-1} (aryl-H); n.m.r. (No. 206, 214, CCl_4), δ 6.96 (m, 4H, aryl), 3.86 (broad d, 1H, C-2 proton), 3.17 (d, 2H, bridgehead C-H), and 2.1-1.56 (norbornyl envelope, 4H); m.s. (No. 119, 120, 80 eV), M^+ at m/e 160 corresponds to $C_{11}H_{12}O$. The i.r. and n.m.r. spectra were identical to an authentic sample of exo-benzonorbornenol obtained from the hydroboration of benzonorbornadiene. endo-Benzonorbornenol: m.p. 69-74° (lit. m.p. 74°[196]); i.r. (No. 178, CCl_4), 3580 (O-H), 3030 (aryl-H), 1155, 1140, 1130, 1115 (C-H), 1072 and 1050 (C-O), and 728 cm^{-1} (aryl-H); m.s. (No. 118, 80 eV), M^+ at m/e 160 corresponds to $C_{11}H_{12}O$. The i.r. was identical to an authentic sample of endo-benzonorbornenol obtained as the minor product in the hydroboration of benzonorbornadiene. An unsymmetrical quartet present at 1155, 1140, 1130 and 1115 cm^{-1} in the endo-alcohol is absent in the exo-alcohol while a band at 862 cm^{-1} in the latter is absent in the endo-alcohol and hence the i.r. fingerprint region can be used to distinguish between the exo- and endo-benzonorbornenol. Benzonorbornenyl acetate: i.r. (No. 180, CCl_4), 3030 (aryl-H), 1742 (>C=O), 1244 and 1029 (>C-OAc), and 728 cm^{-1} (aryl-H); m.s. (No. 121, 80 eV), M^+ at m/e 202 corresponds to $C_{13}H_{14}O_2$ while m/e 159 corresponds to $M^+ - O-\overset{O}{\overset{\|}{C}}-CH_3$.

Injection of several aliquots (0.08 ml) of the ether extract through the 5% SE-30 column established the recovered yield of exo-benzonorbornenol as 0.22 g (39%).

(ii) Hydration in 10% v/v CH_3COOD-D_2O

Benzonorbornadiene (0.43 g, 3.1×10^{-3} mole, b.p. 82-83° at 12 mm) and 10% v/v CH_3COOD-D_2O (3 ml) were introduced into a glass tube (1" in x 0.5 in). The sample was degassed three times by the freeze-pump-thaw method,

sealed and heated at 250° for 3 h. The slightly yellowish reaction mixture was diluted with water (3 ml), neutralized with solid sodium bicarbonate, saturated with NaCl and extracted with ether (4 x 20 ml). The ether extract was washed with water (4 x 25 ml) to remove the exchangeable O-D, dried, concentrated on the rotatory evaporator and quantitatively transferred into a 1 ml volumetric flask. Analytical g.l.p.c. (No. 393, I, 15% C, 140°) showed that the mixture was composed of 6.9% benzonorbornadiene, 11.7% endo-benzonorbornenol, 74.6% exo-benzonorbornenol, 6.1% benzonorbornenyl acetate and 0.7% of an unknown. Injection of several aliquots (0.05 ml) of the ether extract through the 5% SE-30 column established the isolable yield of pure exo-benzonorbornenol as 0.17 g (35%).

Deuterium assay mass spectrometrically (No. 122, 15 eV, Table 7 of Appendix C) established that exo-benzonorbornenol was composed of 3.4% d_3, 18.0% d_2, 73.2% d_1 and 5.4% d_0 species (1.20 atoms of deuterium per molecule).

The exo- and endo-benzonorbornenol from the above experiment containing 1.20 atoms of deuterium was treated with a fresh batch of 10% v/v CH_3COOD-D_2O for 12 h at 250°. Work-up in the usual manner yielded 0.1% benzonorbornadiene, 34.2% endo-benzonorbornenol, 64.2% exo-benzonorbornenol, 0.8% benzonorbornenyl acetate and 0.7% of an unknown.

Deuterium assay mass spectrometrically (No. 123, 15 eV, Table 7 of Appendix C) established that exo-benzonorbornenol was composed of 1.2% d_6, 6.3% d_5, 22.5% d_4, 36.2% d_3, 24.2% d_2, 7.7% d_1 and 1.9% d_0 species (2.95 atoms of deuterium). N.m.r. (No. 220, CCl_4), area integral analysis using the O-H as an internal standard established the following deuterium distribution, 2.00 d in aromatic ring and 1.00 d at C-3 and C-7 (a total of 3.00 atoms of deuterium).

B. Aromatic Systems

1. H-D Exchange of Aniline Hydrochloride (70) in Heavy Water Stability of Aniline Hydrochloride at 275°

Freshly recrystallized aniline hydrochloride (methanol, Eastman Organic Chemicals, 1.42 g, 1.11×10^{-2} mole, m.p. 196-199°) and water (20 ml) were introduced into a glass tube. This sample was degassed three times by the freeze-pump-thaw method, sealed and heated at 275° (840-850 psi) in the Pressure Reaction Apparatus (Parr Instrument Co., Model 4914) filled with water (200 ml) to equalize the pressure in the glass tube. After 24 h, the dark two-phase reaction mixture was basified with conc. NaOH and extracted with ether (4 x 10 ml). The aqueous layer was acidified with 50% v/v conc. HCl-H_2O, saturated with sodium chloride and extracted with ether (5 x 10 ml). These ether extracts were dried, concentrated by distillation of most of the ether through a glass helicies column. The residue was evaporated to dryness on a watch glass giving a pale brown solid (0.33 g, 31%) that was identified as phenol: n.m.r. (No. 243, CCl_4), δ 7.32-6.65 (m, 5H, aromatic) and 5.90 (s, 1H, O-H); i.r. (No. 195, CCl_4), 3610 (sharp, free O-H), 3350 (broad, H-bonded O-H), 3045 (aryl-H), 1600 (aryl C-C), 1246 (C-O) and 690 cm^{-1} (aryl C-H). The n.m.r. and i.r. spectra were identical to those of an authentic sample of phenol. The original ethereal layer was washed with 10% aq. HCl (4 x 8 ml), dried and evaporated to yield unidentified organic compound(s) (0.032 g). The combined aqueous hydrochloric extracts were basified with concentrated sodium hydroxide and extracted with ether (5 x 10 ml). The combined ether extracts were washed with water (2 x 15 ml), brine solution (1 x 10 ml), dried, concentrated on the rotatory evaporator and pumped to

dryness on the vacuum pump to yield pure aniline (0.45 g, 44%, >95% pure by n.m.r.): n.m.r. (No. 244, CCl_4, Fig. 4, Appendix D), δ 6.99 (triplet with fine structure, 2H, meta-protons), 6.59 (doublet with fine structure, 1H, para-proton), 6.44 (m, 2H, ortho-protons), and 3.36 (sharp s, 2H, $-NH_2$); i.r. (No. 196, CCl_4), 3460 and 3390 (d, $-NH_2$), 3040 (aryl C-H), 1625 ($-NH_2$), 1600 (aryl C-C), 1275 (C-N), 1175 (C-N), and 690 cm^{-1} (aryl C-H). The i.r. and n.m.r. spectra were identical to those obtained on an authentic sample of aniline.

Back-exchange of Aromatic Protons on g.l.p.c. Column

As in the previous experiment, recrystallized aniline hydrochloride (methanol, Eastman Organic Chemicals, 0.89 g, 6.85×10^{-3} mole, m.p. 196-199°) was heated with deuterium oxide (12 ml) in a sealed tube at 195° for 6 h. After the usual work-up, aniline (0.516 g, 81%) was obtained but no phenol. Analytical g.l.p.c. (No. 426, 427, I, 10% C, 130°) of the aniline extract established that aniline was the only product. The amino protons were back-exchanged in the work-up and used as an internal standard in the n.m.r. (No. 239, CCl_4) integral analysis of the crude aniline and showed the following deuterium distribution: 1.90 ortho, 0.20 meta, 0.95 para (a total of 3.05 D/molecule). The crude aniline was collected by preparative g.l.p.c. (No. 104, II, 15% C, 175°) for further n.m.r. integral analysis. Using the meta protons as an internal standard, n.m.r. (No. 240, CCl_4) established the following deuterium distribution: 1.10 ortho, 0.20 meta, 0.60 para and 1.20 amino (a total of 3.10 D/molecule). Clearly, by passing the aniline through the 15% Carbowax column scrambles the deuterium from the ortho- and para- positions is exchanged to the amino group. In fact the ortho- and para-positions lost 1.10 deuterium atoms /molecule while the amino group picked up 1.20 deuterium

atoms/molecule. Initially the same column and column conditions did not result in any back-exchange of the ortho- and para-protons. Thus deuterium analysis should be carried out on the crude aniline by n.m.r. or mass spectrometry and care should be exercized in establishing the conditions for preparative g.l.p.c. work.

Exchange in Heavy Water

Recrystallized aniline hydrochloride (Eastman Organic Chemicals, 1.42 g, 1.11×10^{-2} mole, m.p. 196-199°) and deuterium oxide (15 ml) were introduced into a glass tube (11 in x 1 in). The sample was degassed three times by the freeze-pump-thaw method, sealed and heated at 250°C in the Pressure Reaction Apparatus. After 35 h the one phase pale yellow solution was basified with solid sodium hydroxide and extracted with ether (4 x 10 ml). The aqueous layer was acidified with 50% v/v conc. HCl-H_2O, saturated with sodium chloride and extracted with ether (5 x 10 ml). The combined ether extracts were dried and the solvent was removed by distilling through a glass helicies column to yield perdeuterated phenol (0.029 g, 3%). The hydroxy hydrogen was back-exchanged in the work-up and used as an internal standard in the n.m.r. integral analysis which showed that 4.55 deuterium atoms (91% exchange) had been incorporated into the phenol. The ethereal layer was washed with 10% aq. HCl (4 x 8 ml), dried and evaporated to yield traces of organic material. The combined aqueous hydrochloric extracts were basified with concentrated sodium hydroxide and extracted with ether (5 x 10 ml). The combined ether extracts were washed with water (2 x 15 ml), dried, concentrated on the rotatory evaporator and pumped to dryness on the vacuum pump to yield pure aniline (0.74 g, 72%, ≥95% pure). The amino protons were back-exchanged in the work-up and used as an internal standard

in the n.m.r. integral analysis which showed that 1.90, 1.75 and 0.95 deuterium atoms had been incorporated into the ortho-, meta-, and para-positions, respectively, a total of 4.60 deuterium atoms per molecule (92% exchange).

II. Deuterium Exchange in Phenol (26)

(i) Exchange in 10% v/v CH_3COOD-D_2O

Phenol (0.77 g, 8.25×10^{-3} mole) and 10% v/v CH_3COOD-D_2O (3 ml) were introduced into a glass tube (11 in x 0.5 in). The sample was degassed three times by the freeze-pump-thaw method, sealed and heated at 260° for 53 h. The colourless reaction mixture was diluted with water (3 ml), neutralized with solid sodium bicarbonate, saturated with NaCl and extracted with ether (4 x 10 ml). The ether extract was washed with a saturated sodium chloride solution (4 x 10 ml) to remove the exchangeable O-D, dried, concentrated by distillation through a 12 inch glass helicies column and quantitatively transferred into a 2 ml volumetric flask. Analytical g.l.p.c. (No. 409(410), I, 5% SE-30 (10% C), 120°(170°)) showed that phenol was the only product. Injection of several aliquots (0.06 ml) of the ether extract through a 15% Carbowax column (170°) established the recovered yield as 0.33 g (43%): corrected for collection losses, 0.55 g (72%). (see Appendix A).

Deuterium-assay mass spectrometrically (No. 139, 15 eV, Table 9 of Appendix C) established that the phenol was composed of 5.3% d_4, 55.7% d_3, 31.0% d_2, 6.6% d_1 and 1.5% d_0 species (2.55 atoms of deuterium, 51% exchange).

N.m.r. (No. 223, CCl_4; Fig. 9 of Appendix D) integral analysis of the phenol isolated by preparative g.l.p.c. and using O-H as an internal standard, showed that there were 2.5 D in the ortho- and para-positions and a negligible amount of deuterium in the meta-positions, in agreement with the mass spectrometric results. Comparison of the spectra of the un-

deuterated phenol (No. 222, CCl_4; Fig. 8 of Appendix D) and the phenol-2,4,6-d_3 (No. 223, CCl_4; Fig. 9 of Appendix D) clearly shows how the deuterium has simplified the complex spectrum of the phenol.

(ii) Exchange in 4% v/v conc. HCl-D_2O at 200°

Phenol (0.22 g, 2.34×10^{-3} mole) was treated with 4% v/v conc. HCl-D_2O (4 ml) for 48 h at 200° in the Pressure Reaction Apparatus. After cooling, the clear, colourless two-phase reaction mixture was poured into water (5 ml), basified with solid $NaHCO_3$ and extracted with ether (4×10 ml). The combined ether extracts were washed with dilute aqueous HCl (2×10 ml), saturated sodium chloride solution (1×10 ml), dried and concentrated on the rotatory evaporator. Final traces of solvent were removed on the vacuum line to yield a white solid (0.21 g, 95%). Analytical g.l.p.c. established that phenol was the only product.

Deuterium assay mass spectrometrically (No. 164, 15 eV, Table 9 of Appendix C) established that the phenol was composed of 29.0% d_5, 40.3% d_4, 22.5 % d_3, 6.7 % d_2 and 1.5 % d_1 species, a total of 3.90 deuterium atoms per molecule (78% exchange). Using O-H as an internal standard, n.m.r. (No. 268, CCl_4) established the following deuterium distribution: 2.7 D in the ortho and para-positions and only 1.3 D in the meta-positions, a total of 4.0 deuterium atoms per molecule. These results clearly indicated that the aromatic ring has not been equilibrated under these reaction conditions. A longer reaction period or an increase in the temperature, however, would accomplish complete deuteration of phenol in at least 90-95% yield.

III. Deuterium Exchange in Benzene, Biphenyl, o- and m-Xylene

(i) Benzene (84)

Attempted Exchange in 10% v/v CH_3COOD-D_2O at 250°

Benzene (3.0 g, 3.85×10^{-2} mole) and 10% v/v CH_3COOD-D_2O (15 ml) were introduced into a glass tube (11 in x 0.5 in). The sample was degassed three times by the freeze-pump-thaw method, sealed and heated at 250° for 60 h. After the usual work-up of neutralization and extraction, analytical g.l.p.c. analysis (No. 243, I, 10% C, 120°) of the concentrated extract showed benzene as the only product.

Deuterium assay mass spectrometrically (No. 74, 15 eV, Table 8 of Appendix C) showed that no deuterium had been incorporated into benzene.

Exchange in 4% v/v conc. HCl-D_2O at 250°

Benzene (0.622 g, 7.96×10^{-3} mole) and 4% v/v conc. HCl-D_2O (15 ml) in a glass tube was degassed three times, sealed and heated at 250° in the Pressure Reaction Apparatus. After 48 h, the organic layer was withdrawn from the colourless, two-phase reaction mixture to yield benzene (0.61 g, 98%, >95% pure by g.l.p.c.); the n.m.r. (No. 258, CCl_4) and i.r. (No. 203, CCl_4) spectra of the sample indicated that considerable H-D exchange had occurred.

Deuterium assay mass spectrometrically (No. 154, 15 eV, Table 8 of Appendix C) of the benzene isolated by preparative g.l.p.c. (No. 108, II, 15% C, 90°) established the following deuterium distribution: 50.4% d_6, 32.4% d_5, 12.0% d_4, 3.3% d_3 and 1.9% d_2 species, a total of 5.25 deuterium atoms per molecule (88% exchange).

(ii) Biphenyl (85)

Attempted Exchange in 10% v/v CH_3COOD-D_2O at 250°

Biphenyl (Eastman Organic Chemicals, 0.23 g, 1.47×10^{-3} mole, m.p. 80°) and 10% v/v CH_3COOD-D_2O (4 ml) were introduced into a glass tube (11 in x 0.5 in). The sample was degassed three times, sealed and heated

at 250°C for 48 h. After the usual work-up of neutralization with solid $NaHCO_3$ and extraction with ether, the dried extract was concentrated on the rotatory evaporator. Analytical g.l.p.c. (No. 400, I, 5% SE-30, 150°) showed that biphenyl was the only product.

Deuterium assay mass spectrometrically (No. 130, 15 eV, Table 8 of Appendix C) established that no deterium had been incorporated into biphenyl.

