12-1968

The Deamination of Deuterated-2-Hydroxy-2-Phenyl-3-Aminonorbornanes

Michael D. Eckart
University of Tennessee - Knoxville

To the Graduate Council:

I am submitting herewith a dissertation written by Michael D. Eckart entitled "The Deamination of Deuterated-2-Hydroxy-2-Phenyl-3-Aminonorbornanes." I have examined the final electronic copy of this dissertation for form and content and recommend that it be accepted in partial fulfillment of the requirements for the degree of Doctor of Philosophy, with a major in Chemistry.

Clair J. Collins, Major Professor

We have read this dissertation and recommend its acceptance:

William H. Fletcher, George M. Brown, J. F. Eastham, Robert W. Lide

Accepted for the Council:

Carolyn R. Hodges

Vice Provost and Dean of the Graduate School

(Original signatures are on file with official student records.)

August 22, 1968

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Accepted for the Council:

Hilton A. Smith
Vice Chancellor for
Graduate Studies and Research

THE DEAMINATION OF DEUTERATED-2-HYDROXY--2-PHENYL-3-AMINONORBORNANES

A Dissertation

Presented to

the Graduate Council of

The University of Tennessee

In Partial Fulfillment

of the Requirements for the Degree

Doctor of Philosophy

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by

Michael D. Eckart

December 1968

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ABSTRACT

2-endo-Hydroxy-2-phenyl-3-endo-aminonorbornane-5,6-exo-d_2 was synthesized and subjected to nitrous acid deamination in glacial acetic acid. From the cationic rearrangement reaction eight products were isolated by liquid elution chromatography and identified by nuclear magnetic resonance spectroscopy. 2-exo-Hydroxy-2-phenyl-3-endo-aminonorbornane was also synthesized and deaminated under similar conditions. The product yields from this compound as well as the product yields from the 2-endo-hydroxy amine were determined by vapor phase chromatography.

From an examination of the deuterium distribution in the products of the deuterated amine and from the yields of products from both amines it was possible to construct a reasonable reaction sequence for the deamination reaction. In addition, because of the deuterium distribution in the products, it was concluded that the intermediate ions in the reaction are principally classical in nature.

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CHAPTER I

INTRODUCTION

Carbon skeletal rearrangements can frequently be initiated by the nitrous acid deamination of primary amines. In general, the carbonium ion so produced engages in the same types of reactions that are attributed to similar ions produced under solvolytic conditions.[1] However, the extent of rearrangement that occurs is usually greater in the ion resulting from deamination.

The formation of the initial diazonium cation (RN_2^+) does not appear to be in dispute.[2] The process was formulated in 1928, and the reaction-rate expression was given by the following equation.[3]

$$v = k(RNH_2)(HNO_2)^2$$

The function of the nitrous acid is to supply dinitrogen trioxide as illustrated.

$$2\ HNONO \rightarrow O{=}N{-}O{-}N{=}O + H_2O$$

NO^+, however, is a more active nitrosating agent than N_2O_3. It is produced in the presence of a strong acid.

$$HONO + 2H^+ \rightarrow H_3O^+ + NO^+$$

A strong acid though is not desirable especially when dealing with aromatic amines as the following reaction can occur.

$$ArNH_2 + H^+ \rightarrow ArNH_3^+$$

Acetic acid is a good choice as it is not strong enough to form a salt but still is acidic enough to be a reasonably good producer of NO^+.

Though the formation of the diazonium salt is fairly well understood, the route to the carbonium ion from the diazonium cation is a subject which is little understood and is open to question. The difficulty lies in that the decomposition of RN_2^+ is extremely rapid, too rapid to measure. This is the most noticeable difference between conventional solvolytic reactions and diazonium salt decompositions. Solvolysis of halides or sulfonates typically require activation energies of 20 kcal/mole while the diazonium salt's requirements are estimated at no more than 5 kcal/mole. This estimate is based upon their "immeasureably fast" reaction rates.

Nevertheless, it is possible to compare the process of diazotization with that of solvolysis. It appears that

deamination with nitrous acid differs fundamentally from solvolysis in at least two ways.[4]

1. The N_2 leaving group bears no charge and therefore charge-charge interactions in the transition state(s) for its departure are small or absent.
2. Molecular N_2 is an exceptionally stable entity and the driving force for its formation is exceptionally high.

The reactions of diazonium salts then were formally rationalized on either of two bases.[5]

1. Departure of N_2 leaves a "hot" carbonium ion, i.e., it requires less energy than solvolysis. It is less selective in its reactions. So the "hot" ion represents the distribution point in the reaction sequence.
2. The distribution point is located earlier in the mechanism. The products are derived not from "hot" carbonium ions but rather from diazonium cations. These ions require but little activation energy for reaction, are relatively unselective, and distribute themselves among several reaction paths, one of them leading to the "cool" ion.[6]

The latter hypothesis was shown to be incorrect by the work of Collins, Benjamin, et al.[7] The diazonium cation does not represent a distribution point for the reaction. The other hypothesis is still valid and implies the idea of the compression of the normal activation energy differences for competing processes into a narrow range that permits the occurrence of reactions that are not observed in normal solvolysis. As an experimental result one generally observes more products arising from the deamination of an amine rather than from the solvolysis of the corresponding halide or sulfonate. A general rule can be stated that of two reacting systems, each of which can be partitioned into a number of product-forming paths, the more reactive state will be the less selective one. It is in terms of this rule that most deamination reactions can be explained.

In the deamination of bridged bicyclic compounds, Wagner-Meerwein rearrangements, hydride shifts, and solvent capture compete together for this same ion and do so rather successfully. In the deamination of derivatives of bicyclo[2.2.1]heptane the percentage of rearrangement seems to be comparatively insensitive to differences in configuration, i.e., exo- or endo-amine, or reaction medium.[8] In solvolysis though a difference is noticed and the extent of rearrangement increases as the nucleophilicity of the solvent increases. As compared with aliphatic

amines, the bridged bicyclic systems have an important advantage over their chain counterparts in forming mesomeric cations. Whereas the open chain system usually must sustain a large entropy loss when the chain aligns itself for proper three-center interaction of a neighboring carbon with the migration terminus,[2] this penalty is not extracted from the bicyclic cases. In the bicyclic cases the neighboring carbon is already rigidly fixed in the proper position.