Exchange in 4% v/v conc. HCl-D_2O at 250°

Biphenyl (Eastman Organic Chemicals, 0.39 g, 2.51 x 10^{-3} mole, m.p. 80°) and 4% v/v conc. HCl-D_2O (15 ml) were heated in a sealed tube at 250° for 48 h. After cooling, the reaction mixture, containing a white solid, was neutralized with solid $NaHCO_3$ and extracted with ether (4 x 15 ml). The combined ether extracts were dried and concentrated on the rotatory evaporator. Final traces of solvent were removed by pumping on the vacuum line, to yield white crystalline biphenyl (0.38 g, 98%, m.p. 79-81°, lit. m.p. 80°[197]). Analytical g.l.p.c. (No. 411, I, 10% C, 190°) showed that the biphenyl was >99% pure.

Deuterium assay mass spectrometrically (No. 155, 15 eV, Table 8 of Appendix C) established that biphenyl was composed of 55.3% d_{10}, 33.7% d_9 and 8.2% d_8 species, a total of 9.40 deuterium atoms per molecule (94% exchange).

N.m.r. (No. 254, CCl_4) area integration showed that the ratio of ortho:meta:para signals was 2:2:1, indicating that equilibrium had been reached.

(iii) m-Xylene (87)

Exchange in 10% v/v CH_3COOD-D_2O at 250°

m-Xylene (Matheson, Coleman and Bell, 0.29 g, 2.74 x 10^{-3} mole)

and 10% v/v CH_3COOD-D_2O (4 ml) were introduced into a glass tube (11 in x 0.5 in). The sample was degassed three times by the freeze-pump-thaw method, sealed and heated at 250° for 48 h. The colourless reaction mixture was diluted with water (4 ml), neutralized with solid sodium bicarbonate and extracted with ether (4 x 10 ml). The ether extract was dried and concentrated on the rotatory evaporator. Analytical g.l.p.c. (No. 402, I, 10% C, 85°) showed m-xylene as the only product.

Some of the m-xylene, isolated by preparative g.l.p.c. (No. ~~95~~ II, 10% C, 100°) was subjected to mass spectrometric deuterium assay (No. 128, 15 eV), Table 10 of Appendix C) which established that m-xylene was composed of 6.9% d_3, 19.3% d_2, 35.1% d_1 and 38.7% d_0 species (0.95 atoms of deuterium per molecule).

Exchange in 4% v/v conc. HCl-D_2O.

m-Xylene (1.00 g, 9.45 x 10^{-3} mole) was treated with 4% v/v conc. HCl-D_2O (15 ml) for 40 h at 250° as described above. After cooling, the colourless organic layer was withdrawn from the two-phase reaction mixture with a pipette to give m-xylene (0.97 g, 97%). Analytical g.l.p.c. (No. 432, I, 5% SE-30, 100°) established that it was >99% pure.

Deuterium assay mass spectrometrically (No. 156, 15 eV, Table 10 of Appendix C) established that the m-xylene was composed of 5.7% d_5, 72.7% d_4, 17.2% d_3 and 4.4% d_2 species (3.80 D/molecule). N.m.r. (No. 257, CCl_4) integral analysis, using methanol as an internal standard, showed that there were 3.6 deuterium atoms in the aromatic ring (91% exchange) and 0.3 deuterium atoms in the methyl groups. N.m.r. analysis also indicated that the four positions in the aromatic ring had been equilibrated (Fig. 13 and 15 of Appendix D).

Check for Isomerization of m-Xylene

m-Xylene (Matheson, Coleman and Bell, 0.45 g, 4.25×10^{-3} mole) and 10% v/v CH_3COOH-1% conc. HCl-H_2O (5 ml) were introduced into a glass tube (11" in x 0.5 in). The sample was degassed three times by the freeze-pump-thaw method, sealed and heated at 250° for 48 h. The colourless reaction mixture was diluted with water (5 ml), neutralized with solid sodium bicarbonate and extracted with ether (4 x 10 ml). The combined ether extracts were dried and concentrated on the rotatory evaporator. Last traces of solvent were removed by the vacuum pump to yield m-xylene (0.43 g, 94%). Analytical g.l.p.c. (No. 402, 1, 10% C, 85°) analysis showed that there was only one product present, m-xylene. N.m.r. and i.r. analysis corroborated this evidence. The i.r. (No. 209, neat) with bands at 1170, 1095, 1045, 906, 875, 770 and 690 cm^{-1} in the fingerprint region was identical to an authentic sample of m-xylene (No. 206, neat) which was different and thus distinguishable from the o- and m-isomers. The n.m.r. (No. 225, CCl_4) of the product was also identical to an authentic sample of m-xylene (Fig. 13 of Appendix D), δ 7.08-6.62 (m, 4H, aromatic) and 2.28 (sharp s, 6H, methyl). The aromatic protons of o- and p-xylene consist of a sharp singlet at 6.95 and 6.90 ppm respectively.

(iv) o-Xylene (86)

Large-Scale Exchange in 4% v/v conc. DCl-D_2O at 250°

o-Xylene (J. T. Baker Chem. Co., 50 g, 0.47 mole, b.p. 143-4°) and 4% v/v conc. DCl-D_2O (diluting 38% wt/wt DCl-D_2O, 200 ml) were added to the Pressure Reaction Apparatus fitted with a glass liner. After heating at 250° for 43 h, the two-phase solution was poured into a separatory funnel. The brown aqueous phase was withdrawn, to yield a yellowish o-xylene (46 g,

g.l.p.c. (No. 432, I, 5% SE-30, 100°)]. The o-xylene (b.p. 144°) has a longer retention time than both the m- and p-xylene (b.p. 139° and 138°, respectively) under the conditions used. Using anhydrous methanol as an internal standard, n.m.r. integral analysis established that there were 3.50 deuterium atoms in the aromatic ring (88% exchange) and no deuterium in the methyl groups.

The above deuterated o-xylene (46 g) was divided into two equal portions and introduced into two separate glass tubes and treated with fresh 4% v/v conc. DCl-D_2O (70 ml into each tube). The tubes were degassed three times by the freeze-pump-thaw method, sealed and heated at 250° for 42 h. After cooling, the two reaction mixtures were combined, poured into a separatory funnel, and separated from the aqueous phase to yield o-xylene (46 g, 100% yield, >98% pure by g.l.p.c.).

Deuterium assay mass spectrometrically (No. 158, 15 eV, Table 10 of Appendix C) established that the o-xylene was composed of 3.7% d_5, 87.3% d_4, 4.7% d_3 and 4.3% d_2, a total of 3.90 deuterium atoms per molecule. N.m.r. (No. 260, CCl_4) integration, using anhydrous methanol as an internal standard, established that there were 3.90 deuterium atoms in the aromatic ring (98% exchange) and 0.06 deuterium atoms in the methyl groups.

Check for Isomerization of o-Xylene

o-Xylene (J. T. Baker Chem. Co., 0.21 g; 2.0×10^{-3} mole) and 4% v/v conc. HCl-H_2O (3 ml) were introduced into a glass tube, degassed thrice, sealed and heated at 250° for 65 h. After cooling, the colourless organic layer was withdrawn with a pipette to give 0.20 g (95% yield) of product. Analytical g.l.p.c. (No. 432, I, 5% SE-30, 100°) established that o-xylene only was present with a purity >98%. m- and p-Xylene which have b.p.'s of

139° and 138°, respectively, have the same but lower retention times than o-xylene (b.p. 144°), under the column conditions used. Corroborating evidence for the identity of o-xylene is given by the i.r. and n.m.r. data. I.r. (No. 208, neat) with bands at 1120, 1054, 1022, 985 and 740 cm^{-1} in the fingerprint region was identical to an authentic sample of o-xylene (No. 207, neat) and distinguishable from both the m- and p-xylene. The n.m.r. spectrum (No. 274, CCl_4), τ 6.95 (sharp s, 4H, aromatic) and 2.20 (s, 6H, methyl) was also identical to that of an authentic sample.

IV. Deuterium Exchange in Benzoic Acid (101)

Benzoic acid (Fisher Scientific Co., 0.30 g, 2.46×10^{-3} mole, m.p. 118-119°) and 4% v/v conc. HCl-D_2O (10 ml) were introduced into a glass tube. The sample was degassed thrice, sealed and heated at 275° in the Parr Pressure Reaction Apparatus. After 75 h and cooling, the fine white crystalline solid was collected by suction filtration from the colourless aqueous phase, and then dissolved in 5% NaOH (10 ml). The basic aqueous phase was washed with ether (3 x 10 ml) and then acidified with 15% conc. HCl-H_2O to yield a precipitate which was extracted with ether (3 x 10 ml). This ether extract was dried, evaporated on the rotatory evaporator, and pumped on the vacuum line to yield benzoic acid (0.29 g, 97%, m.p. 118-118.5°).

Using the O-H as an internal standard, n.m.r. integral analysis established that there were 4.7 deuterium atoms per molecule, corresponding to 94% exchange in one cycle.

V. Deuterium Exchange in Pyridine (102)

Exchange in 4% v/v HCl-D_2O at 250°

Pyridine (0.60 g, 7.6×10^{-3} mole) and 4% v/v conc. HCl-D_2O (5 ml)

were introduced into a glass tube (10 in x 0.5 in). The sample was degassed three times by the freeze-pump-thaw method, sealed and heated at 250° in the Pressure Reaction Apparatus. After 48 h, the cooled black reaction mixture was basified with solid sodium bicarbonate, extracted with ether (4 x 15 ml), dried and concentrated on the rotatory evaporator. The dark brown extract was quantitatively into a 1 ml volumetric flask and made up to volume. G.l.p.c. analysis (No. 413, I, 10% C, 110°) established that the extract contained pyridine (95%) and three unidentified products (5%).

Preparative g.l.p.c. (No. 99, 15% C, 110°) using a liquid air cooled U-tube, established that the isolable yield of pyridine was 0.14 g (23%). Mass spectrometry (No. 147, 15 eV, Table 9 of Appendix C) of the pyridine collected by g.l.p.c. established that it was composed of 45.7% d_5, 36.4% d_4, 14.3% d_3, and 3.6% d_2 species, a total of 4.25 deuterium atoms per molecule (84% exchange). N.m.r. (No. 230, CCl_4) integral analysis showed that all the aromatic positions had been equilibrated.

Exchange in 1% v/v HCl-D_2O at 245°

Pyridine (5.76 g, 7.3×10^{-2} mole) was treated with 1% v/v conc. HCl-D_2O (30 ml) for 40 h at 245° as described above. The pale yellow reaction mixture was basified with solid $NaHCO_3$, saturated with NaCl and extracted with ether (4 x 10 ml). The combined ether extracts were dried and the solvent was stripped off by distillation. Vacuum distillation at 54° (120 mm) gave 3.4 g (60%) of pyridine. N.m.r. (No. 278 and 279, CCl_4) integral analysis using anhydrous methanol as an internal standard established the following deuterium distribution: 1.9, 0.1 and 0.0 deuterium atoms (40% exchange) in the 2,6, 3,5 and 4 positions, respectively.

APPENDIX A

G.l.p.c. Collection Loss Determinations

Preparative g.l.p.c. collection losses were determined by injecting various concentrations of a standard solution of a substrate into a preparative g.l.p.c., weighing the substrate collected and consequently determining the % recovery of the substrate at the varipus concentrations. The yield of a particular product from a solvolysis reaction was obtained by collecting the material by preparative g.l.p.c., weighing it and correcting the amount according to the previously determined % recovery data.

All results are based on the average of at least three or more reproducible injections using a 0.1 ml Lab-Crest syringe and a 15-ft x 3/8 in 15% Carbowax on Chromosorb W column.

Norcamphor (14)

Using the 15% Carbowax column at 175-180° with the injector and detector temperatures at 240 and 250° respectively and a helium flow rate of 35 ml/minute, the following results were obtained. For standard injections of 0.0045 g per 0.1 ml, 0.0097 g per 0.1 ml, 0.0130 g per 0.1 ml, and 0.0172 g/0.05 ml, the recovery, with an air-cooled straight glass tube (13 mm x 0.5 mm), was 0.0016 g (36%), 0.0056 g (58%), 0.0101 g (79%) and 0.0143 g (83%) respectively. The appropriate % recovery factor, determined from the weight of norcamphor collected per injection, was used for solutions containing norcamphor of unknown concentration. For example, from the "Solvolysis of Nortricyclanol in Deuterated Medium" (Section II-A-I), the injection of several aliquots (0.05 ml) of the pentane extract showed that 0.0160 g was collected

per injection. Assuming all the pentane extract (10 ml) was passed through the column, the total isolated yield of norcamphor would be 3.2 g ($\frac{0.016}{0.05} \times 10$), which corresponds to 27% ($\frac{3.2}{12.1} \times 100$). The g.l.p.c. collection loss studies showed that for the isolation of 0.016 g per injection, the % recovery is about 53%. Thus the corrected yield and % yield are 4.0 g ($\frac{3.2}{83} \times 100$) and 33% ($\frac{4.0}{12.1} \times 100$), respectively.

3-(Cyclohexene)carboxaldehyde (13)

Using the same column and g.l.p.c. conditions as in norcamphor, the following results were obtained. For a standard injection of 0.0061 g in 0.05 ml of pentane, the % recovery was 56% (0.0034 g) in an air-cooled U-tube and 62% (0.0038 g) in a U-tube plugged with glass wool. These results suggest that the % recovery is not significantly affected by the method of collection. For a standard injection of 0.0037 g in 0.1 ml of ether, the % recovery was 49% (0.0018 g in a liquid air cooled U-tube (13 mm x 0.5 mm). Henceforth, when the average weight of sample collected per injection, was in the range of 0.002 g, the 49% recovery factor was applied while the 60% recovery factor was used when approximately 0.004 g was collected per injection. For example, from the "Solvolysis of Nortricyclanol in Deuterated Medium" (section II-A-1), the injection of several aliquots (0.05 ml) of the pentane extract showed that 0.0053 g of aldehyde was collected per injection. Assuming all the pentane extract (10 ml) was passed through the column, the isolated yield of aldehyde would be 1.1 g ($\frac{0.0053}{0.05} \times 10$), which corresponds to 9% ($\frac{1.1}{12.1} \times 100$). The collection loss studies showed that for the isolation of 0.005 g/injection, the % recovery is about 60%. Thus the actual yield and % yield are 1.8 g ($\frac{1.1}{60} \times 100$) and 15% ($\frac{1.8}{12.1} \times 100$), respectively.

Since standard solutions of 2- and 3-(cyclopentene)acetaldehydes were

difficult to obtain, the results of 3-(cyclohexene)carboxaldehyde were used for collection loss calculations of the (cyclopentene)acetaldehydes.

exo-Norborneol (56)

Using a 15% Carbowax column at 160° with the injector and detector temperatures at 240 and 250° respectively, and a helium flow rate of 50 ml/minute, the following results were obtained. From a standard solution (0.2644 g/5 ml of ether), various sized aliquots (0.01 ml to 0.09 ml) were injected into the g.l.p.c. For injections of 0.0025 g, 0.0051 g, 0.0101 g, 0.0126 g, 0.0177 g, and 0.0228 g, the recovery was 0.0018 g (72%), 0.0044 g (86%), 0.0088 g (88%), 0.0106 g (84%), 0.0154 g (87%), and 0.0196 g (86%), respectively. Thus for the collection of 0.002 g to 0.020 g per injection, the % recovery is 86%.

A typical example of how the yield of norborneol is established via correction for collection losses is as illustrated in the section on Hydration of Norbornene at 250°. Injection of several aliquots (0.05 ml) of the ether extract (10 ml volumetric flask) showed that 0.0088 g was collected per injection. If all the ether extract (10 ml) was passed through the column, the isolable yield and % yield of norborneol would be 1.76 g ($\frac{0.0088}{0.05}$ x 10) and 29% ($\frac{1.76}{6.13}$ x 100), respectively. The collection loss determinations here established that for the isolation of 0.009 g/injection, the % recovery is 86%. Thus the yield and % yield, corrected for collection losses, are 2.05 g ($\frac{1.76}{86}$ x 100) and 33% ($\frac{2.05}{6.13}$ x 100), respectively.

Phenol (76)

With the column, injector and detector temperatures at 175, 200 and 200° respectively and a helium flow rate of 75 ml/minute, the following collection loss results were obtained using a U-tube (10 cm x 4 mm) cooled

in liquid air. From a standard solution (0.433 g of phenol in a 2 ml volumetric flask containing ether), various sized aliquots (0.01 ml to 0.09 ml) were injected into the g.l.p.c. For injections of 0.0022 g, 0.0065 g, 0.0105 g, 0.0151 g, and 0.0194 g, the recovery was 0.0011 g (50%), 0.0037 g (57%), 0.0068 g (63%), 0.0073 g (62%), and 0.0116 g (60%). Thus when the amount of phenol collected per injection is less than 0.004 g, the % recovery is 50% while if the amount of phenol collected per injection is >0.004 g, the % recovery is 60%.

From Exchange in 10% DOAc-D_2O (Section II-B-II), injection of several aliquots (0.06 ml) of the ether extract (2 ml, volumetric flask), established that 0.0100 g of phenol was collected per injection. For the total 2 ml extract, the isolable and % yield of phenol are 0.333 g ($\frac{0.0100}{0.06}$ x 2) and 43% ($\frac{0.33}{0.77}$ x 100), respectively. From the previously determined g.l.p.c. collection loss determinations, a recovery of 0.0100 g/injection corresponds to 60% recovery and hence the yield and % yield, corrected for collection losses, are 0.55 g ($\frac{0.33}{60}$ x 100) and 72% ($\frac{0.55}{0.77}$ x 100), respectively.

APPENDIX B

Deuterium Assay by Mass Spectrometry

Mass spectrometric deuterium analyses were carried out on a Hitachi-Perkin-Elmer RMU-6A spectrometer at 11 or 15 eV. Assay were determined by comparison of the relative peak heights of parent ions from labelled and unlabelled substrates. Isotopic distributions were calculated as described by Herstiuk.[198] Mass spectra were obtained on natural abundance (unlabolled) compounds to obtain values for M-3, M-2, M-1, M+1, M+2 and M+3 as listed below in Tables 1 and 2. A typical sample calculation is also illustrated. Appendix C gives the uncorrected intensities of all isotopic samples.

Table 1. Relative Abundances of Ions for Norbornyl and Aromatic Derivatives

Compound	M-3	M-2	M-1	M+1	M+2	M+3
Norcamphor (14)			7.75	8.27	0.81	
2- and 3-(Cyclopentene)acetaldehyde (14:85) (11+12)			27.7	12.60	4.94	
3-(Cyclohexene)carboxaldehyde (13)		3.30	7.49	8.77	1.08	
endo- and exo-2-Norbornyl acetate (80:20) (55)			2.00	11.14	1.19	
exo- and endo-2-Norbornyl acetate (3:1) (55)			2.17	11.13	1.10	
Nortricyclanol (9c)		2.10	18.90	8.50	1.00	
exo-Benzonorbornenol (65)		2.93	2.85	13.35		
2-Phenylnorbornane (60)			7.24	14.24	1.88	
Benzene (84)				7.00		
Biphenyl (85)	3.13	16.0	21.93	13.63		
Phenol (76)			1.63	7.13		
o-Xylene (86	2.92	2.92	22.58	10.54		
m-Xylene (87)	3.20	3.10	26.00	9.73		
Aniline (69)			5.05	8.85		
Pyridine (102)			11.20	6.00		

Table 2. Relative abundances of ions of norbornyl diacetates using M$^+$-43 ($CH_3-C^{=O}$) peaks (these diacetates were obtained from "Solvolysis of Nortricyclanol" in Section III-A-I(i)

m/e	Peak 1, No. 68	Peak 2, No. 71	Peak 3, No. 72
168(M-1)	-	5.10	21.00
169(M$^+$)	100.00	100.00	100.00
170(M+1)	13.40	47.44	50.50
171(M+2)	4.90	19.03	10.07
172(M+3)	3.90	13.89	7.00
173(M+4)	3.30	10.53	6.66
174(M+5)	-	4.16	2.30

No. refers to mass spectrum number.

Sample Calculation: Deuterated Norcamphor (M.S. No. 47)

m/e	polyisotopic spectrum	contribution to M+1	contribution to M+2	monoisotopic spectrum
110	22.20	-	-	22.20
111	100.00	1.84	-	98.16
112	73.40	8.12	0.18	65.10
113	38.60	5.38	0.80	32.42
114	15.30	2.68	0.53	12.09
115	4.70	1.00	0.26	3.44
116	1.10	0.28	0.10	0.72

m/e	monoisotopic spectrum	contribution to M-1	corrected intensities	% intensity[a]	deuterium content
116	0.72	-	0.72	-	-
115	3.44	0.06	3.38	1.6	0.080
114	12.09	0.26	11.83	5.4	0.216
113	32.42	0.92	31.50	14.5	0.435
112	65.10	2.44	62.66	28.8	0.576
111	98.16	4.86	93.30	42.9	0.429
110	22.20	7.23	14.97	6.9	
					1.75[b]

[a]Corrected intensities <2.5% are not included in the % intensity.

[b]All deuterium assays are rounded to 0.05 of one deuterium.

APPENDIX C

Mass Spectral Data (uncorrected relative intensities) of Deuterated Species*

*Throughout Appendix C, No. refers to the mass spectrum number and entry refers to the appropriate entry in the Results and Discussion.

Table 1. Uncorrected intensities of isotopic species for Table 1 of the Results and Discussion

m/e	Entry 4 No.15	Entry 11 No.26	Entry 11 No.24	Entry 11 No. 6	Entry 12 No.41	Entry 12 No.42	Entry 12 No.47	m/e	Entry 1 No.108	Entry 7 No.107
110	1.98	3.45	1.30	6.85	24.00	22.90	22.20	154	28.00	19.00
111	9.28	7.62	5.52	34.00	77.50	100.00	100.00	155	92.33	77.50
112	10.55	10.45	6.30	30.20	100.00	98.80	73.40	156	100.00	96.50
113	10:08	8.90	4.40	17.60	71.60	62.80	38.60	157	89.88	100.00
114	9.30	4.98	2.34	7.08	33.70	30,00	15.30	158	74.30	90.80
115	8.21	2.25	0.98	3.16	11.80	11.00	4.70	159	58.30	87.30
116	6.48	0.74	0.33	1.10	3.40	3.60	1.10	160	43.08	81.00
117	4.16							161	30.92	62.41
118	1.86							162	15.33	28.81
D/molecule	3.60	2.40	2.20	1.90	2.15	2.00	1.75		3.20	3.75

Spectra No.'s 15, 6 and 47 are norcamphor.

Spectra No.'s 26 and 41 are 2- and 3-(cyclopentene)acetaldehyde.

Spectra No.'s 24 and 42 are 3-(cyclohexene)carboxaldehyde.

Spectra No.'s 107 and 108 are the norbornyl acetates obtained from LAH reduction and acetylation of the norcamphor from which the enolizable deuterium was washed out.

Table 2. Uncorrected intensities of deuterated norcamphor for Table 2 of Results and Discussion

m/e	Entry 3 No. 112	Entry 6 No. 116	Entry 9 No. 114	Entry 13 No. 110
110	4.77	1.00	97.18	90.47
111	31.20	7.50	100.00	100.00
112	55.50	17.70	74.52	85.00
113	100.00	100.00	46.04	63.20
114	94.17	86.00	24.02	42.50
115	67.33	65.47	10.20	26.80
116	42.87	44.40	4.00	14.60
117	24.73	27.13	-	7.07
118	12.13	14.43	-	2.30
119	4.93	6.10	-	-
120	1.25	2.03	-	-
D/molecule[a]	3.9	4.3	-	-
Enolizable D[b]	1.3	1.5	-	-
D/molecule[c]	2.6	2.8	1.50	2.05

[a] D/molecule in norcamphor which includes the enolizable deuterium.

[b] These values were determined by n.m.r. integral analysis of the corresponding endo-norborneol in the presence of $Eu(DPM)_3$.

[c] D/molecule in norcamphor which does not include the enolizable deuterium.

Table 3. Uncorrected intensities of ions from deuterated nortricyclanol (No. 57) and norbornyl diacetates (No.'s 70,60 and 59) which were obtained from "A Check of the Deuterium Content in Nortricyclanol and the Norbornanediols" (Experimental, II-A-1(i)).

m/e	No. 57	m/e	Peak 1, No. 70	Peak 2, No. 60	Peak 3, No. 59
110	38.55	169	5.73	7.90	24.12
111	100.00	170	100.00	100.00	100.00
112	28.20	171	31.25	59.83	67.84
113	5.93	172	6.00	17.33	19.70
114	2.10	173	1.00	4.80	5.00
D/molecule	1.00		1.10	1.10	1.10

Table 4. Uncorrected intensities of ions from norcamphor (obtained from "Check for Acid-catalyzed Homoenolization" (Experimental, III-A-1(viii)).

m/e	No. 16	No. 17	No. 19
110	7.45	7.10	5.78
111	11.52	2.92	0.76
112	2.28	0.42	0.12
113	0.14	-	-
D/molecule	0.75	0.30	0.05

Table 5. Uncorrected intensities of ions from deuterated 2- and 3-(cyclopentene)-acetaldehyde (No. 62), 3-(cyclohexene)carboxaldehyde (No. 54), and norcamphor (No. 51) which were obtained from "Hydration of Norbornadiene at 250°" (Table 4 of Results and Discussion).

m/e	No. 62	No. 54	No. 51
110	6.73	13.78	9.50
111	51.68	30.83	36.20
112	100.00	100.00	100.00
113	85.63	77.75	60.10
114	44.68	40.85	27.00
115	16.75	16.25	10.50
116	4.95	5.55	4.10
D/molecule	2.55	2.60	2.40

Table 6. Uncorrected intensities of ions from a deuterated exo- and endo-norbornyl acetate mixture (ca. 80:20) (Tables 7 and 8 of Results and Discussion)

m/e	Entry 1 No. 85	Entry 2 No. 93	Entry 3, No. 96	Entry 4 No. 88	Entry 5 No. 77	Entry 7 No. 80	Entry 8 No. 92	Entry 1* No. 94	Entry 2* No. 98	Entry 3* No. 97	Entry 4* No. 99
154	6.16	15.53	-	-	-	3.65	-	-	-	-	-
155	100.00	88.33	-	-	-	-	-	-	-	-	-
156	58.53	72.40	-	-	-	-	-	-	-	-	-
157	44.40	56.40	-	-	-	-	-	-	-	-	-
158	32.23	46.40	-	-	-	-	-	-	-	-	-
159	17.43	47.20	-	-	-	-	-	1.52	-	-	-
160	8.07	60.33	1.70	3.0	1.33	-	-	20.40	-	1.13	-
161	3.00	66.53	6.00	11.67	5.33	2.08	5.17	5.60	-	5.87	-
162	-	83.93	21.67	34.67	19.67	8.00	20.20	10.80	11.50	22.07	3.16
163	-	100.00	58.83	75.00	56.33	31.78	56.23	38.78	42.00	59.47	16.47
164	-	90.16	100.00	100.00	100.00	80.85	100.00	92.20	93.90	100.00	57.10
165	-	38.66	79.17	65.37	87.73	100.00	78.67	100.00	100.00	76.23	100.00
166	-	-	-	7.93	9.33	10.96	-	-	9.10	-	9.90
D/molecule	2.20	5.90	9.80	9.55	9.90	10.05	9.85	9.80	10.25	9.80	10.45

*Refer to Table 8 of the Results and Discussion.

Table 7. Uncorrected intensities of ions from exo-benzonorbornenol (No.'s 122, 123, and 124) and 2-phenylnorbornane (No.'s 137 and 153) (for Tables 9 and 10 of the Results and Discussion)

m/e	Entry 1 No. 122	Entry 3 No. 123	Entry 4 No. 124
159	2.10	-	-
160	11.00	6.90	1.80
161	100.00	24.33	6.20
162	37.33	67.00	15.67
163	7.76	100.00	44.87
164	1.25	68.13	90.60
165	-	23.20	100.00
166	-	5.00	44.80
167	-	-	6.57
D/molecule	1.20	2.95	4.30

m/e	Entry 2 No. 137	Entry 4 No. 153
172	50.07	23.57
173	92.10	53.13
174	100.00	62.27
175	83.00	38.6
176	66.10	26.07
177	57.80	27.47
178	52.87	63.73
179	44.13	100.00
180	33.20	36.77
181	23.40	9.03
182	14.77	3.17
183	7.00	-
184	2.40	-
D/molecule	3.80	4.40

Table 8. Uncorrected intensities of ions from benzene (No.'s 74, 154, 159 and 161) and biphenyl (No.'s 130, 155, 163 and 165) for Table 13 of the Results and Discussion

m/e	Entry 1 No. 74	Entry 2 No. 154	Entry 3 No. 159	Entry 4 No. 161	m/e	Entry 5 No. 130	Entry 6 No. 155	Entry 7 No. 163	Entry 8 No. 165
78	100.00	-	100.00	100.00	151	3.13	-	-	2.40
79	7.00	1.36	37.41	41.30	152	16.00	-	-	9.47
80	-	3.70	18.28	8.40	153	21.93	-	-	21.03
81	-	6.42	15.15	1.00	154	100.00	-	8.60	100.00
82	-	23.28	13.75	-	155	13.63	-	24.10	60.67
83	-	63.04	10.90	-	156	-	-	52.33	20.10
84	-	100.00	5.90	-	157	-	-	84.33	4.33
85	-	7.32	-	-	158	-	1.90	100.00	-
D/molecule	0.00	5.25	1.25	0.35	159	-	4.00	82.50	-
					160	-	9.20	41.87	-
					161	-	16.10	10.00	-
					162	-	41.65	1.53	-
					163	-	79.75	-	-
					164	-	100.00	-	-
					165	-	13.80	-	-
					D/molecule	0.00	9.40	4.05	0.50

Table 9. Uncorrected intensities of ions from deuterated phenol (Nos. 139, 140, 164 and 166), and pyridine (No. 147) for Table 12 of the Results and Discussion and for Exchange in Pyridine (II-B-V)

m/e	Entry 1 No. 139	Entry 2 No. 140	Entry 3 No. 164	Entry 4 No. 166	m/e	No. 147
94	2.67	2.65	0.90	1.73	79	2.20
95	12.33	4.70	3.95	8.07	80	2.20
96	55.81	12.68	16.90	33.27	81	10.92
97	100.00	56.10	55.75	100.00	82	38.60
98	16.00	100.00	100.00	51.73	83	88.44
99	1.93	83.18	75.33	9.00	84	100.00
100	-	10.80	8.93	-	85	5.80
D/molecule	2.55	3.90	3.90	3.05		4.25

Table 10. Uncorrected intensities of ions from deuterated o-xylene and m-xylene for the results listed in Table 15 of the Results and Discussion

m/e	Entry 9	Entry 10 No. 158	Entry 11 No. 128	Entry 12 No. 156	Entry 13 No. 160	Entry 14 No. 162
104	Deuterium content determined by n.m.r.	-	6.00	-	-	-
105		-	27.20	-	-	-
106		2.90	100.00	2.10	4.60	2.95
107		3.25	92.73	4.25	12.35	10.68
108		9.20	51.50	14.93	42.00	37.51
109		28.00	18.47	48.08	100.00	100.00
110		100.00	2.00	100.00	56.53	16.78
111		14.40	-	16.80	5.55	1.06
112		1.00	-	1.58	-	-
113						
D/molecule	3.50	3.90	0.95	3.80	3.15	2.85

APPENDIX D

I.r. and N.m.r. Spectra

(Figures 1 to 15)