The deamination of a bridged bicyclo[2.2.1]heptyl amine was first reported in the research literature in 1934 by two different groups, Komppa and Beckmann, and Adler, Stein, Roland, and Schulze.[9] Both groups deaminated the 3-exo-methyl-2-endo-norbornylamine and the 3-endo-methyl-2-exo-norbornylamine in aqueous acetic acid and sodium nitrite to give a mixture of acetates and alcohols. Later in 1937 Hückel and Nerdell reported the formation of substantial quantities of α-terpineol, camphor, and camphene hydrate from the deamination of bornylamine (Figure 1).[10] At the same time an interpretation suggesting two different routes was offered (Figure 2). This interpretation was clarified by Nevell, de Salas, and Wilson in 1939 and became the first suggestion in the research literature of the existence of electronic delocalization in a saturated carbonium ion.[11]

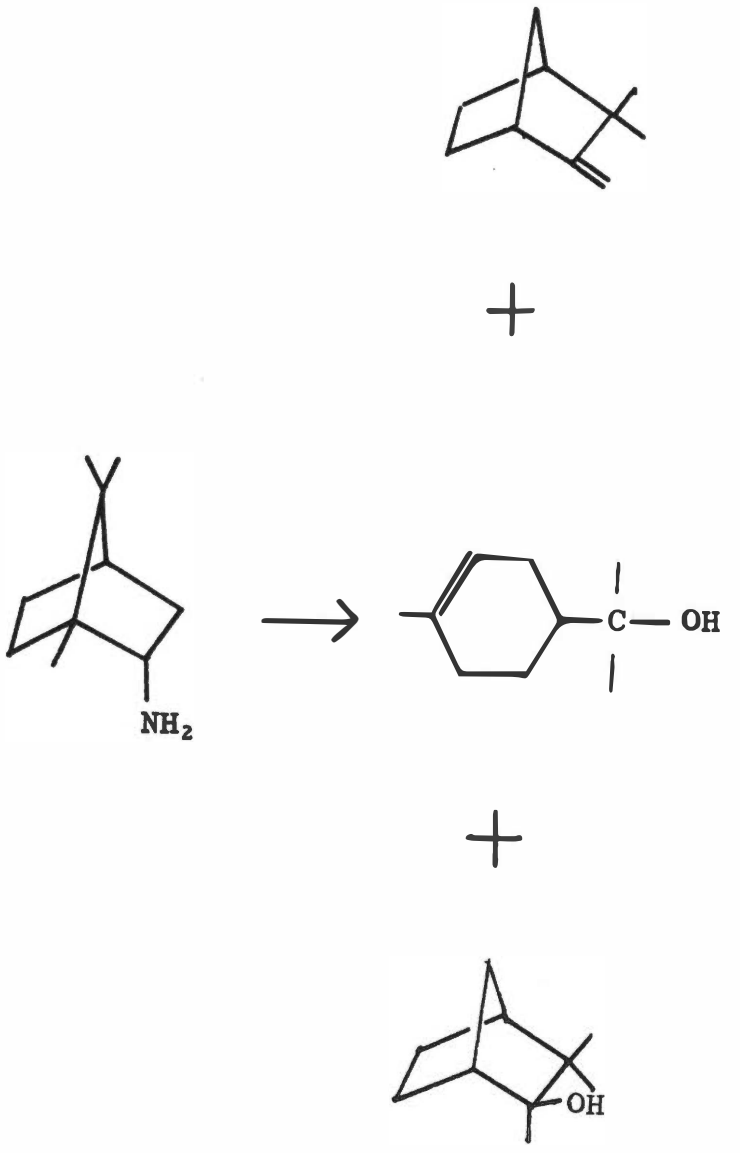


Figure 1. Deamination of bornylamine.

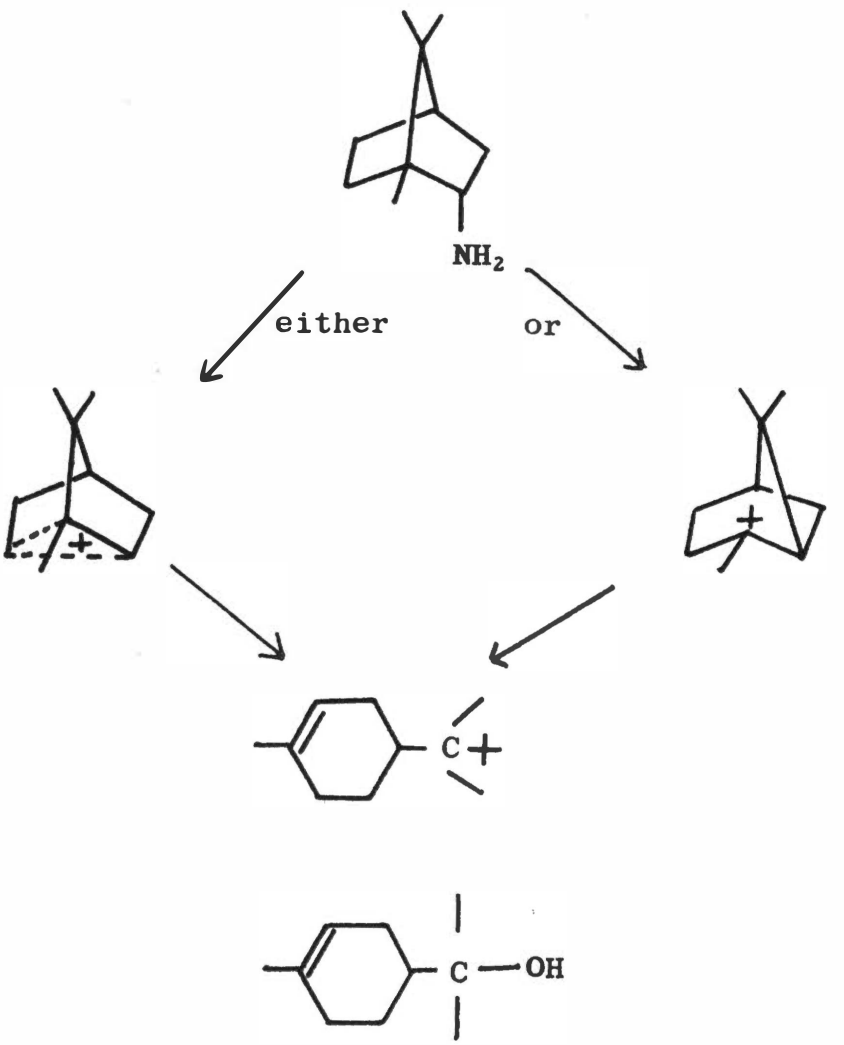
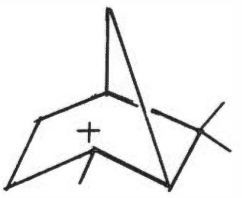
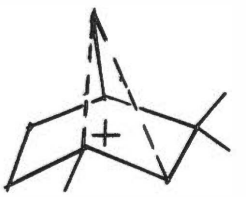


Figure 2. Mechanism for formation of α-terpineol.

Hückel and co-workers in 1947 and in 1954 reported on the nitrous acid deamination of endo- and exo-fenchylamines.[12] In addition to other products the endo amine formed α-terpineol, but this compound was missing as a product from the exo amine. Berson in commenting on these puzzling results concluded that α-terpineol must proceed from either cation "A" or its bridged variant "B."



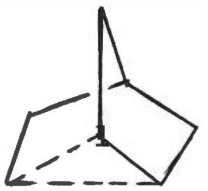
"A"



"B"

No explanation was ventured at this time for the lack of formation of α-terpineol from the exo amine.[13] Ion "B" is an example of what has come to be known as a nonclassical ion. The ion is defined to be nonclassical if its ground state has delocalized bonding sigma electrons.[14] Admittedly this definition may need restricting when discussing other compounds such as phenonium ions but it is perfectly adequate for bicyclic compounds. In 1949 Winstein and Trifan in a published communication provided an impetus for the nonclassical ion concept. They reported that based on

chemical and kinetic evidence the norbornyl cation possessed a nonclassical structure and contained a plane of symmetry.[15] In such an ion,



C_6-C_1 and C_6-C_2 would have bond lengths different from those that would be characteristic of the open classical ion. Because of the partial covalency between C_6, C_1, and C_2 bimolecular attack at either C_1 or C_2 would occur with Walden inversion, i.e., attack would occur from the topside.[16]

In solvolysis an anchimerically assisted ionization[17] is responsible for the formation of the nonclassical ion. Not only are the bridging and the ionization simultaneous acts but the bridging assists the ionization as evidenced by a very large rate increase as compared to similar compounds that do not undergo anchimeric assistance during solvolysis.[17] However, in deaminations which are held to generate carbonium ions in unassisted fashion a nonclassical ion must form subsequent to ionization. In either case there remains the question of whether the structure in which the migrating group forms a bridge to the other carbon atom is a

relatively stable intermediate or just a transient on the way to a new rearranged carbonium ion.