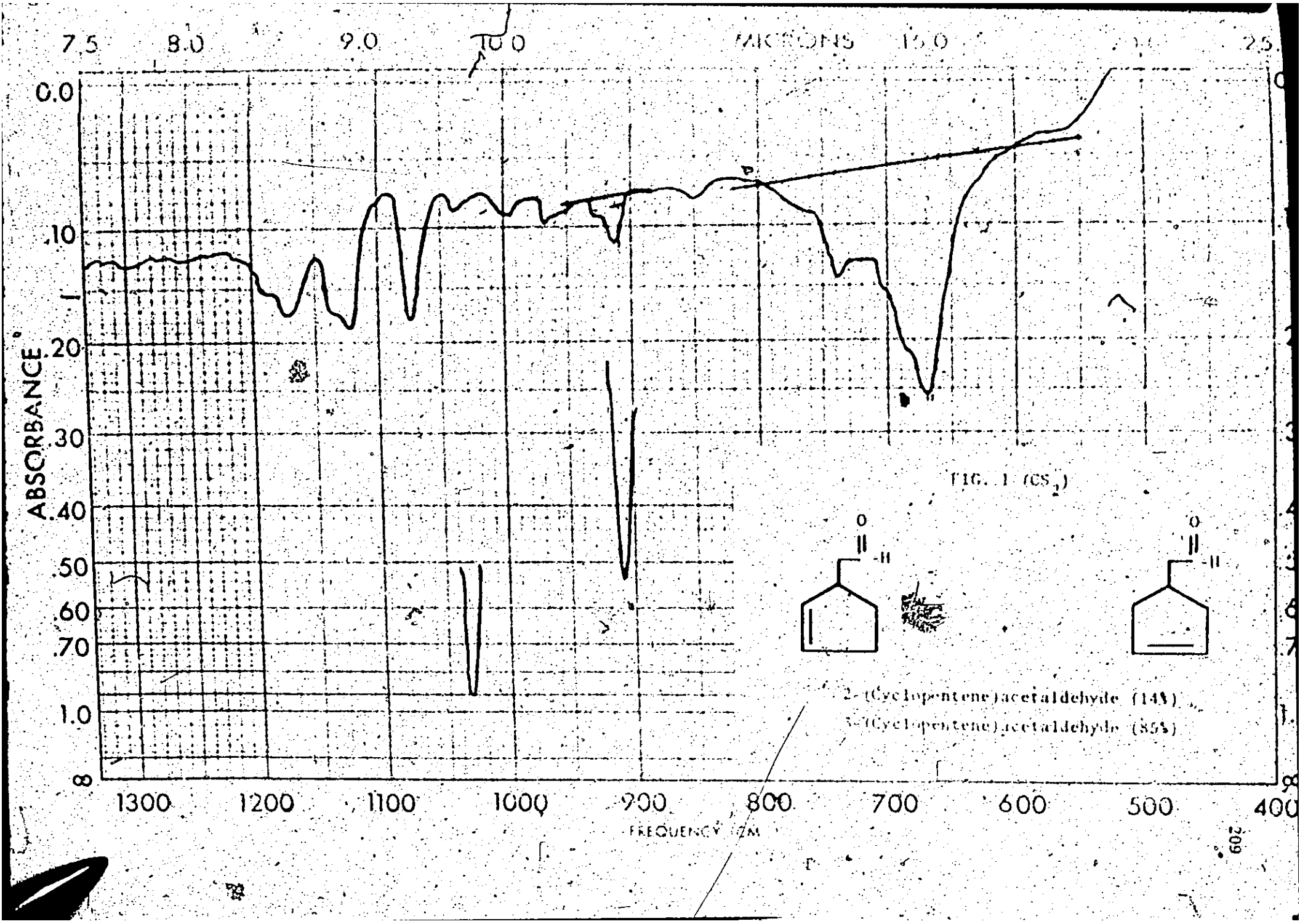
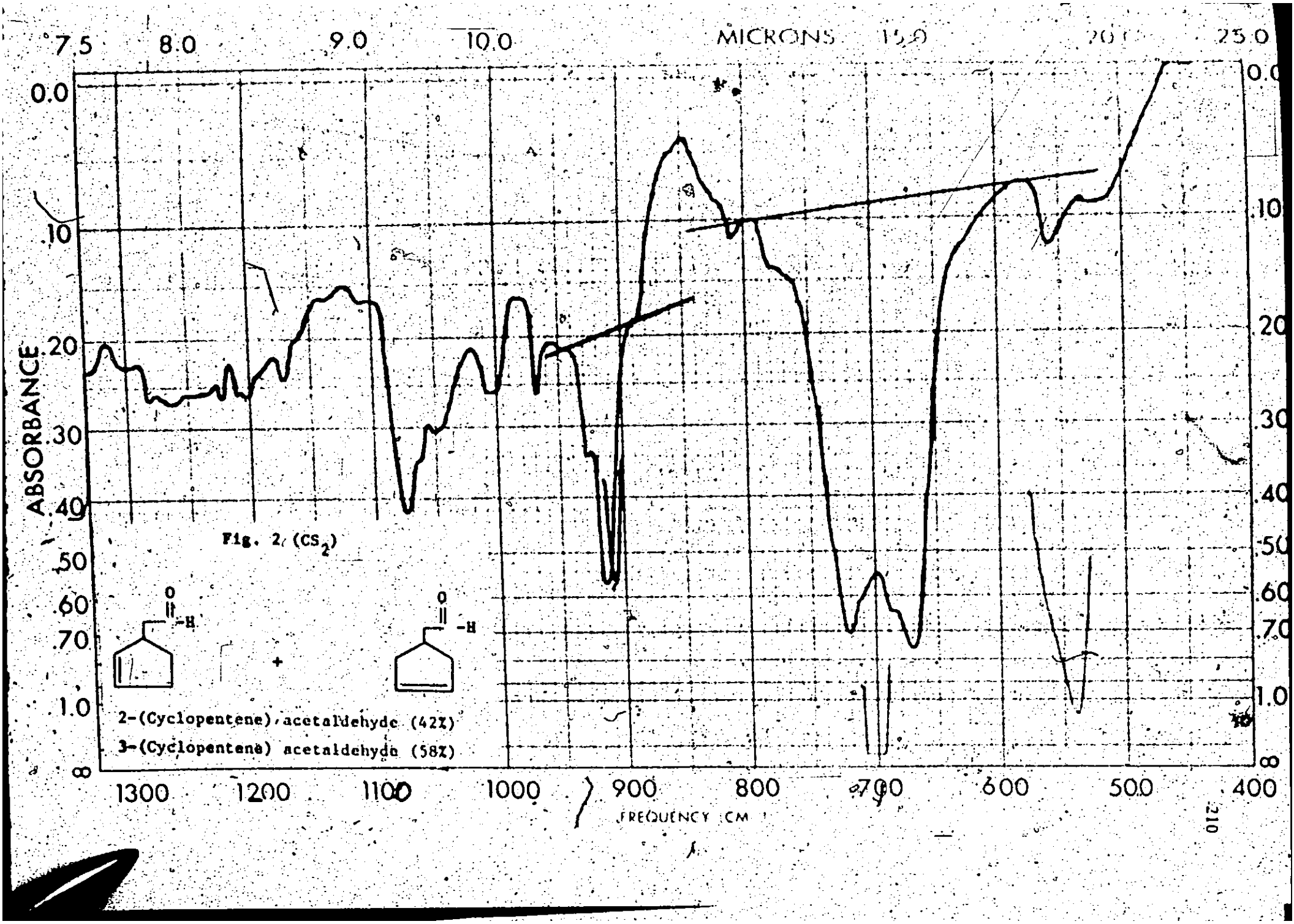


FIG. 1 (CS_2)

2-(Cyclopentene)acetaldehyde (14%)

3-(Cyclopentene)acetaldehyde (86%)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8.0
9.0
10.0
MICRONS
15.0
20
25.0
0.0
.10
.20
.30
.40
.50
.60
.70
1.0
ABSORBANCE
1300
1200
1100
1000
900
800
700
600
500
400
FREQUENCY CM⁻¹
2-(Cyclopentene) acetaldehyde (42%)
3-(Cyclopentene) acetaldehyde (58%)

Fig. 2, (CS_2)

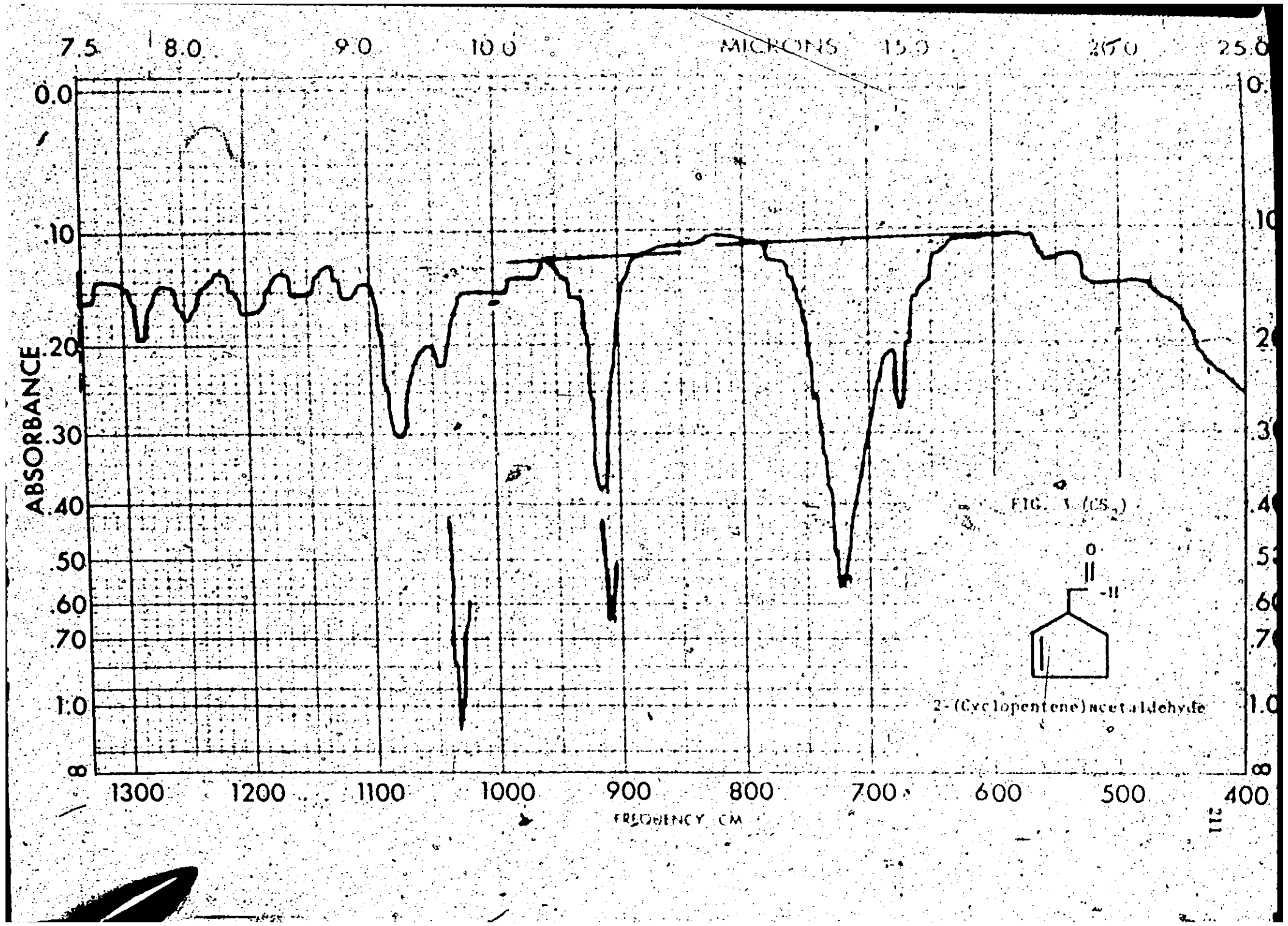
7.5
8.0
9.0
10.0
MICRONS
15.0
20.0
25.0
0.0
.10
.20
.30
.40
.50
.60
.70
1.0
ABSORBANCE
1300
1200
1100
1000
900
800
700
600
500
400
FREQUENCY CM
O
-H
2-(Cyclopentene)acetaldehyde

FIG. 1 (CS_2)

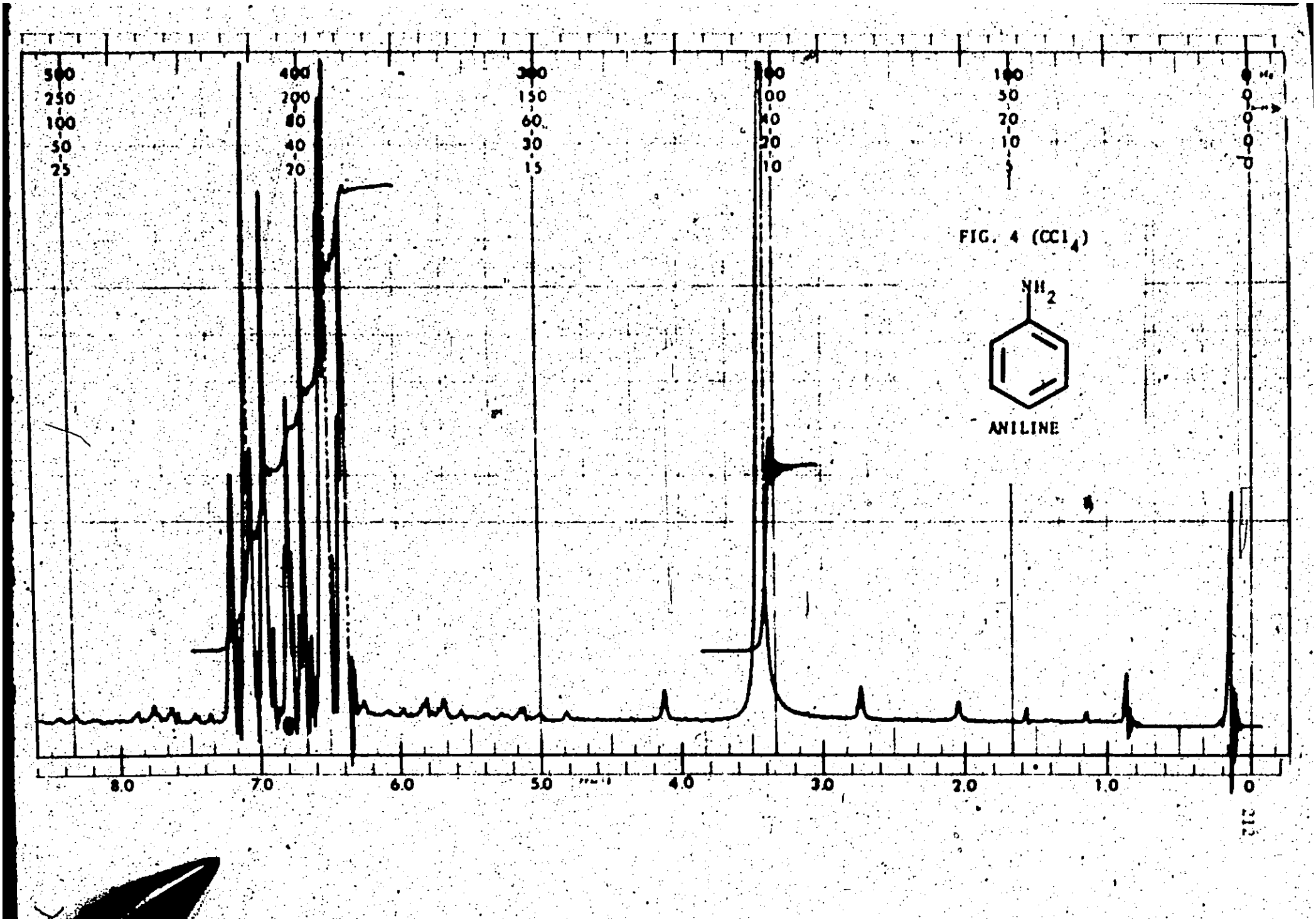
500
250
100
50
25
400
200
80
40
20
300
150
60
30
15
200
100
40
20
10
100
50
20
10
5
0
8.0
7.0
6.0
5.0
4.0
3.0
2.0
1.0
0
NH2
ANILINE

FIG. 4 (CCl_4)

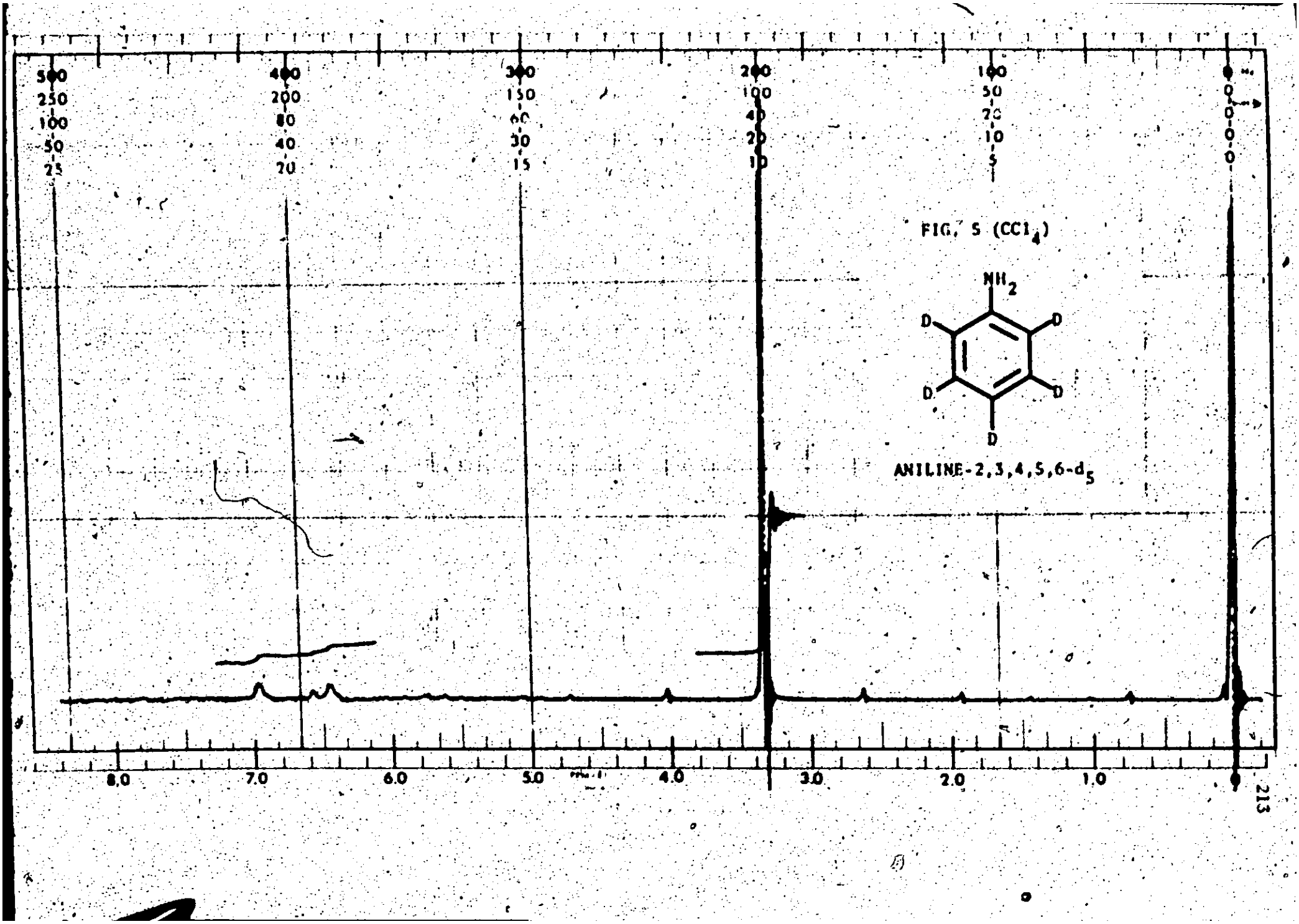

FIG. 5 (CCl_4)

ANILINE-2,3,4,5,6-d_5

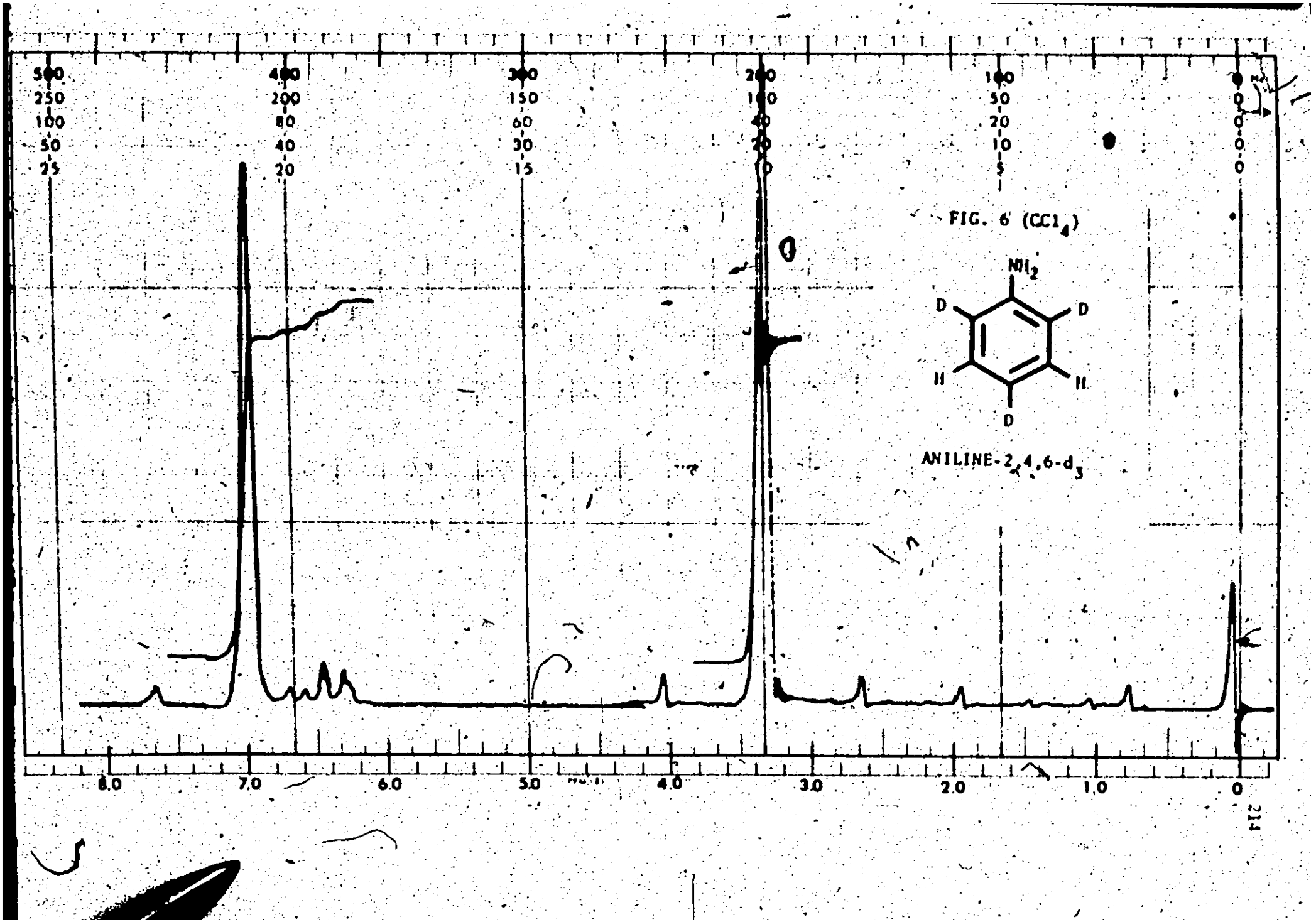

FIG. 6 (CCl_4)

ANILINE-2,4,6-d_3

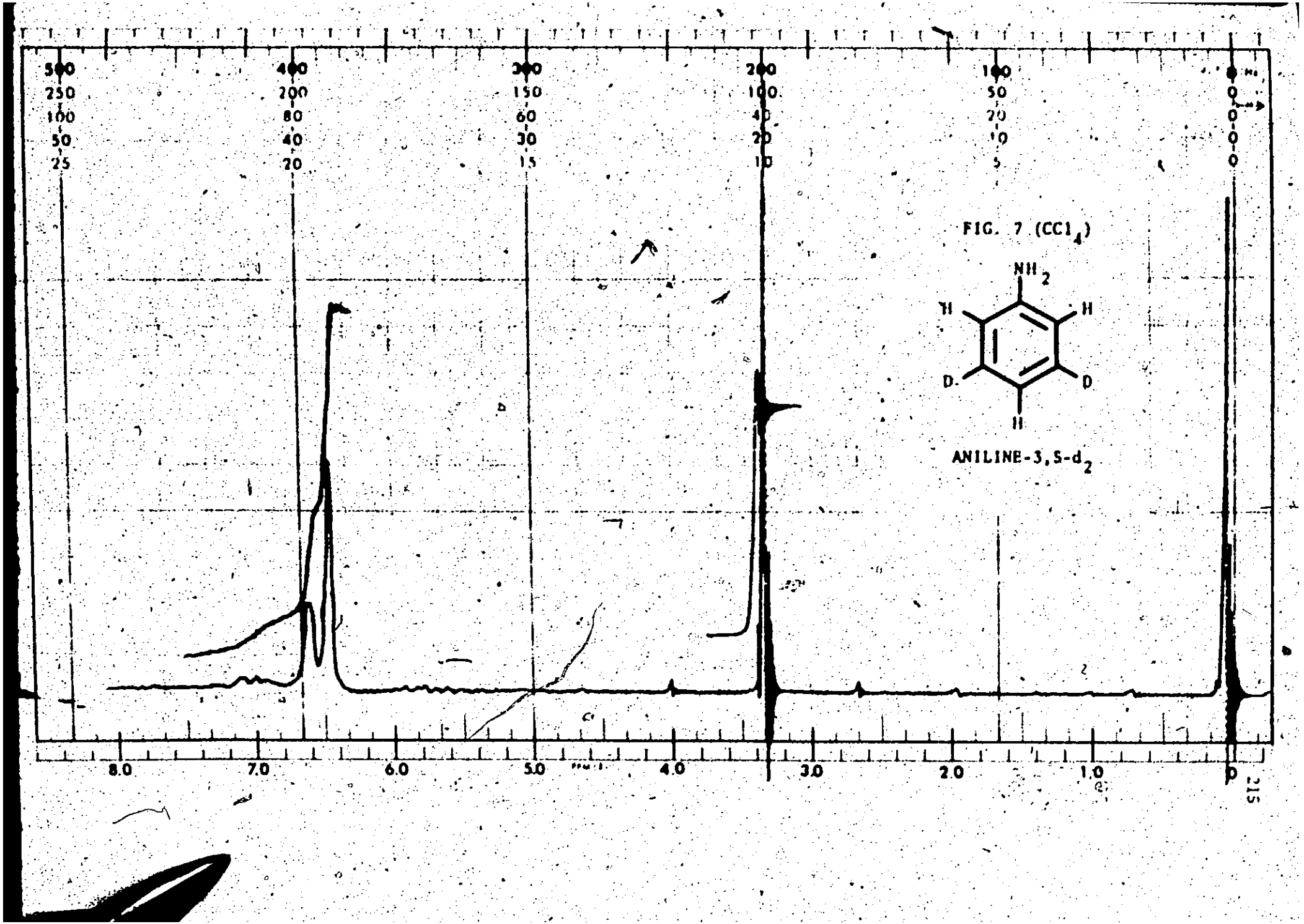

FIG. 7 (CCl_4)

ANILINE-3,5-d_2

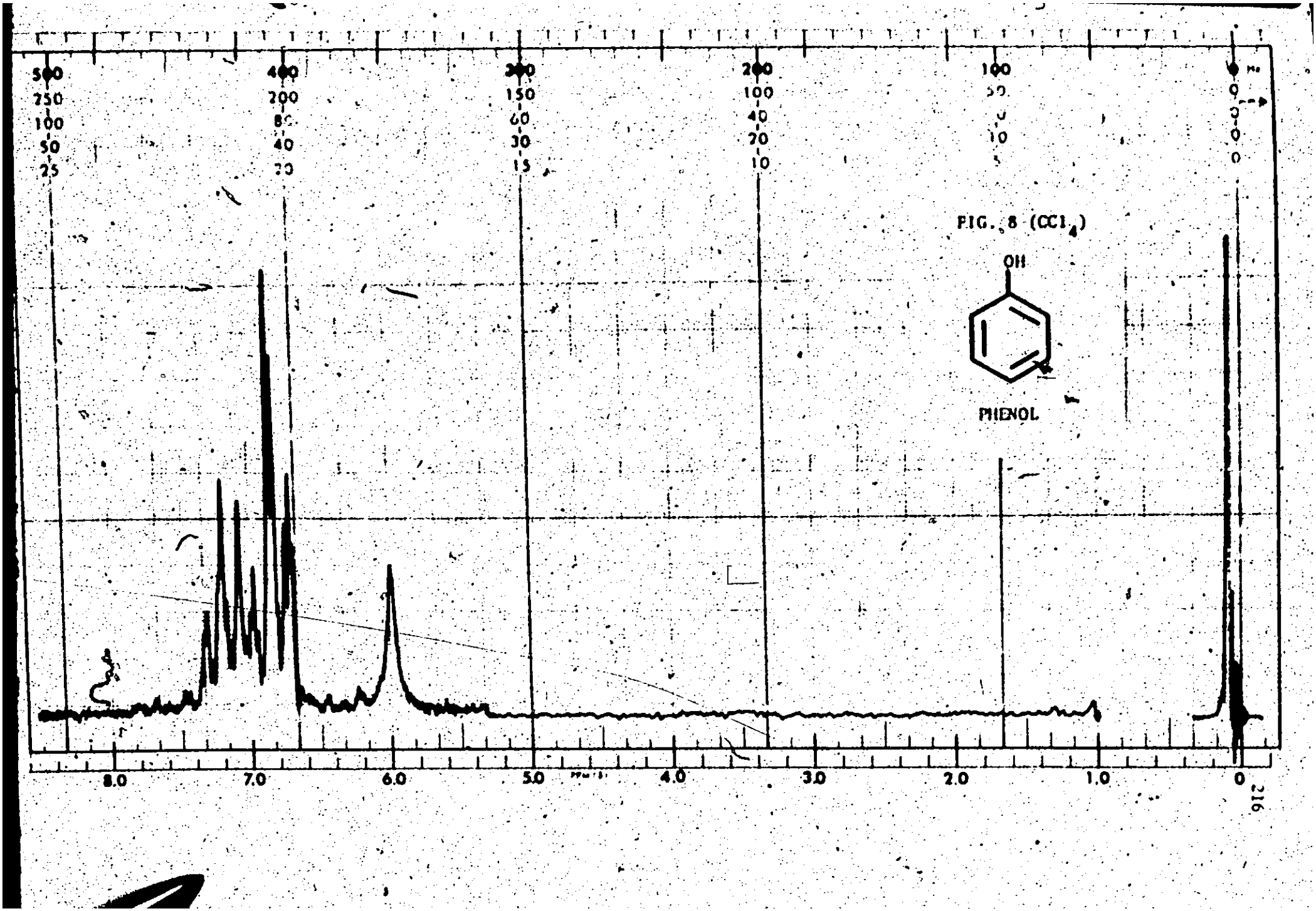
FIG. 8 (CCl_4)
OH
PHENOL
500
250
100
50
25
400
200
80
40
20
300
150
60
30
15
200
100
40
20
10
100
50
10
0
8.0
7.0
6.0
5.0
4.0
3.0
2.0
1.0
0
216

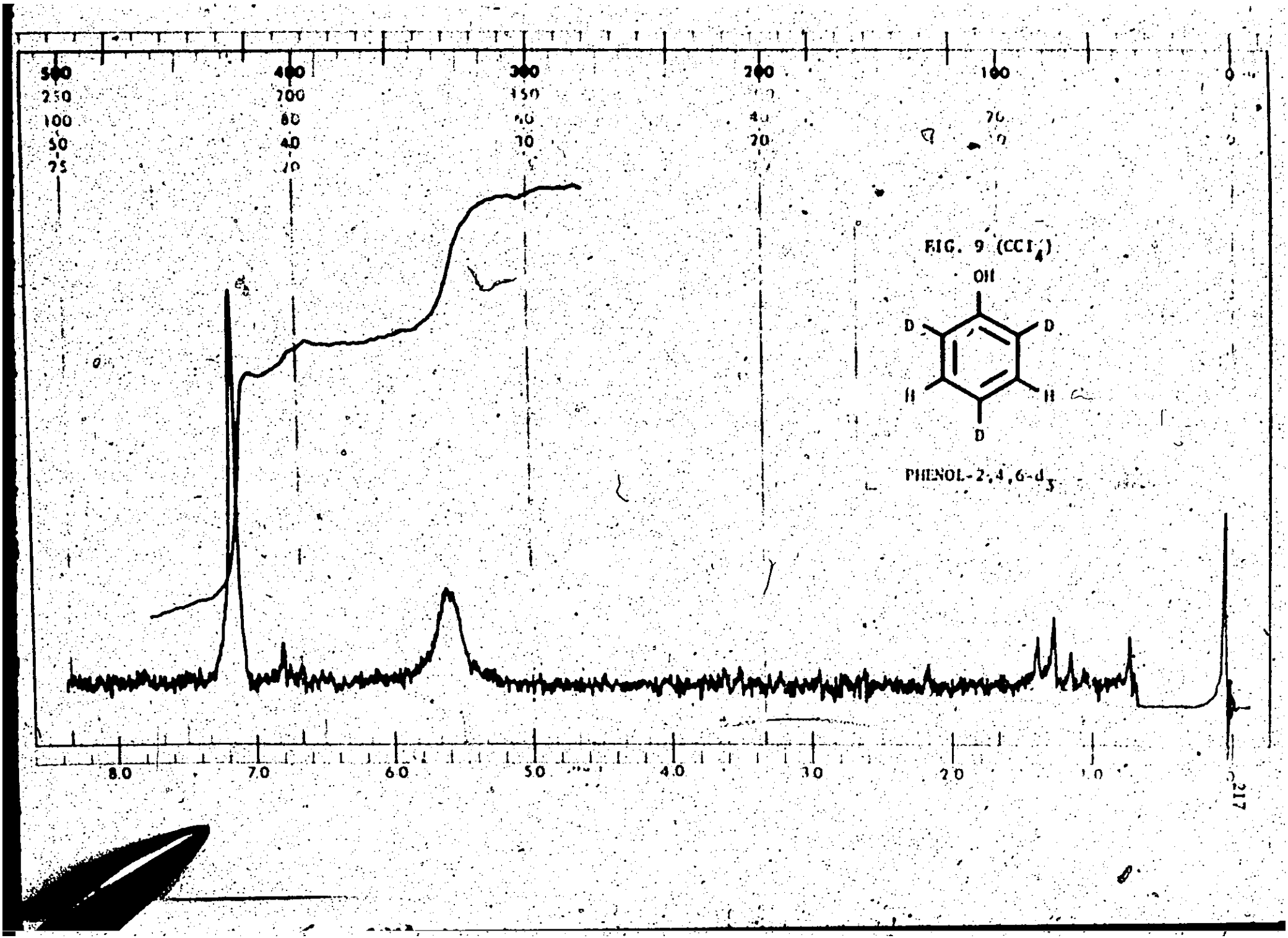

FIG. 9 (CCl_4)