In 1961 Collins, Benjamin, and Wilder while working with aliphatic amines made the following contribution concerning the replacement of the amino group by the hydroxyl group.[18] This replacement with predominant inversion of configuration (Walden inversion) had previously been ascribed to direct displacement through an "SN_2"-like process. Their alternate explanation suggested that open nonbridged ions do not suffer attack equally from both sides by the entering group. This, they reported, had been demonstrated for the 1,2,2-triphenylethyl carbonium ion.

In 1963 Corey, Casanova, Vatakencherry, and Winter after investigating the deaminations of both the exo- and endo-norbornylamines in acetic acid reported essentially the same conclusion.[19] They concluded that the norbornylamines in acetic acid produce an unsymmetrical, essentially classical carbonium ion.

The following year Berson and Remanick repeated essentially the same experiment, differing only in the method of product analysis.[20] Using capillary gas chromatography they were able to extend the limit of detectability of products. Berson and co-workers disagreed not only with Corey's conclusions but also with the experimental results. They report that their results do not require the postulate

of a common carbonium ion precursor of the products from the two amines.

P. D. Bartlett in a commentary discussing the results of both Corey and Berson stated that the different conclusions reached by the two teams reflect ". . . attempts to push the data to the limit of their accuracy under different conditions, without any way of establishing what the ultimate limits of reliability of the data really were."[21]

Berson in continuing his investigation of deaminations and related reactions reported in 1967 a rather extensive investigation involving the solvolysis and the nitrous acid deamination of methylnorbornylamines and the corresponding brosylates.[22] In studying the ratio of nucleophilic capture of cations at Wagner-Meerwein-related sites the group reached the conclusion that the ratios observed in solvolytically produced ions apply also to deaminatively produced ones, the major difference between the two processes being the excess of "direct substitution" observed in deamination. This conclusion is the same as what was hypothesized earlier in that cations from deamination in general undergo the same reactions as those produced from solvolysis.

Therefore, it would be expected that the results of Collins, Benjamin, and Ponder published in 1966 concerning the solvolysis of the 2-<u>endo</u>-phenyl-2-hydroxy-3-norbornyl-tosylate would have some application in the corresponding

amine.[23] The group demonstrated a stereospecific elimination of deuterium and stereospecific 5,4 migration (corresponding to a 6,1 migration in unsubstituted norbornane). In addition they also demonstrated that in hydrolysis consecutive hydride shifts are possible. These same rearrangements would be expected to occur in a deamination reaction but because of the compressed energy scale the relative importance of each would be altered. The processes that are slow to occur during solvolysis because of high-energy barriers would be more likely to occur when this scale is compressed by the generation of the so-called "hot" carbonium ion.

CHAPTER II

STATEMENT OF PROBLEM

The purpose of this dissertation is to propose a reasonable reaction pathway for the nitrous acid deamination of a substituted norbornylamine. In addition it is hoped that the information acquired will give some evidence as to whether the intermediate ions involved in the cationic rearrangement are open classical ions or bridged nonclassical ions.

To accomplish this purpose it was necessary to synthesize three amines:

I) 2-endo-hydroxy-2-phenyl-3-endo-aminonorbornane-5,6-exo-d_2

Ia) 2-endo-hydroxy-2-phenyl-3-endo-aminonorbornane-3-exo-d_1

II) 2-exo-hydroxy-2-phenyl-3-endo-aminonorbornane

From compounds No. I and No. Ia it is possible to isolate eight products from the deamination reaction and identify the location of deuterium in each. This gives the sequence of hydride shifts and Wagner-Meerwein rearrangements. The yield of each product serves to help evaluate the classical or nonclassical character of the intermediate ions. Amine II differing only in the spatial arrangement of the phenyl and hydroxyl groups should give products and yields

complementary to those derived from the first two amines. Since the leaving group is on the opposite side, the reaction should demonstrate the steric and solvation effects that are present.

CHAPTER III

EXPERIMENTAL

Unless otherwise indicated, all melting points reported were obtained by means of a Kofler hot bench.

Nuclear magnetic resonance (nmr) spectra were obtained with a Varian Model A-60 with attached spin decoupler. The instrument was calibrated with a chloroform-tetramethylsilane (TMS) mixture with chloroform being 436 cycles per second (cps) downfield from TMS. All chemical shifts are reported in sigma (ppm) values. The temperatures used when obtaining the spectra were that of the magnet.

Vapor phase chromatography (vpc) results were obtained from a Barber-Coleman Model 5005 instrument equipped with a flame ionization detector. The glass columns used were 6 ft long with an inside diameter of 5 mm. Column packings and operating conditions are as indicated.

The liquid elution chromatography tubes were packed with activated alumina. The alumina was conditioned prior to use by being dried in an oven at 125^{o} for a period of not less than 3 hr; after removal from the oven 10 ml of water were added per pound of alumina to partially deactivate it.

All chemicals used were reagent grade unless otherwise specified.

A. 2-*endo*-HYDROXY-2-PHENYL-3-*endo*-AMINONORBORNANE-5,6-*exo*-d_2

1. Synthesis

The amine was prepared by the reaction sequence outlined in Figure 3.

a. *2-endo/exo-Norborneol-5,6-exo-d_2*. Fifty g (0.445 moles) of 5-norbornene-2-ol (a mixture of *endo* and *exo* isomers) were dissolved in 250 ml of absolute alcohol. For a catalyst 1 gm of 20 per cent palladium on Norit was added. Deuterium was supplied by the electrolysis of heavy water. Prior to the introduction of the deuterium gas the reaction flask was evacuated. The rapid uptake of the gas by the olefin maintained a reduced pressure during the course of the reaction. When the pressure inside the flask reached atmospheric pressure the generation of deuterium automatically ceased and the reaction was judged complete.

Since the deuterium oxide was contaminated with water, deuteration was not complete. An analysis revealed 1.84 deuterium atoms instead of 2.00 deuterium atoms in the 5,6-*exo* positions, the difference being hydrogen. Virtually all of the addition was in the *exo* position with not more than 3 per cent being in the *endo* position.[24]

The product was recovered by first filtering the catalyst and then distilling the solvent away through a

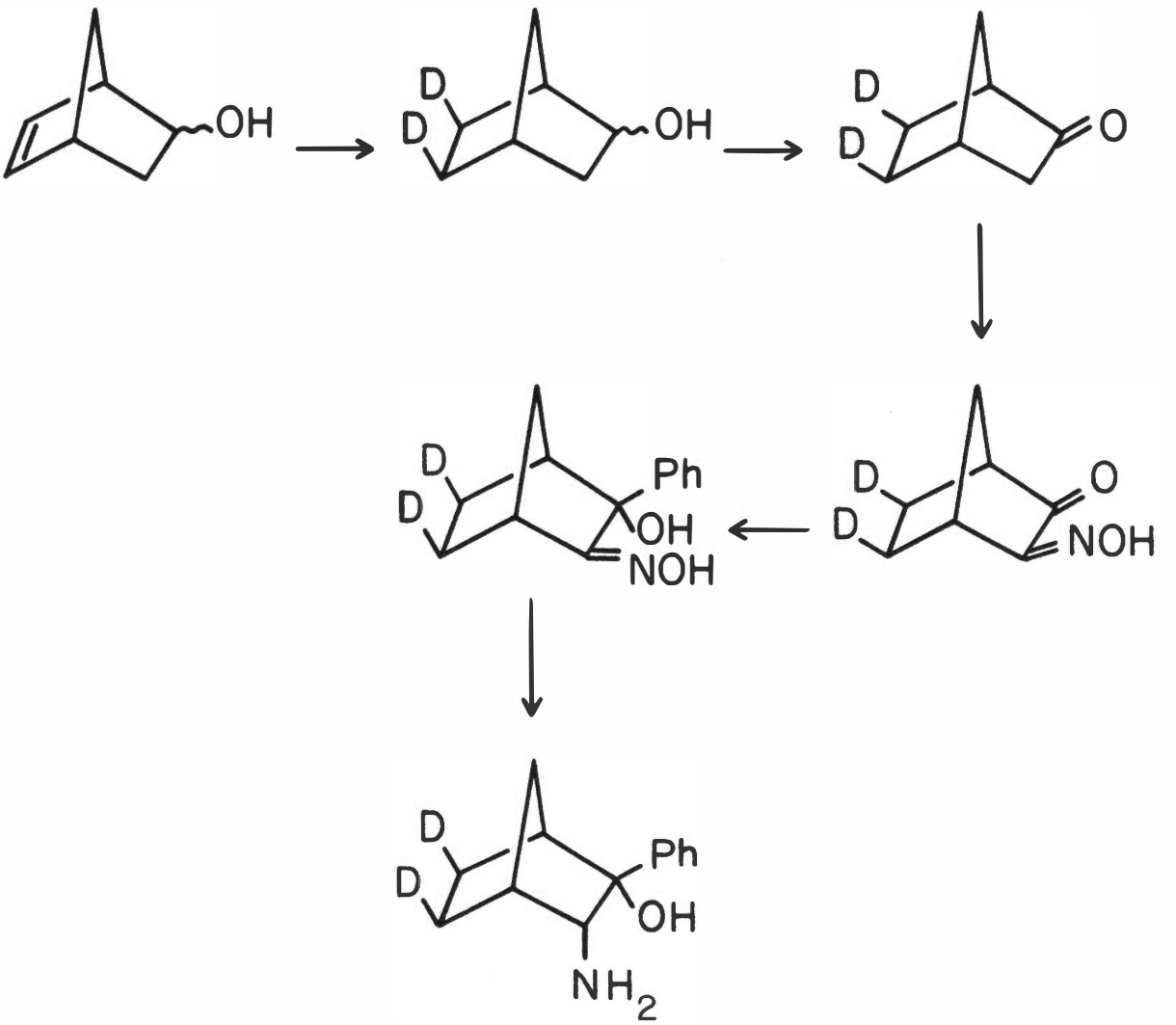


Figure 3. 2-endo-Hydroxy-2-phenyl-3-endo-aminonorbornane-5,6-exo-d_2.

Vigreux column under reduced pressure. The product, 52.0 g (0.454 moles; 100%), was a white waxy solid. A melting point (mp) was not taken.

b. 2-Norcamphor-5,6-exo-d_2. The deuterated alcohol was oxidized with an 8 N (8 N with respect to oxygen) chromic acid solution. The oxidizing solution was prepared by first dissolving 26.0 g of chromium trioxide in a small amount of water. Then 26.0 g of sulfuric acid was added and the contents were diluted with water to volume in a 100-ml volumetric flask.[25]

To 23.0 g (0.200 moles) of the alcohol dissolved in 300 ml of acetone, 50.0 ml (0.400 moles) of the chromic-acid solution was added dropwise with stirring and cooling. After addition was complete the black tarry reaction mixture was stirred with difficulty for an additional 30 min. The temperature during the addition and subsequent stirring period was maintained at 15° by immersion of the reaction flask in an ice-water bath. The mixture was then allowed to come slowly to room temperature. The bulk of the acetone was distilled from the flask through a Vigreux column under the pressure of a water aspirator using a minimum amount of heat. Some loss of the norcamphor was unavoidable as it is a fairly volatile compound. The reaction mixture was then diluted with water, washed with sodium bicarbonate solution, and extracted with several portions of ether (total volume,

300 ml). The ether solution was dried over magnesium sulfate, then filtered. The ether was stripped off through a Vigreux column under the pressure of a water aspirator. Norcamphor precipitates, 5.38 g (0.048 moles; 24%), and remains in the flask. A mp was not taken.

c. 3-Oximino-2-ketobicyclo[2.2.1]heptane-5,6-exo-d_2. A solution of potassium tert-butoxide was prepared by dissolving 8.6 g (0.22 moles) of potassium in 280 ml (2.91 moles) of tert-butyl alcohol. To this solution was added 22.4 g (0.200 moles) of the deuterated norcamphor. After cooling the reaction vessel to 0^{o} by immersion into an alcohol-ice water bath 24.6 g (0.200 moles) of freshly prepared and distilled iso-amyl nitrite[26] was slowly added while the reaction flask was swirled gently by hand. After addition was complete the reaction mixture was continuously swirled for the next 20 min. Following this action 50 ml of light petroleum ether ($30-60^{o}$) was added, and the flask was agitated intermittently for the next 2.5 hr while the temperature was maintained at slightly less than 0^{o}. After a total reaction time of 3 hr the mixture was diluted with 300 ml of light petroleum ether, and the potassium salt of the oxime was extracted with successive small portions of water (total volume, 150 ml). The combined aqueous layer was then washed once with light petroleum ether. The water solution

containing the salt was then cooled to 0°, and ammonium chloride and dilute hydrochloric acid were added to adjust the pH to the 7-8 range. If the pH falls below 7 a Beckman-type rearrangement occurs which destroys the oxime. The slightly alkaline solution was extracted with many small successive portions of ether (total volume, 300 ml). The ether extracts were combined and dried over magnesium sulfate and sodium bicarbonate, then filtered. Solvent was removed through a Vigreux column under reduced pressure. Then with heating to 35° and under high vacuum (0.5 mm Hg) the last traces of tertiary butyl alcohol and iso-amyl alcohol were removed. The product was a brown viscous oil, 15.81 g (0.112 moles; 56%), and was stored in the refrigerator.

d. 2-endo-Hydroxy-2-phenyl-norbornane-5,6-exo-d_2-3-oxime. A solution of phenylmagnesium bromide was prepared by adding 7.00 g (0.29 moles) of magnesium to 40.0 g (0.255 moles) of phenyl bromide in anhydrous ether. Using inverse addition the Grignard reagent was added slowly to a solution of 13.0 g (0.092 moles) of the oxime also in anhydrous ether. After addition was complete the reaction mixture was refluxed for 7 hr and then allowed to stand overnight. Previous experience had shown that a long reflux time increased the yield significantly because the initial complex formed was relatively insoluble

in ether. The reaction was worked up in the customary manner using water and ammonium chloride except that careful attention was given to maintaining the pH greater than 7 to avoid a Beckman-type rearrangement of the oxime. The material was extracted into ether, dried over magnesium sulfate, and then filtered. Most of the ether was then removed through a Vigreux column while being heated on the steam bath. Before the flask went to dryness chloroform and hexane were added, and then the remainder of the ether was allowed to distill. The material was placed in the refrigerator to crystallize. The crystals, 2.948 g (0.0184 moles; 20%; mp 138°), were collected by suction filtration.