PHENOL-2,4,6-d_3

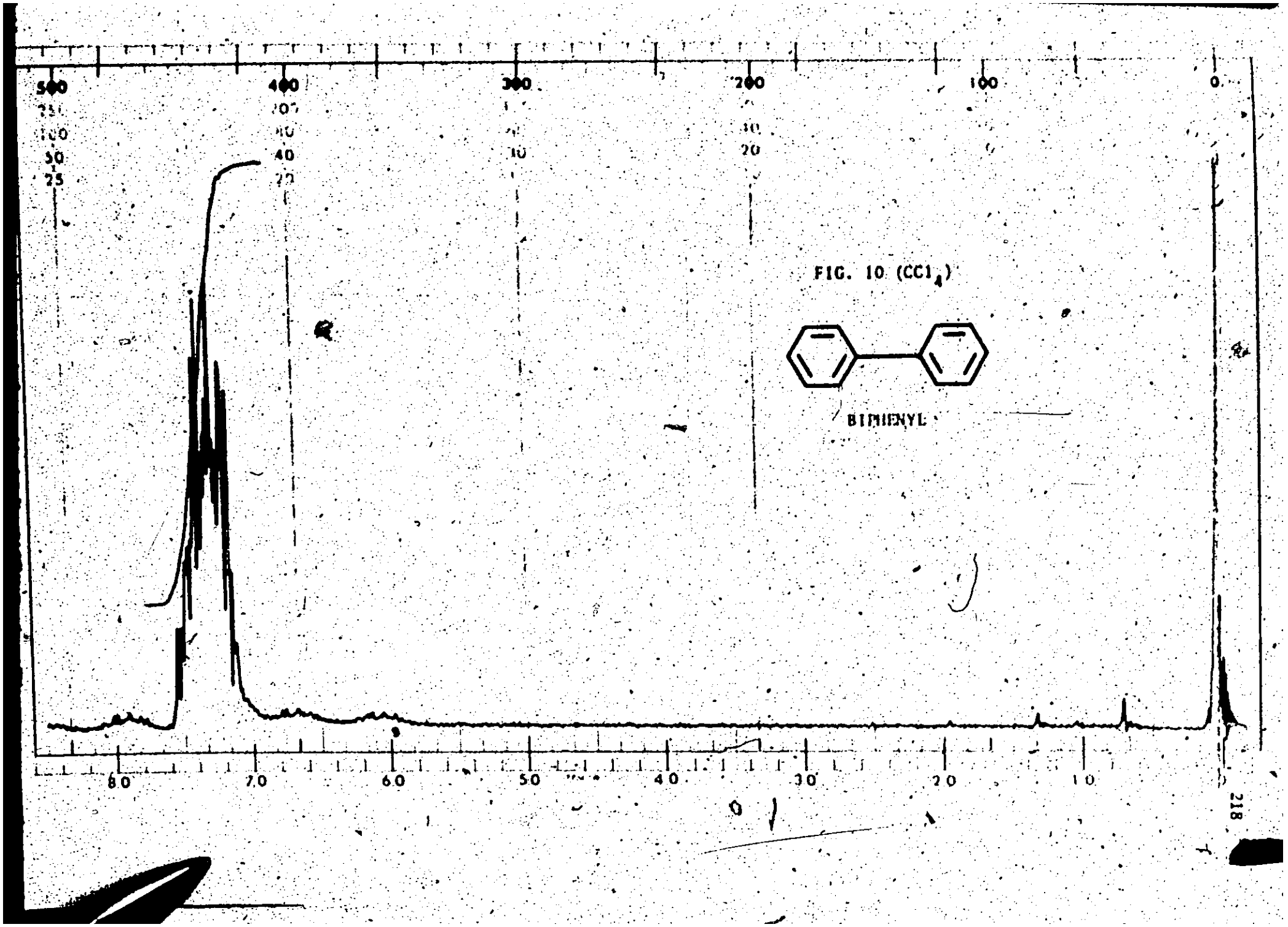

FIG. 10 (CCl_4)

BIPHENYL

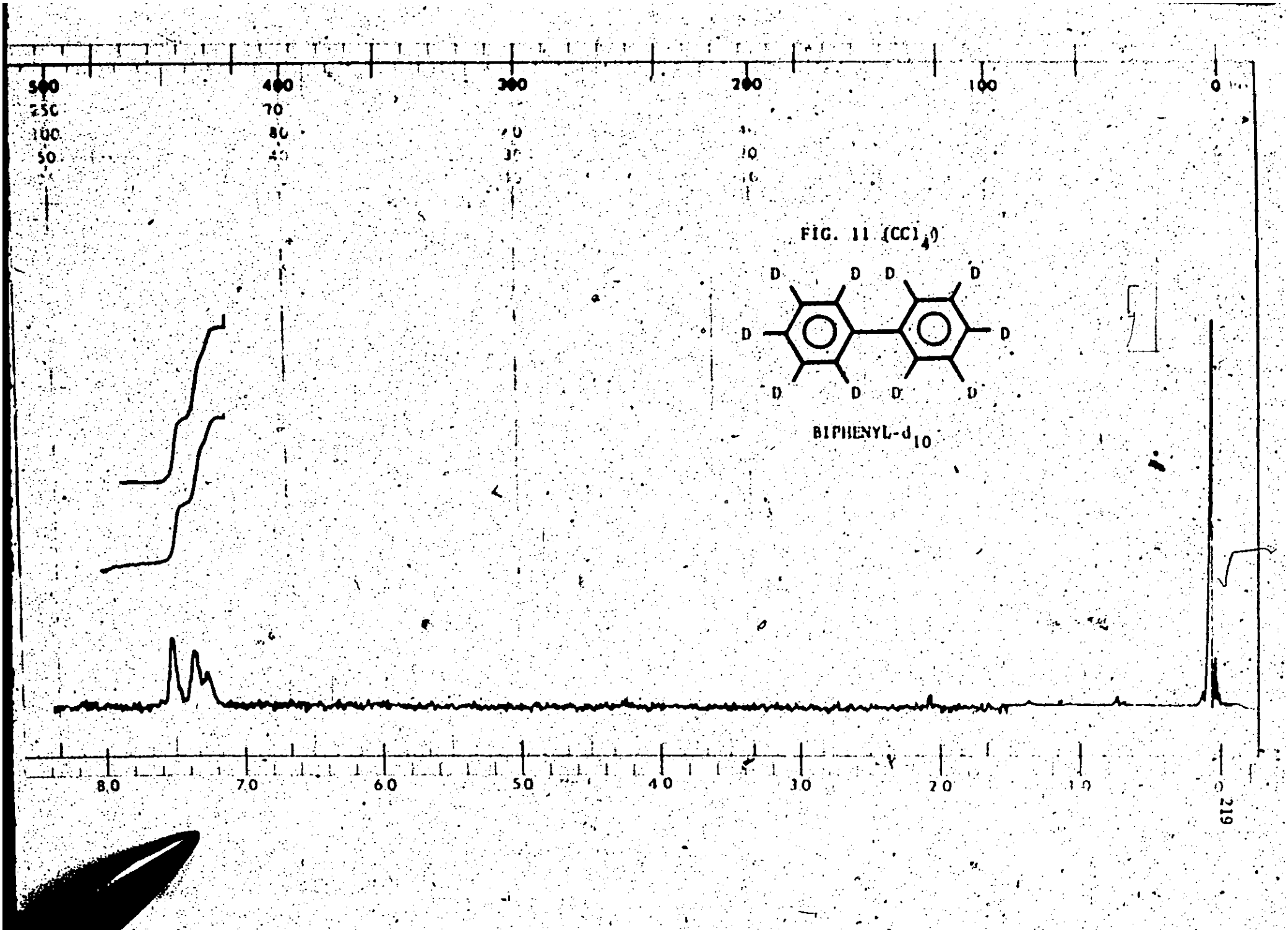

FIG. 11 (CCl_4)

BIPHENYL-d_{10}

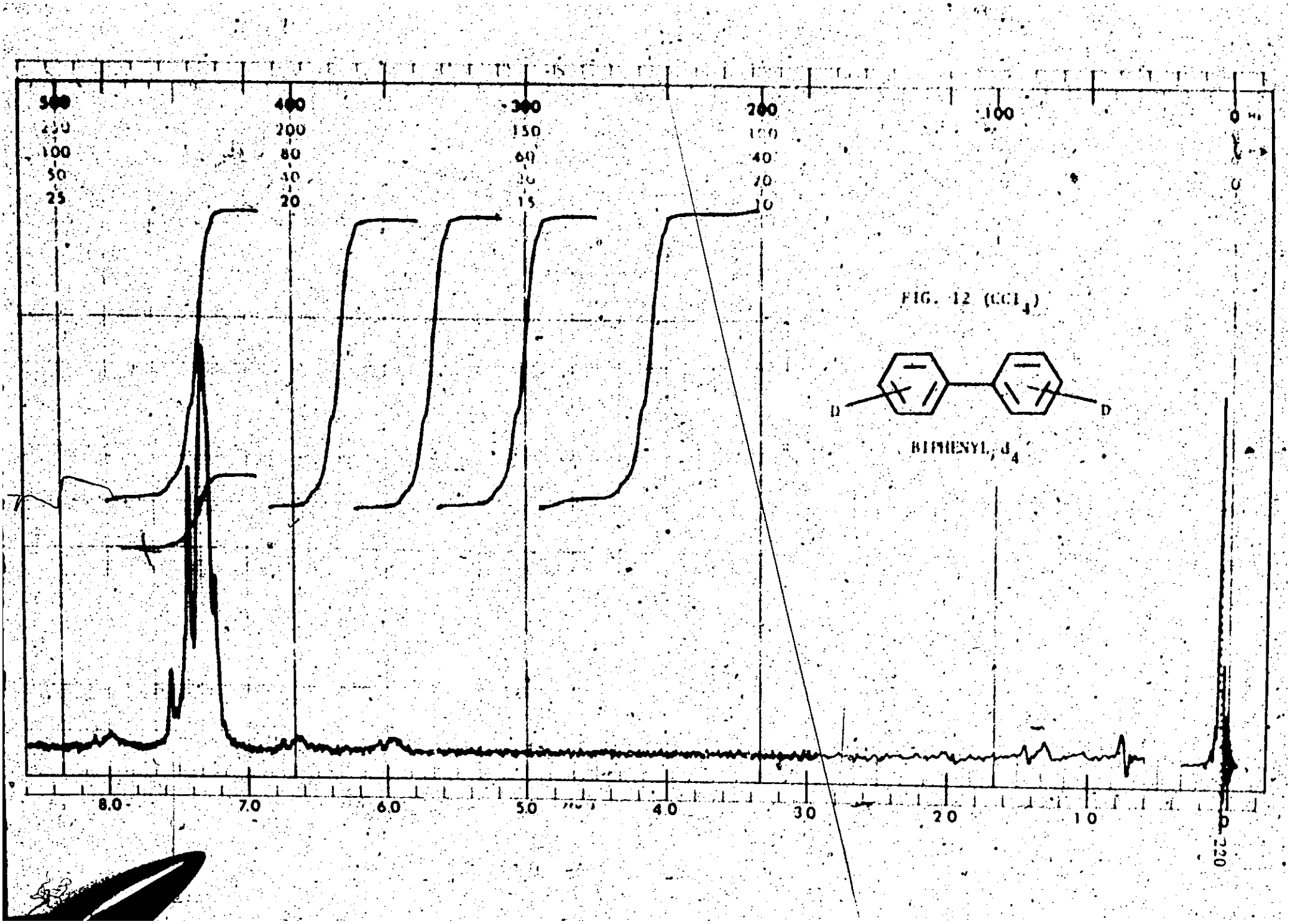

FIG. 12 (CCl_4)

BIPHENYL, d_4

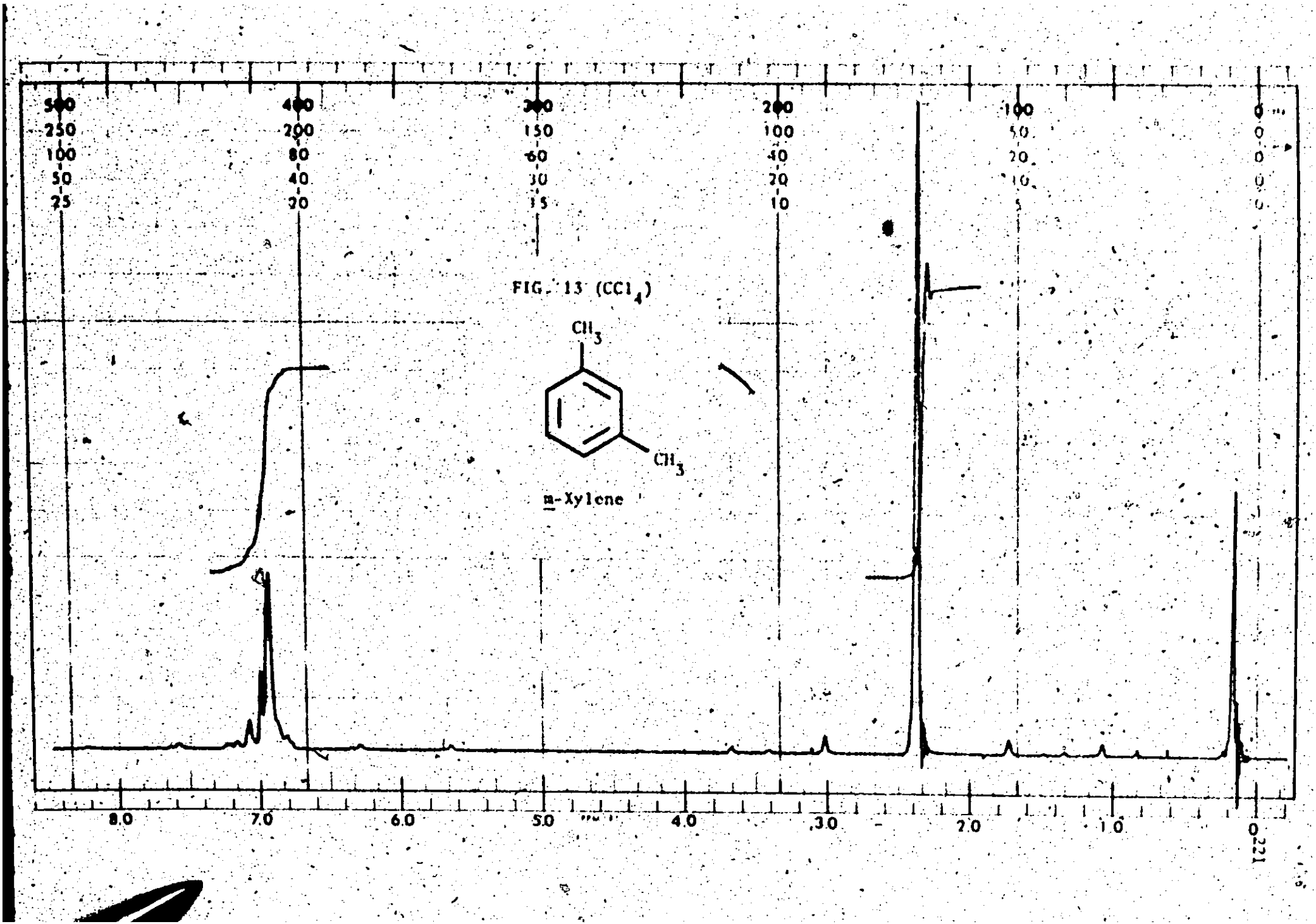

FIG. 13 (CCl_4)