e. 2-endo-Hydroxy-2-phenyl-3-endo-aminonorbornane-5,6-exo-d_2. To a slurry of 2.60 g (0.0682 moles) of freshly powdered lithium aluminum hydride in 77 ml of anhydrous ether was added 5.0 g (0.023 moles) of the deuterated 2-endo-hydroxy-2-phenyl-norbornane-3-oxime dissolved in 80 ml of anhydrous ether. The mixture was refluxed for 6 hr and then stirred overnight at room temperature. The excess hydride was decomposed with sodium hydroxide and water in the approved fashion to produce a granular precipitate of the aluminate salts. The precipitated salts were filtered and then heated with ether under reflux to remove the last traces of the amine. The ether extracts were combined,

dried over magnesium sulfate, and filtered. Into the resultant anhydrous ether solution was bubbled dry hydrogen chloride gas (from a cylinder) in order to precipitate the amine hydrochloride. The salt was collected by suction filtration and purified by recrystallization from an ethanol ether solution to give 5.04 g (0.0209 moles; 91%, mp 234°), of pure material.

The free amine was obtained by warming the hydrochloride salt in a water solution of sodium hydroxide and sodium bicarbonate. The amine was then extracted into ether, treated with decolorizing charcoal, dried over magnesium sulfate, and filtered. The solvent was removed through a Vigreux column under the pressure of a water aspirator to leave 4.20 g (0.0205 moles; 98%; mp 94°), of the amine, a white solid.

The over-all conversion from 5-norbornene-2-ol to the 2-endo-hydroxy-2-phenyl-3-endo-aminonorbornane-5,6-exo-d_2 was 2.5 per cent.

2. Deamination of 2-endo-hydroxy-2-phenyl-3-endo-aminonorbornane-5,6-exo-d_2

To 27.89 g (0.1380 moles) of the free amine and 84.21 g (0.505 moles) of anhydrous sodium acetate dissolved in 609 g (10.1 moles) of glacial acetic acid was added 70.5 g (1.01 moles) of sodium nitrite. The sodium nitrite was added slowly in small 2-g quantities over a 3-day

period. After the addition was complete the reaction was allowed to stand for 2 additional days. During the 5-day reaction period the 1-l, round-bottomed flask was maintained at room temperature and swirled by hand frequently during the day. The mixture was then poured over 250 g of ice and 250 ml of ether. While being stirred vigorously the mixture was partially neutralized with 248 g (6.21 moles) of sodium hydroxide which was added in the form of a 10 per cent aqueous solution at 0^{o}. A large quantity of sodium bicarbonate was used to buffer the mixture. The organic material was extracted with ether. The combined extracts were dried over magnesium sulfate, treated with decolorizing charcoal, and then filtered. Distillation of the filtrate through a Vigreux column under the pressure of a water aspirator removed the bulk of the solvent. Continued distillation under high vacuum (0.5 mm Hg) with heating to 30^{o} for 2 hr completed the removal of solvent. The resulting acetates, 31.53 g (0.127 moles; 92%), these are approximate values as all of the products do not have the same molecular weight, were a dark-brown viscous oil and remained in the flask.

3. Separation of Products

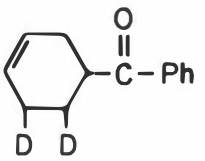
The 31.53 g (approximately 0.124 moles) mixture of acetates were placed on a column (2.5 cm x 120 cm) of alumina. Using hexane as the eluent, only one product was

recovered, the cyclohexenyl phenyl ketone ($C_6H_5COC_6H_7D_2$). The ketone, 5.37 g (0.0288 moles), however, was not pure. When the eluted material dropped to less than 0.012 g of nonvolatiles per 100 ml of eluent, collection of the ketone was stopped, and the column was washed with a solution of 10 per cent methanol in ether. This solution eluted the remainder of the products, a mixture of 7. The alumina was removed from the column and washed with methanol, ether, and water to assure as complete a recovery as possible. This material, mg quantities, was added to the other eluted material to give a total of 23.306 g (approximately 0.0892 moles) of recovered acetates in addition to the 5.373 g (0.0288 moles) of the cyclohexenyl phenyl ketone. The column yield was 0.1181 moles (93%).

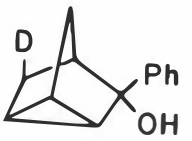
The acetates were then reduced to their corresponding alcohols with lithium aluminum hydride by the following procedure. Twelve g (0.316 moles) of freshly ground lithium aluminum hydride were placed in anhydrous ether, and the slurry was slowly added to the 23.31 g (approximately 0.0892 moles) of acetates also dissolved in anhydrous ether. After the addition was complete the reaction mixture was refluxed for 4 hr and then stirred overnight at room temperature. Water and sodium hydroxide were added in the usual fashion in order to produce a granular precipitate which was filtered. Ether was then distilled from the

filtrate through a Vigreux column under the pressure supplied by a water aspirator to give 18.60 g (approximately 0.0892 moles; 100%), of alcohols which remained in the flask.

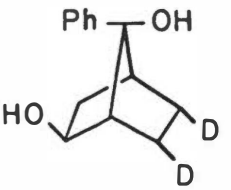
The alcohols were then placed on a column (2.5 cm x 120 cm) of alumina. Eluents used in their order of use were benzene, benzene and ether, ether, and methanol and ether. When the nonvolatile eluted material reached a value of less than 0.006 g per 100 ml of eluent the alumina was removed from the column and refluxed in methanol to remove residual traces of compounds that may have been retained on the column. Figure 4 shows the order of retention of the compounds on the alumina and the solvent mixtures necessary to elute them. The solvent ratios should be interpreted as only approximate as they will vary from column to column depending upon the activity of the alumina used. Only the gross ratios are represented while in actual practice when introducing another solvent component the per volume value of the added material was on the order of less than 1 per cent. By changing the ratios slowly it is possible to obtain a fairly good separation based solely on elution chromatography. Approximately 31 liters of solvent were employed in the process. Of the 18.60 g (0.0892 moles) of alcohols placed on the column 18.58 g (0.0892 moles; 100%) were recovered.



1 hexane



2 benzene



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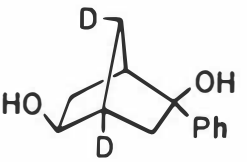
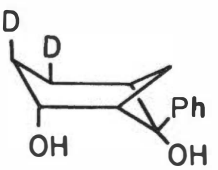
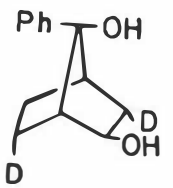


4 ether:benzene 1:1



5 ether



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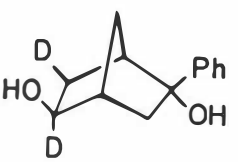
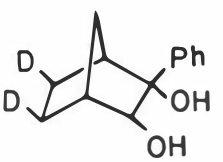


7 methanol:ether 1:100



8 methanol:ether 5:100

Figure 4. Retention order of products on activated alumina.

4. Purification of Products

The Δ^3-(cis-5,6-dideutero)-cyclohexenyl phenyl ketone (compound 1, Figure 4, page 26) was distilled to give seven fractions boiling in the range from 104-145°/ 0.5 mm, none of which was pure. First for identification purposes the semicarbazone derivative was prepared by the procedure outlined in "The Systematic Identification of Organic Compounds."[27] Derivatives were prepared from both a low-boiling and a high-boiling fraction. Both derivatives after purification by crystallization had a mp of 146°. From a known sample of the alcohol, prepared by I. T. Glover, a previous investigator, the same derivative was prepared after the alcohol had been oxidized to the corresponding ketone by a mild chromic-acid oxidation. A mixture of semicarbazones, the known compound and the suspected compound, had a mixed mp of 146°.

The nmr spectrum of the ketone was too complex to analyze in order to determine the position of deuterium in the molecule. If the ketone could have been purer this might have been possible. Therefore, it was necessary to find a derivative of the ketone that would not change the position of deuterium in the molecule but would allow easy purification and analysis by nmr spectroscopy. Oxidation of the olefinic bond to give the dicarboxylic acid (3-benzoyl-4,5-dideuteroadipic acid) was such a compound.

The reaction was carried out by the procedure of Leumiuex and von Pudoff.[28] One g (0.0053 moles) of the ketone was dissolved in 10 ml of dioxane. Water was added until the ketone just began to precipitate then an additional 1 ml of dioxane was added. This was followed by the addition of 2.21 g (0.0159 moles) of potassium carbonate, 9.8 g (0.042 moles) of potassium iodate, and 2.71 g (0.0171 moles) of potassium permanganate. The reaction mixture was stirred for 2 days at room temperature. After acidification with sulfuric acid the organic material was extracted into ether. Evaporation of the ether extract through a Vigreux column while being heated on the steam bath left an amorphous brown mass in the flask. Crystallization of the material from a chloroform-hexane mixture gave a white solid with a mp of 130°. The compound was the dicarboxylic acid $(C_6H_5)COCH(CH_2CO_2H)(CHDCHDCO_2H)$.

Anal. Calcd for $C_{13}H_{14}O_5$: C, 62.40; H, 5.65. Found: C, 62.48; H, 5.53.

The impure anti-6-deutero-2-phenyl-2-nortricyclenol (compound 2, Figure 4, page 26) was a liquid. Initial attempts to purify by sublimation proved unsuccessful as a liquid condensate always collected on the cold finger of the sublimation apparatus. Success was obtained though after installing a "bucket" immediately under and suspended from the cold finger. The liquid that condensed then fell

into the bucket, but since the container did not reach into the bottom of the tube it was not heated; the liquid impurity was then effectively removed from the sublimation process. Repeating the process three times at a temperature of 50° under a vacuum of 0.5 mm Hg gave a white crystalline compound with a mp of 56°.

The 5,6-endo-dideutero-7-hydroxy-7-syn-phenyl-2-exo-hydroxynorbornane (compound 3, Figure 4, page 26), more easily referred to as the anti-diol, was obtained as a solid following evaporation of the eluent. It was easily recrystallized from chloroform-hexane to give a light, fluffy material that was quite distinctive in appearance. The mp of the recrystallized material was 98°.

The following two compounds were eluted almost together. The 4,5-dideutero-2,5-exo-dihydroxy-2-phenyl-norbornane (compound 4, Figure 4, page 26) preceded the 4,5-cis-exo-dideutero-2,6-endo-dihydroxy-2-phenyl bicyclo-[3.1.1]heptane (compound 5, Figure 4, page 26) only slightly. Compound 4 can be crystallized readily from chloroform-hexane. The residue is principally compound 5 and associated impurities. Compound 5 is difficult to crystallize and will not crystallize from a chloroform-hexane mixture. The residue was evaporated to leave an amorphous residue. This residue was placed on a sintered glass filter and washed with ether. Compound 5 is soluble in ether, but the

other compound is only sparingly soluble. Subsequent evaporation of the filtrate ether and successive repetition of the process proved to be an effective means for removing gross contamination. Compound 5 then was crystallized from an ether-hexane mixture with 1-2 drops of ethanol added. Repeated crystallization gave relatively pure 5 with a mp of 78°. Compound 4 after three crystallizations melted at 155°.

The next two compounds were also eluted from the chromatographic column together. The 3,6-endo-dideutero-2,7-syn-dihydroxy-7-phenylnorbornane (compound 6, Figure 4, page 26) is known more simply as the syn-7-diol. This compound was eluted with the 5-endo-6-exo-dideutero-2-endo-5-exo-dihydroxy-2-phenylnorbornane (compound 7, Figure 4, page 26). Compound 7 is present in much larger quantities than the syn-7-diol and therefore tends to crystallize first from a chloroform-hexane mixture. Continued crystallization of 7 eventually gave after five operations a compound with a mp of 165°. The residue from this crystallization then becomes relatively richer in the syn-7-diol. Evaporation of the chloroform-hexane residue left a brown amorphous material that was placed in a sintered glass funnel and washed with ether. Compound 7 is relatively insoluble in ether, but compound 6 is readily soluble. Repeating the operation several times gave a solution from which 6 would crystallize. Crystallization

was effected from an ethanol-carbon tetrachloride mixture to give a product that melted at 105°.

The last compound to be eluted from the column of alumina was the 5,6-exo-dideutero-2,3-endo-dihydroxy-2-phenylnorbornane (compound 8, Figure 4, page 26). For reasons of simplicity, this compound is referred to as the di-endo-diol. Compound 8 was not eluted as a pure compound. The principal impurity was compound 7. Crystallization of the eluted material from an ethanol-carbon tetrachloride mixture gave two different types of crystals. When the crystallization was carried out slowly over a period of 3 wk the different crystals were discernible enough so that with the aid of a magnifying glass and tweezers a physical separation could be achieved between compounds 7 and 8. Repetition of this procedure three times provided a relatively pure sample of the di-endo-diol with a mp of 85°.

B. 2-endo-HYDROXY-2-PHENYL-3-endo-AMINONORBORNANE-3-exo-d_1

1. Synthesis

The amine was prepared by the reaction sequence outlined in Figure 5. The amine was prepared in the same manner as the preceding amine that is illustrated in Figure 3 (page 17). However, the following differences exist. The starting material was undeuterated norcamphor

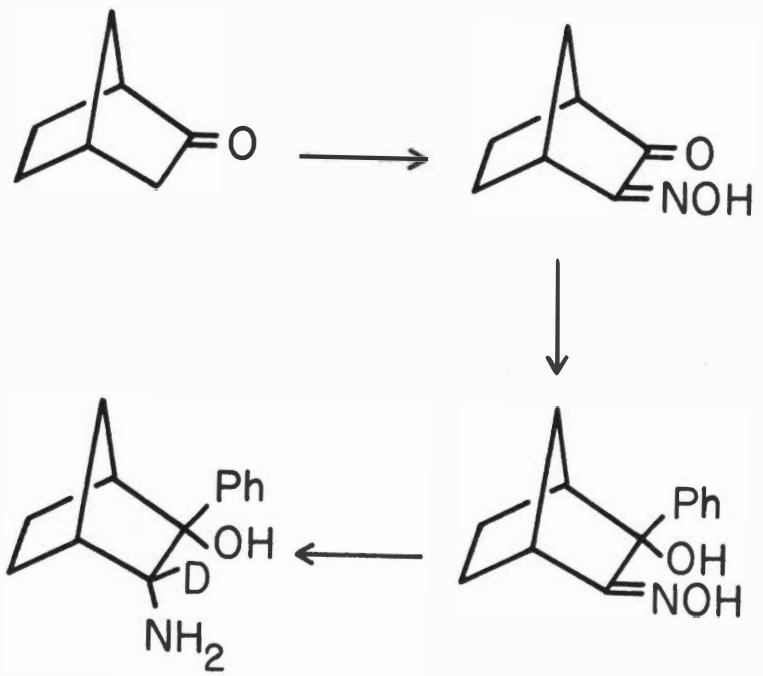


Figure 5. 2-endo-Hydroxy-2-phenyl-3-endo-aminonorbornane-3-exo-d_1.

and the reduction of the oxime was accomplished with lithium aluminum deuteride instead of hydride. The sequence is shown in Figure 5.