m-Xylene

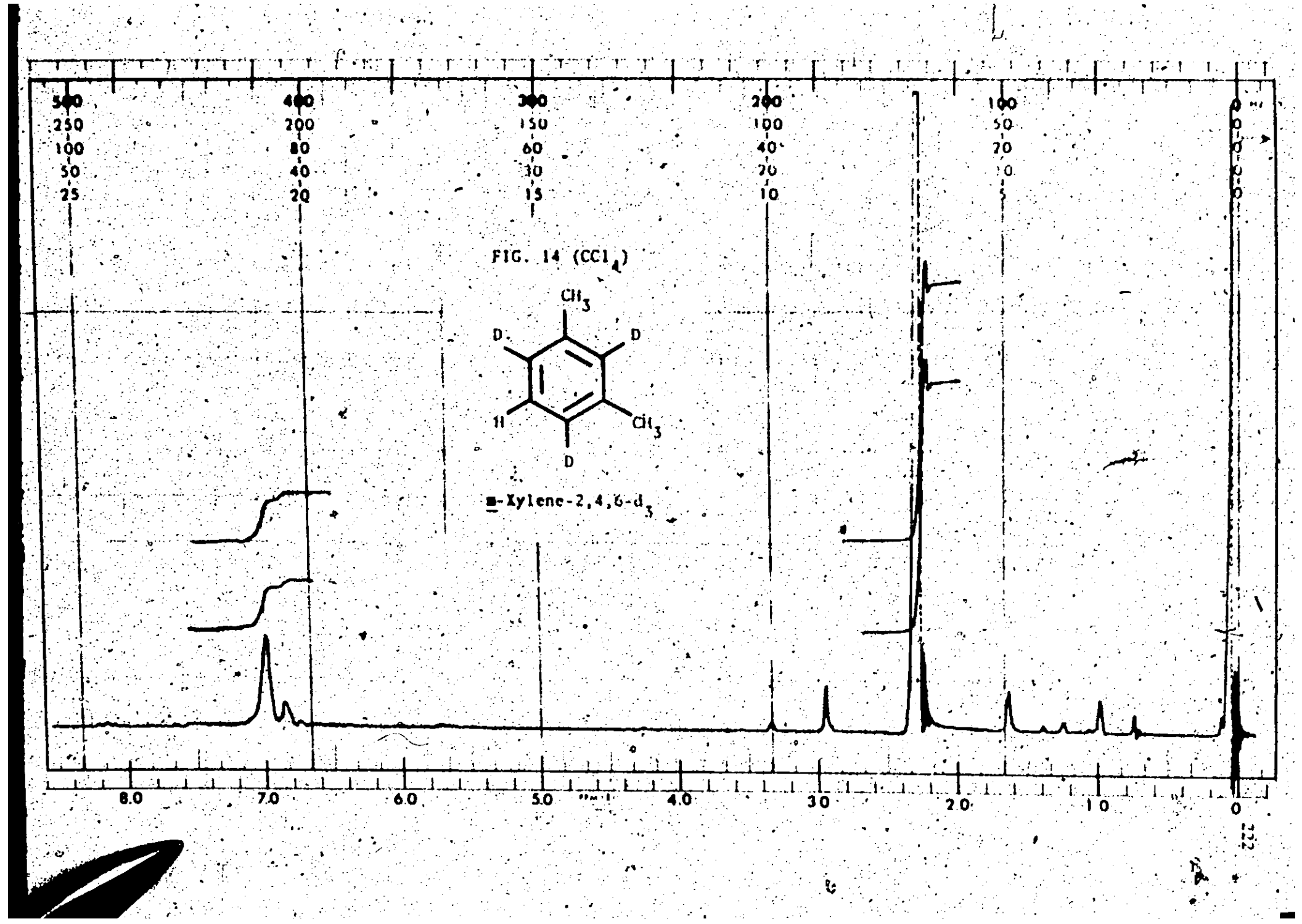

FIG. 14 (CCl_4)

m-Xylene-2,4,6-d_3

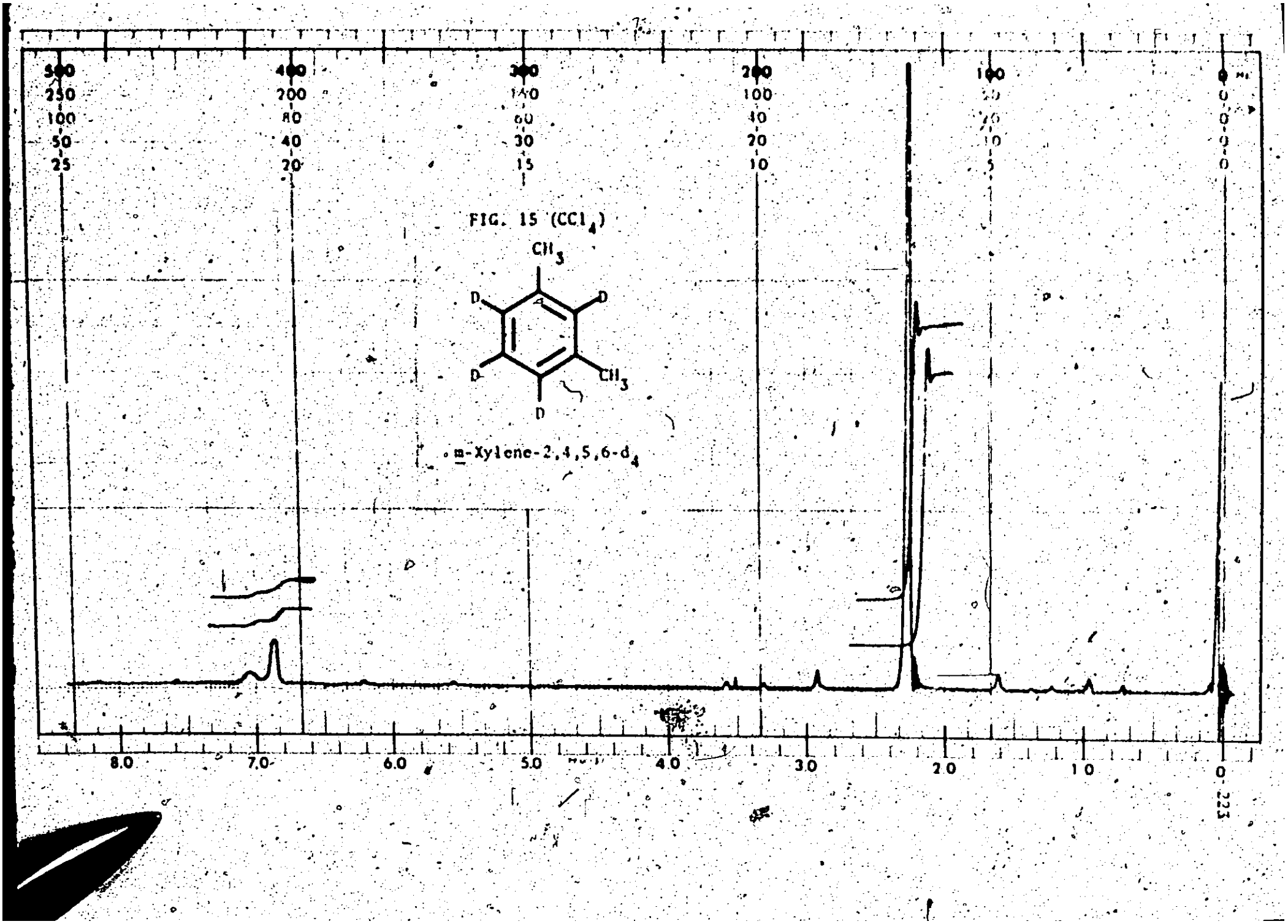

FIG. 15 (CCl_4)

m-Xylene-2,4,5,6-d_4

REFERENCES

1. L. Benati, M. Tiecco, A. Tundo and F. Taddei, J. Chem. Soc. (B), 1443 (1970).

2. B. Lunelli and C. Pecile, Can. J. Chem. 46, 391 (1968).

3. R. G. Cooks, I. Howe, S. W. Tam and D. H. Williams, J. Amer. Chem. Soc. 90, 4064 (1968).

4. A. A. Bothner-By and E. Moser, J. Amer. Chem. Soc. 90, 2347 (1968).

5. M. Tanabe, J. Tagg, D. Yasuda, S. E. LeValley and C. Mitoma, J. Med. Chem. 13, 30 (1970); E. Kutter and H. Machleidt, J. Med. Chem. 14, 931 (1971); R. D. Kimbrough, Jr., J. Med. Chem. 15, 409 (1972); J. M. Perel, D. K. Dawson, P. G. Dayton and L. I. Goldberg, J. Med. Chem. 15, 714 (1972).

6. J. G. Atkinson and M. O. Luke, Ger. Offen. 2,162,535, 6 July, 1972 (Can. Appl. 100,961, 17 December, 1970).

7. A. I. Scott and M. Yalpani, Chem. Comm. 945 (1967); E. Lederer, J. Biochem. 93, 449 (1964).

8. H. Budzikiewicz, C. Djerassi and D. H. Williams, "Structural Elucidation of Natural Products by Mass Spectrometry", Vol. 1, Holden Day, San Francisco, Calif., 1964, Chapter 2.

9. H. House and V. Kramar, J. Org. Chem. 28, 3362 (1963).

10. G. Fréjaville and J. Jullien, French Pat. 1,424,496 (C.N.R.S., Appl. Dec. 1, 1964). [Chem. Abs. 65, 10169 (1966)].

11. A. I. Shatenshtein, Advan. Phys. Org. Chem. 1, 161 (1963).

12. L. H. P. Weldon and C. L. Wilson, J. Chem. Soc. 244 (1946).

13. E. R. Lippincott and E. J. O'Reilly, J. Chem. Phys. 23, 238 (1955).

14. (a) J. E. Katon and E. R. Lippincott, Spectrochim. Acta 1, 627 (1959).
    (b) S. Califano, J. Chem. Phys. 36, 903 (1962).

15. (a) G. H. Coleman, W. H. Holst and R. D. Maxwell, J. Amer. Chem. Soc. 58, 2310 (1936).
    (b) J. S. Meek and J. S. Fowler, J. Amer. Chem. Soc. 89, 1967 (1967).
    (c) S. Oae, W. Tagaki, K. Uneyama and I. Minamida, Tetrahedron, 24, 5283 (1968).
    (d) M. Chaimovich, R. J. Vaughan and F. H. Westheimer, J. Amer. Chem. Soc. 90, 4088 (1968).
    (e) R. D. Guthrie and D. P. Wesley, J. Amer. Chem. Soc. 92, 4057 (1970).

16. J. Seibl and T. Gaumann, Helv. Chim. Acta 46, 2857 (1963).

17. D. S. Weinberg and C. Djerassi, J. Org. Chem. 31, 115 (1966).

18. A. Mislow, M. A. Glass, H. B. Hopps, E. Simon and G. H. Wahl, Jr., J. Amer. Chem. Soc. 86, 1710 (1964).

19. M. Senn, N. J. Richter and A. L. Burlingame, J. Amer. Chem. Soc. 87, 680 (1965).

20. D. K. Albert and S. Meyerson, Analyt. Chem. 39, 1004 (1967).

21. G. J. Kallos and L. E. Nestover, Tet. Letters 1223 (1967).

22. N. H. Werstiuk and T. Kadai, unpublished results.

23. A. Frakas, L. Frakas and E. K. Rideal, Proc. Roy. Soc. A166, 630 (1934).

24. J. Horiuti and M. Polanyi, Nature 132, 819, 931 (1933).

25. A. Frakas and L. Frakas, Trans. Far. Soc. 35, 917 (1939).

26. R. J. Harper, S. Siegel and C. Kemball, J. Catal. 6, 72 (1966).

27. J. G. Atkinson, M. O. Luke and R. S. Stuart, Chem. Comm. 283 (1969).

28. J. A. Dixon and J. W. Marr, J. Org. Chem. 28, 3085 (1963).

29. J. G. Atkinson, M. O. Luke and R. S. Stuart, Can. J. Chem. 45, 1512 (1967).

30. L. C. Leitch, Can. J. Chem. 32, 813 (1954).

31. R. R. Fraser and R. N. Renaud, J. Amer. Chem. Soc. 88, 4365 (1966).

32. S. D. Paul, J. Ramamurthy and A. S. Chawla, Ind. J. Chem. 3, 369 (1965).

33. Ng. Dinh-Nguygen and E. Stenhagen, French Pat. 1,466,088 (Jan. 13, 1967).

34. K. Kirota and T. Ueda, Proc. 3rd. Int. Congr. Catalysis, Vol. II, p. 1238.

35. B. S. Gudkov, N. A. Balandin and E. P. Savin, Dokl. Akad. Naud. S.S.S.R. 162, 843 (1965).

36. G. E. Calf and J. L. Garnett, J. Phys. Chem. 68, 3887 (1964).

37. L. Horner and D. Mayer, Annal. 680, 1 (1964).

38. K. Kirota and T. Ueda, Bull. Chem. Soc. Japan 35, 228 (1962).

39. C. G. MacDonald and J. S. Shannon, Aust. J. Chem. 15, 771 (1962).

40. C. G. MacDonald and J. S. Shannon, Tet. Letters, 1349 (1963).

41. V. N. Setkina, D. N. Kursanov, O. D. Sterlinov and A. L. Liberman, Dokl. Akad. Nauk. S. S. S. R. 85, 1045 (1952).

42. C. G. MacDonald and J. S. Shannon, Aust. J. Chem. 18, 1009 (1965) and 20, 297 (1967).

43. C. G. MacDonald and J. S. Shannon, Tet. Letters 3351 (1964).

44. (a) J. L. Garnett and R. J. Hodges, Chem. Comm. 1001 (1967).
(b) J. L. Garnett and R. J. Hodges, J. Amer. Chem. Soc. 89, 4546 (1967).

45. J. L. Garnett, M. A. Long and R. F. W. Vining, J. Amer. Chem. Soc. 94, 5913 (1972).

46. (a) F. A. L. Anet and M. St. Jacques, J. Amer. Chem. Soc. 88, 2585 (1966).
(b) K. Schrage and R. L. Burwell, Jr., J. Amer. Chem. Soc. 88, 4549 (1966).
(c) J. L. Garnett, Catal. Rev. 5, 229 (1971).
(d) G. E. Calf and J. L. Garnett, Chem. Comm. 373 (1969).

47. N. Dinh-Nguygen and R. Ryhage, Acta Chem. Scand. 13, 1032 (1959).

48. (a) D. R. Arnold, D. J. Trecker and E. B. Whipple, J. Amer. Chem. Soc. 87, 2596 (1965).
(b) B. Franzus, W. C. Baird, Jr., and J. H. Surridge, J. Org. Chem. 33, 1288 (1968).

49. (a) A. J. Birch and K. A. M. Walker, Tet. Letters 4939 (1966).
(b) C. Djerassi and J. Gutzwillier, J. Amer. Chem. Soc. 88, 4537 (1966).

50. J. F. Biellmann and H. Liesenfelt, C. R. Acad. Sci. [D] Paris, 263, 251 (1966).

51. D. Gagnaire and P. Vottero, Bull. Soc. Chim. 164 (1970).

52. A. J. Birch and K. A. M. Walker, Tet. Letters 1935 (1967).

53. E. E. van Tamelen and R. J. Timmons, J. Amer. Chem. Soc. 84, 1067 (1962) and references cited therein.

54. D. H. Williams, J. M. Wilson, H. Budzikiewicz and C. Djerassi, J. Amer. Chem. Soc. 85, 2091 (1963).

55. A. F. Thomas, B. Willhalm and J. H. Bowie, J. Chem. Soc. (B) 392 (1967).

L. Friedman and A. T. Jurewicz, J. Org. Chem. 33, 1234 (1968).

M. Wiewiorowski, O. L. Edwards and M. D. Bratek-Wiewiorowski, Can. J. Chem. 45, 1447 (1967).

G. Wilke and H. Muller, Annalen, 618, 267 (1958).

H. O. Kuivila, Synthesis, 499 (1970).

R. R. Varma and E. Caspi, Tetrahedron, 24, 6305 (1968).

N. G. Gaylord, "Reduction with Complex Metal Hydrides", Interscience, New York, 1956.

G. Fraenkel, D. G. Adams and R. R. Dean, J. Phys. Chem. 72, 944 (1968).

J. P. Colpa, C. MacLean and E. L. Mackor, Tetrahedron, 19, Suppl. 2, 65 (1963); L. Havinga, R. C. de Jongh and M. E. Kronenberg, Helv. Chim. Acta 50, 2550 (1967).