Twelve g (0.0568 moles) of the oxime which had been previously prepared was dissolved in anhydrous ether. To this solution was added a slurry of 3.6 g (0.068 moles) of freshly ground lithium aluminum deuteride in anhydrous ether. The reaction mixture was heated under reflux for 6 hr, then allowed to stand overnight at room temperature. Excess deuteride was destroyed with the alternate additions of water and aqueous sodium hydroxide in order to produce a granular precipitate which was filtered. The filtrate was dried over magnesium sulfate. The drying agent was removed by filtration and dry hydrogen chloride gas (from a cylinder) was then passed into the anhydrous ether solution to precipitate the amine hydrochloride salt, 11.5 g (0.0498 moles; 88%), which was filtered and dried in air.

The free amine was recovered by dissolving the salt in an aqueous solution that was made basic by the addition of sodium carbonate and bicarbonate. The material was extracted into ether. The extract was dried, filtered, and evaporated to leave 9.58 g free amine (0.0488 moles; 98%; mp 94^{o}) of a white solid.

2. Deamination of 2-endo-hydroxy-2-phenyl-3-endo-amino-norbornane-3-exo-d_1

A 5.9 g (0.025 moles) portion of the amine was deaminated with 18.8 g (0.229 moles) of sodium acetate and 15.75 g (0.227 moles) of sodium nitrite in 166 g (2.77 moles) of acetic acid. The sodium nitrite was added slowly in small quantities over a 3-day period. The deamination procedure and the work-up of the reaction was identical to that described earlier (page 22). The weight of the deamination product was 6.0 g (approximately 0.024 moles; 96%).

3. Separation of Products

The products of the deamination were placed on a column of alumina (2.5 cm x 75 cm) and eluted with hexane. A center fraction gave a reasonably pure sample of the cyclohexenyl phenyl ketone. Since this was the only compound of interest no attempt was made to isolate the remainder of the compounds. The rest of the products were eluted with a solution of methanol in ether and saved for future use. The object here was to secure enough of the ketone in sufficient purity for nmr analysis. Purification by oxidation of the olefinic bond was not possible because the deuterium was located on one of the olefinic carbons.

C. 2-exo-HYDROXY-2-PHENYL-3-endo-AMINONORBORNANE

1. Synthesis

The amine was prepared by the reaction sequence outlined in Figure 6.

a. 2-endo-Hydroxy-2-phenylnorbornane. Using inverse addition 54.4 g (0.0300 moles) of freshly prepared phenylmagnesium bromide in anhydrous ether was slowly added to an anhydrous ether solution of 27.55 g (0.250 moles) of norcamphor. The reaction mixture was refluxed and stirred for the next 5 hr and allowed to stand overnight at room temperature. The following day the mixture was worked up in the usual manner using ammonium chloride and water, and the organic material was separated by extraction into ether. The ether extracts were combined, dried over magnesium sulfate, and filtered. The product remained in the flask after evaporation of the ether solvent on the steam bath. The 45.2 g (1.20 moles; 96%) product was a nearly colorless oil that solidified when placed in the refrigerator.

b. 2-Phenyl-2-norbornene. Into a solution containing 132.7 g (1.30 moles) of acetic anhydride and 190 g (2.40 moles) of pyridine was dissolved in 133.0 g (1.20 moles) of the 2-endo-hydroxy-2-phenylnorbornane. The resulting solution was heated on the steam bath with stirring for 16 hr. The material was then distilled through a Vigreux column

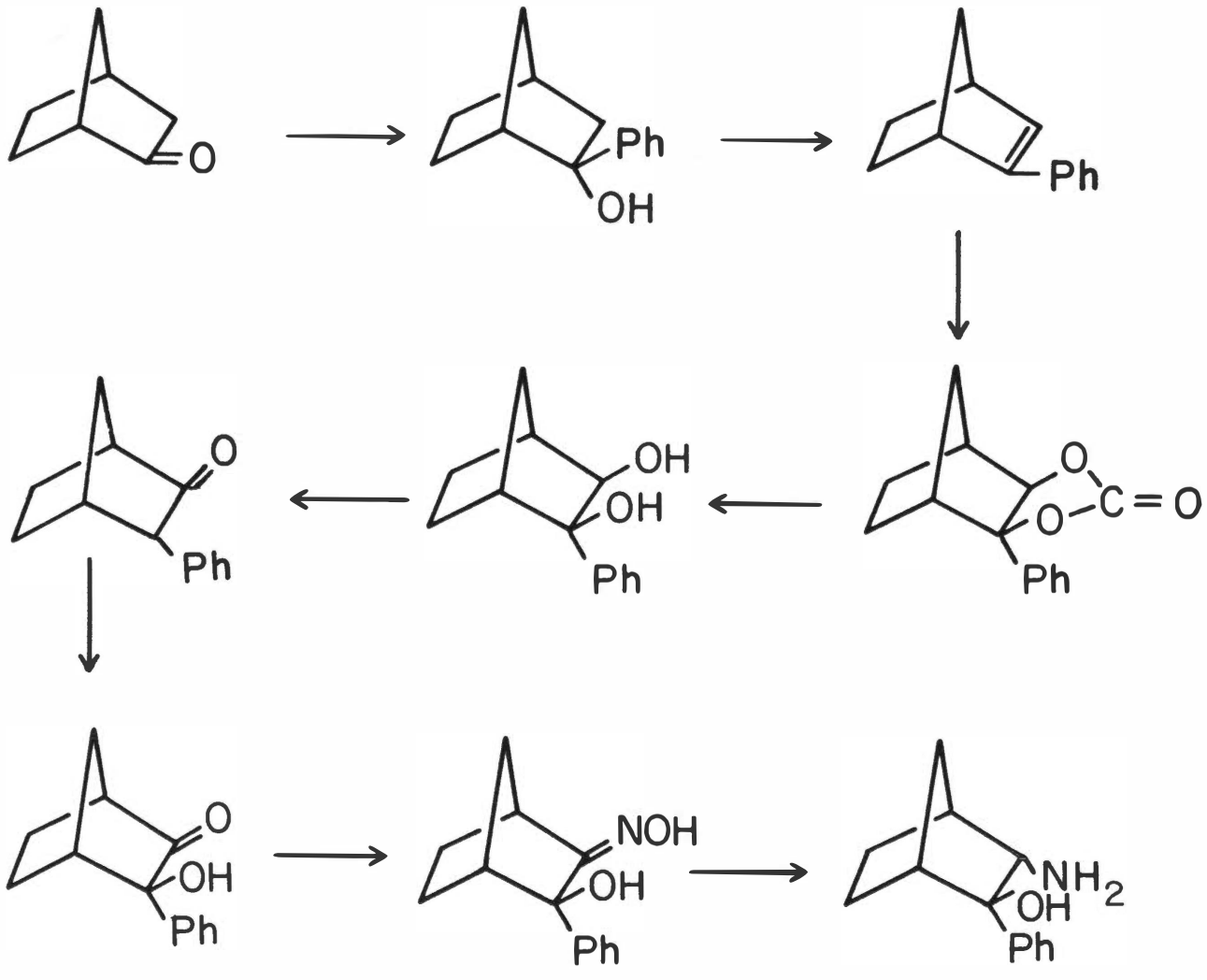


Figure 6. 2-<u>exo</u>-Hydroxy-2-phenyl-3-<u>endo</u>-aminonorbornane.