R. G. Wilson, J. H. Bowie and D. H. Williams, Tetrahedron, 24, 1407 (1968).

H. M. Walborsky and G. E. Niznik, J. Amer. Chem. Soc. 91, 7778 (1969).

A. F. Thomas, "Deuterium Labelling in Organic Chemistry", Appleton-Century-Crofts, New York, 1971.

J. W. Otvos, D. P. Stevenson, C. D. Wagner and O. Beeck, J. Amer. Chem. Soc. 73, 5741 (1951).

N. C. Deno, "Carbonium Ions", Progr. Phys. Org. Chem. 2, 129 (1964).

H. W. Whitlock, Jr., and M. W. Siefken, J. Amer. Chem. Soc. 90, 4929 (1968).

P. Bey and G. Ourisson, Bull. Soc. Chim. France, 2468 (1968).

J. C. Stephens and L. C. Leitch, J. Label. Compounds, 3, 65 (1967).

G. A. Olah and P. von R. Schleyer, "Carbonium Ions", Vol. II, John Wiley and Sons, Inc., New York, 1970.

G. E. Calf, B. D. Fisher and J. L. Garnett, Aust. J. Chem. 21, 947 (1968).

C. K. Ingold, C. G. Raisin and C. L. Wilson, Nature, 134, 734 (1934).

C. K. Ingold, C. G. Raisin and C. L. Wilson, J. Chem. Soc. 915, 1037 (1936).

G. A. Olah and S. J. Kuhn, J. Amer. Chem. Soc. 80, 6535 (1958).

77. R. T. Morrison and R. N. Boyd, "Organic Chemistry", Allyn and Bacon, Inc., Boston, 1962.

78. E. L. Mackor, P. J. Smit and J. H. Van der Waals, Trans. Far. Soc. 53, 1309 (1957).

79. C. K. Ingold, C. G. Raisin and C. L. Wilson, J. Chem. Soc. 1637 (1936).

80. A. R. Katritzky and B. J. Ridgewell, J. Chem. Soc. 3753 (1963).

81. V. Gold, "Friedel-Crafts and Related Reactions", G. A. Olah, ed., New York, Interscience, 1963.

82. C. E. Frosst and Co., Ger. Offen. 2,122,254, 18 Nov. 1971 [Chem. Abs. 76, 33419 r (1972)].

83. A. F. Best and C. L. Wilson, J. Chem. Soc. 239 (1946).

84. J. A. Dixon and R. W. Schiessler, J. Amer. Chem. Soc. 76, 2197 (1954).

85. M. Brüllmann, H.J. Gerber and D. Meier, Helv. Chim. Acta, 41, 1831, (1958).

86. W. B. Person, G. C. Pimentel and O. Schnepp, J. Chem. Phys. 23, 250 (1955).

87. G. M. Whitesides, B. A. Pawson and A. C. Cope, J. Amer. Chem. Soc. 90, 639 (1968).

88. S. Meyerson and E. K. Fields, Org. Mass Spec. 2, 241 (1969).

89. (a) J. A. Zoltewicz and C. L. Smith, J. Amer. Chem. Soc. 89, 3358 (1967).
(b) A. R. Katritzky, M. Kingsland and O. S. Tee, J. Chem. Soc. (B), 1484 (1968).

90. (a) R. Baker, C. Eaborn and R. Taylor, J. Chem. Soc. 4927 (1961).
(b) A.I.Shatenshtein and P. P. Alikhanov, Zhur. Obshch. Khim. 30, 992 (1960).

91. R. N. Renaud, D. Kovachic and L. C. Leitch, Can. J. Chem. 39, 21 (1961).

92. D. I. Lobanov, E. N. Tsvetkov, E. V. Saltanova, E. Y. Yakovleva, M. I. Kabachnik and A. I.Shatenshtein, Izv. Akad. Naud S. S. S. R., Ser. Khim. 2050 (1968).

93. R. G. Cooks, I. Howe, S. W. Tam and D. H. Williams, J. Amer. Chem. Soc. 90, 4064 (1968).

94. P. C. Wszolak, F. W. McLafferty and J. H. Brewster, Org. Mass Spec. 1, 127 (1969).

96. L. M. Kosower, "An Introduction to Physical Organic Chemistry", John Wiley and Sons, Inc., New York, 1968.

97. P. P. Alikhanov and I. Shatenshtein, Zhur. Obshch. Khim. 38, 218 (1968) [Chem. Abs. 69, 3099 (1968)].

98. D. M. Brouwer, E. L. Mackor and C. MacLean, Rec. Trav. Chim. 85, 109, 114 (1966).

99. M. J. S. Dewar and R. C. Fahley, J. Amer. Chem. Soc. 85, 2245, 2248 (1963).

99. N. H. Werstiuk and T. Kadai, Chem. Comm. 1549 (1971).

100. N. H. Werstiuk and T. Kadai, Chem. Comm. 1613 (1970).

101. N. H. Werstiuk and T. Kadai, Can. J. Chem. 50, 3350 (1972); 51, 1455 (1973).

102. J. Moravek, Chem. Listy, 62, 307 (1968).

103. M. Frangopol, Isotopes and Radiation Technology, 9, 447 (1972) and references cited therein.

104. J. L. Garnett, B. Halpern and R. S. Kenyon, Chem. Comm. 135 (1972).

105. J. D. Roberts, W. Bennett and R. Armstrong, J. Amer. Chem. Soc. 72, 3329 (1950).

106. (a) S. Winstein, H. M. Walborsky and K. Schreiber, J. Amer. Chem. Soc. 72, 5795 (1950).
(b) S. J. Cristol, T. C. Morrill and R. A. Sanchez, J. Amer. Chem. Soc. 88, 3087 (1966).

107. S. J. Cristol, N. K. Seifert, D. W. Johnson and J. B. Jurale, J. Amer. Chem. Soc. 84, 3918 (1962).

108. F. P. Cappelli, G. Timmins and N. H. Werstiuk, Can. J. Chem. 50, 2165 (1972) and references cited therein.

109. W. E. Trahanovsky, P. J. Flask and L. M. Smith, J. Amer. Chem. Soc. 91, 5068 (1969).

110. J. D. Roberts, F. O. Johnson and R. A. Carboni, J. Amer. Chem. Soc. 76, 5692 (1954).

111. A. Nickon, J. L. Lambert, R. O. Williams, and N. H. Werstiuk, J. Amer. Chem. Soc. 88, 3354 (1966).

112. R. B. Turner, P. Goebel, B. J. Mallon, W. von E. Doering, J. F. Coburn, Jr., and M. Pomerantz, J. Amer. Chem. Soc. 90, 4315 (1968).

113. S. J. Cristol, T. C. Morrill and R. A. Sanchez, J. Org. Chem. 31, 2726, 2733 (1966).

114. C. C. Lee, Bo-Sup Hahn and L. K. M. Lam, Tet. Letters, 35, 3049 (1964).

115. G. Fraenkel, P. D. Ralph and J. P. Kim, Can. J. Chem. 43, 674 (1965).

116. (a) J. A. Berson and P. W. Grubb, J. Amer. Chem. Soc. 87, 4016 (1965).
(b) C. J. Collins and B. M. Benjamin, J. Amer. Chem. Soc. 88, 1556 (1966).

117. J. A. Berson, J. H. Hammons, A. W. McRowe, R. G. Bergman, A. Remanick and D. Houston, J. Amer. Chem. Soc. 89, 2590 (1967).

118. A. W. Bushell and P. Wilder, J. Amer. Chem. Soc. 89, 5721 (1967).

119. J. M. Cox, M. P. Hartshorn and A. J. Lewis, Aust. J. Chem. 24, 1009 (1971).

120. (a) A. Colter, E. C. Friederich, N. J. Holness and S. Winstein, J. Amer. Chem. Soc. 87, 378 (1965).
(b) J. A. Berson, R. G. Bergman, J. H. Hammon and A. W. McRowe, J. Amer. Chem. Soc. 89, 2581, 2573 (1967).

121. P. G. Gassman, J. M. Hornback and J. L. Marshall, J. Amer. Chem. Soc. 90, 6238 (1968).

122. (a) L. H. Zalkow and A. C. Oehlschlager, J. Amer. Chem. Soc. 86, 4208 (1964).
(b) C. A. Grob, Gazz. Chem. Ital. 92, 902 (1962).

123. P. G. Gassman and J. M. Hornback, Tet. Letters, 17, 1325 (1969).

124. (a) W. Kraus and W. Rothenwohrer, Tet. Letters, 8, 1013 (1968).
(b) W. Kraus, C. Chassin and R. Chassin, Tetrahedron, 25, 3681 (1969).
(c) W. Kraus and C. Chassin, Liebigs Ann. Chem. 747, 98 (1971).

125. Z. Chabudzinski, U. Lipnicka and Z. Rykowski, Roczniki Chemii Ann. Soc. Chim. Polonorum, 44, 2181 (1970).

126. B. Arbusow, Ber. 68, 1430 (1935).

127. D. E. Gwynn and L. Skillern, Chem. Comm. 9, 490 (1968).

128. T. E. Maggio and J. English, J. Amer. Chem. Soc. 83, 968 (1961).

129. L. L. Jones and V. K. Jones, J. Org. Chem. 36, 1017 (1971).

130. C. J. Collins, V. F. Raaen, B. M. Benjamin, I. T. Glover, J. Amer. Chem. Soc. 89, 3940 (1969).

131. J. K. Crandall, J. Org. Chem. 29, 2830 (1964).

132. B. Rickborn and R. M. Gerkin, J. Amer. Chem. Soc. 93, 1693 (1971).

133. S. J. Cristol and R. M. Bly, J. Amer. Chem. Soc. 82, 6155 (1960).

134. C. J. Collins, V. F. Raaen, B. M. Benjamin and I. T. Glover, J. Amer. Chem. Soc. 89, 3040 (1967).

135. C. J. Collins, V. F. Raaen, B. M. Benjamin, I. T. Glover and M. D. Eckart, Liebigs Ann. Chem. 739, 7 (1970).

136. C. C. Lee, Bo-Sup Hahn, L. K. M. Lam and D. J. Woodcock, Can. J. Chem. 48, 3531 (1970).

137. (a) J. B. Corfield and S. Trippett, Chem. Comm. 721 (1971).
(b) Z. W. Wolkowski, Tet. Letters, 825 (1971).
(c) J. St. Pyrek, Chem. Comm. 98 (1971).
(d) C. Beaute, Z. W. Wolkowski, J. P. Merda and D. Lelandais, Tetrahedron, 2473 (1971).

138. (a) J. Reich, M. Christl and J. D. Roberts, J. Amer. Chem. Soc. 93, 3463 (1971).
(b) J. Briggs, F. A. Hart, G. P. Moss and E. W. Randall, Chem. Comm. 364 (1971).

139. C. C. Hinckley, J. Amer. Chem. Soc. 91, 5160 (1969) and J. Org. Chem. 35, 2834 (1970).

140. J. K. M. Sanders and D. H. Williams, Chem. Comm. 422 (1970).

141. J. A. Pople, W. G. Schneider and H. J. Bernstein, "High Resolution Nuclear Magnetic Resonance", McGraw-Hill, p. 210, 1959.

142. (a) D. R. Eaton, J. Amer. Chem. Soc. 87, 3097 (1965).
(b) F. A. Hart, J. E. Newberry and D. Shaw, Nature (London) 216, 261 (1967).

143. G. H. Wahl and M. R. Peterson, Chem. Comm. 1467 (1970).

144. J. Paasivirta, Suomen Kemistilehti, 44 B, 131 (1971).

145. P. V. Demarco, T. K. Elzey, R. B. Lewis and E. Wenkert, J. Amer. Chem. Soc. 92, 5734 (1970).

146. J. D. Roberts, "An Introduction to the Analysis of Spin-Spin Splitting in High-Resolution Nuclear Magnetic Resonance Spectra", W. A. Benjamin, Inc., New York, N. Y., 1961.

147. H. S. Gutowsky, M. Karplus and D. M. Grant, J. Chem. Phys. 31, 1278 (1959).

148. M. Karplus, J. Chem. Physics, 30, 11 (1959).

149. J. D. Roberts, "Nuclear Magnetic Resonance", McGraw-Hill Book Co., Inc., New York, N. Y., Chapter 3, 1959.

150. J. Meinwald and A. Lewis, J. Amer. Chem. Soc. 83, 2769 (1961) and references cited therein.

151. F. A. L. Anet, Can. J. Chem. 39, 789 (1961).

152. S. Sternhell, Rev. Pure and Appl. Chem. 14, 15 (1964).

153. M. Barfield, J. Chem. Phys. 41, 3825 (1964).

154. R. E. Rondeau and R. E. Sievers, J. Amer. Chem. Soc. 93, 1522 (1971).

155. P. Ayras and J. Paasivirta, Suomen Kemistilehti, B, 42, 61 (1969).

156. D. R. Eaton, A. D. Josey, W. D. Phillips and R. E. Benson, J. Chem. Phys. 39, 3513 (1963).

157. R. W. King and P. E. Butler, Abstracts, 142nd National Meeting of the American Chemical Society, Atlantic City, N. J., Sept. 1962, p. 58 Q.

158. H. C. Brown, J. H. Kawakami and K. T. Liu, J. Amer. Chem. Soc. 92, 5536 (1970).

159. (a) J. M. Brown and M. C. McIvor, Chem. Comm. 5, 238 (1969).
(b) J. K. Stille and R. D. Huges, J. Org. Chem. 36, 340 (1971).

160. T. Goto, A. Tatematsu, Y. Hata, R. Muneyuki, H. Tanida and K. Tori, Tetrahedron, 22, 2213 (1966).

161. A. P. Best and C. L. Wilson, J. Chem. Soc. 239 (1946).

162. A. Rieker and P. Ziemer, Z. Naturforsch., 20B, 640 (1965).

163. V. Gold and D. P. N. Satchell, J. Chem. Soc. 3609, 3619, 3622 (1955).

164. A. J. Kresge and V. Chiang, J. Amer. Chem. Soc. 81, 5509 (1959); 83, 2877 (1961).

165. J. Colapietro and F. A. Long, Chem. and Ind. (London), 1056 (1960).

166. J. R. Blackborow and J. H. Ridd, Chem. Comm. 132 (1967).

167. (a) A. P. Best and C. L. Wilson, J. Chem. Soc. 28 (1938).
(b) G. E. Hall, E. M. Libby and E. L. James, J. Org. Chem. 28, 511 (1963).

168. W. S. Trahanovsky and P. W. Mullen, J. Amer. Chem. Soc. 94, 5912 (1972).

169. A. T. Ainsworth and G. W. Kirby, J. Chem. Soc. (C), 1438 (1968).

170. D. H. R. Barton, Pure Appl. Chem. 9, 35 (1964).

171. G. W. Kirby and L. Ogunkoya, J. Chem. Soc. 6914 (1965).

172. A. Murray and D. L. Williams, "Organic Syntheses with Isotopes", Part II, Interscience Publishers, New York, 1958.

173. B. Bak, J. J. Led and E. J. Pedersen, Acta Chemica Scanda. 23, 3051 (1969).

174. S. Oae and R. Kiritani, Bull. Chem. Soc. Japan, 39, 611 (1966).

175. D. A. McCauley and A. P. Lien, J. Amer. Chem. Soc. 74, 6246 (1952).

176. J. A. Zoltewicz and C. L. Smith, J. Amer. Chem. Soc. 89, 3358 (1967).

177. J. Meinwald, J. Crandall and W. E. Hymans, Org. Syn. 45, 74 (1965).

178. J. D. Roberts, F. O. Johnson and R. A. Carboni, J. Amer. Chem. Soc. 91, 5068 (1969).

179. H. M. Walbersky and D. F. Loncrini, J. Amer. Chem. Soc. 76, 5396 (1954).

150. J. Paasivirta and P. Ayras, Suomen Kemistilehti B 41, 51 (1968).

181. P. R. Story, J. Org. Chem. 26, 287 (1961).

182. J. R. Moyer and N. C. Manley, J. Org. Chem. 29, 2099 (1964).

183. S. B. Soloway and S. J. Cristol, J. Org. Chem. 25, 327 (1960).

184. R. G. Lawton, J. Amer. Chem. Soc. 83, 2399 (1961).

155. M. Fetizon and M. Golfier, Comptes Rendus de l'Academie des Sciences, Series C, 267 (1968); M. Fetizon, V. Balogh and M. Golfier, J. Org. Chem. 36, 1339 (1971).

186. C. W. Whitehead, J. J. Traverso, H. R. Sullivan and F. J. Marshall, J. Org. Chem. 26, 2814 (1961).

187. P. G. Gassman, J. L. Marshall and J. M. Hornback, J. Amer. Chem. Soc. 91, 5811 (1969).

188. W. Wayne and H. Adkins, Org. Syn. Coll. Vol. 3, 48 (1955).

189. J. Meinwald and B. C. Cadoff, J. Org. Chem. 27, 1539 (1962).

190. H. Kwartz and W. G. Vosburgh, J. Amer. Chem. Soc. 76, 5400 (1954).

191. P. D. Bartlett and A. Barley, J. Amer. Chem. Soc. 60, 2416 (1938).

192. J. B. Lambert and A. G. Holcomb, J. Amer. Chem. Soc. 93, 2994 (1971).

193. S. Winstein, E. T. Morse, Jr., D. Trifan and H. Marshall, J. Amer. Chem. Soc. 74, 1127 (1952).

194. D. G. Farnum, J. Org. Chem. 28, 870 (1963).

195. G. Wittig and E. Knauss, Chem. Ber. 91, 895 (1958).

196. P. D. Bartlett and W. P. Giddings, J. Amer. Chem. Soc. 82, 1240 (1960).

197. "Handbook of Chemistry and Physics", 46th Edition, The Chemical Rubber Co., Cleveland, Ohio, 1965-66.

198. N. H. Werstiuk, Ph.D. Dissertation, The John Hopkins University (1964).

199. T. Kadak and N. H. Werstiuk, unpublished results.