under high vacuum to give 133 g (0.781 moles; 69%; bp 70-80°/ 0.5 mm) of the olefin.

c. 2-endo-Phenyl-2,3-exo-norbornyl carbonate. Eighty-three g (0.488 moles) of the norbornene was added dropwise at a temperature < 45° to 150 ml (2.0 moles) of 30 per cent hydrogen peroxide and 350 ml (9.0 moles) of 97 per cent formic acid. After addition was complete the mixture was stirred overnight at room temperature. Isolation of the product was achieved by extraction into chloroform with many small volumes (total volume 500 ml). The bulk of the chloroform (400 ml) was then removed by means of a rotatory evaporator. The chloroform remaining was washed with an aqueous solution of sodium bicarbonate to remove residual traces of acid. The material was allowed to crystallize then from a chloroform-hexane solution. Recrystallization from the same system gave 67.0 g (0.291 moles; 37%; mp 54°) of pure product.

d. 2-exo-Hydroxy-2-phenyl-3-exo-hydroxynorbornane. Sixty-seven g (0.291 moles) of 2-endo-phenyl-2,3-exo-norbornyl carbonate was added to a solution composed of 28 g (0.5 moles) of potassium hydroxide, 100 ml of water, and 25 ml of ethanol. The mixture was stirred magnetically at reflux temperatures for 5 hr. Ethanol was then removed by distillation at reduced pressure leaving an oil which

was dissolved in water, salted out with sodium chloride, and extracted into ether. The ether extract was dried over magnesium sulfate, filtered, then distilled. The glycol product distilled at 135-140°/3 mm. Crystallization of the distillate from ether gave 35.0 g (0.171 moles; 59%; mp 60°) of product which were washed with hexane and dried in air.

e. 2-endo-Phenyl-3-norcamphor. Ten g (0.049 moles) of the di-exo-hydroxy compound was dissolved in a minimum amount of dioxane and added dropwise to concentrated sulfuric acid at 0°. After the addition was complete the reaction mixture was maintained at 0° and stirred for an additional 30 min. The mixture was then poured over ice and extracted into ether. The ether extract was washed with aqueous sodium bicarbonate, dried over magnesium sulfate, filtered, and distilled at high vacuum. The product, 11.2 g (0.049 moles; 100%; bp 110-113°/0.5 mm), was a viscous oil at room temperature.

f. 2-exo-Hydroxy-2-phenyl-3-norcamphor. The Biltz reaction was conducted in small batches of less than 5 g each as larger quantities proved difficult to control.

To 3.5 g (0.019 moles) of the 2-endo-phenyl-3-norcamphor dissolved in 25 ml (0.450 moles) of acetic acid was added 5 ml of concentrated nitric acid. The mixture was placed on the steam bath for a 10-15 min period.

After removal it was cooled and poured on 20 g of ice from which the organic material was extracted into ether. The ether extract was washed with aqueous sodium bicarbonate, dried over magnesium sulfate, and filtered. Evaporation of the ether gave a 4.6 g crude product. The crude products from multiple runs were collected to give a total of 41 g of unpurified material from an initial 35 g (0.186 moles) of the phenyl norcamphor. The material was placed on a column (2.3 cm x 100 cm) of alumina. Hexane, the first eluent, removed from the column material that solidified and a small amount of unreacted material. A mixture (1/1 on a v/v basis) of hexane-benzene eluted 8.6 g (0.043 moles; 23%) of pure product. The product was a viscous oil whose identity was confirmed by nmr analysis. Further elution of the column with more polar materials gave products that turned brown on exposure to air.

g. 2-exo-Hydroxy-2-phenyl-3-oximino-norbornane. To 8.6 g (0.042 moles) of the 2-exo-hydroxy-2-endo-phenyl-3-norcamphor dissolved in 24 ml (0.285 moles) of pyridine was added a total of 12.6 g (0.181 moles) of hydroxylamine hydrochloride. Eight g of the hydroxylamine was added initially to the reaction mixture. After the reaction flask had been heated on the steam bath for 30 min the remainder of the hydroxylamine was added. The reaction was allowed to stand overnight at room temperature. The following day water was

added to the mixture and the organic material was extracted into ether. Pyridine was removed from the ether extract by washing with 6 N hydrochloric acid and then extracting the salt into water. The remaining ether solution was washed once with water and with sodium bicarbonate solution to remove the last traces of acid. This was followed by drying over magnesium sulfate, filtration, and evaporation of the ether from an open flask on the steam bath by passing a stream of air over the volatile solvent. The residue was crystallized from chloroform-hexane to give 2.55 g (0.013 moles; 27%; mp 133°) of pure material.

h. 2-exo-Hydroxy-2-phenyl-3-endo-aminonorbornane. To 2.55 g (0.013 moles) of the oxime dissolved in anhydrous ether a slurry of freshly ground lithium aluminum hydride in anhydrous ether was added dropwise. Addition of the hydride continued until hydrogen evolution ceased. Then a small additional quantity was added and the reaction mixture was allowed to stand at room temperature with stirring for 30 min. Following this period additional hydride was added and the mixture was again allowed to stand with stirring for a similar time period. The reduction reaction was worked up in the usual fashion with the excess lithium aluminum hydride being decomposed by alternate additions of water and sodium hydroxide solution. The organic material was extracted into ether and the extract was dried over

magnesium sulfate, then filtered. Dry hydrogen chloride gas (from a cylinder) was bubbled into the resulting anhydrous ether solution to form the amine hydrochloride salt which precipitated as an oil. Evaporation of the ether by passing a stream of air over it left an oily residue which was dissolved in water. The aqueous solution was extracted once with ether to remove any hydrocarbons, and then was heated with sodium hydroxide until the solution was strongly basic. The free amine was extracted back into ether and the extract was dried over magnesium sulfate and filtered. Dry hydrogen chloride was again bubbled into the ether solution which again caused an oil to separate. The oil was recovered from the ether by using the same method employed before. The oily residue was taken up in a small quantity of acetone which was allowed to evaporate at room temperature. The semidry material was placed in a vacuum desiccator with 4A molecular sieve. After drawing a relatively high vacuum (1.0 mm Hg), crystallization occurred to give 0.428 g (0.00189 moles; 15%; mp 189°) of the amine hydrochloride. The over-all conversion from norcamphor to the amine hydrochloride was 0.13 per cent.

2. Deamination of 2-exo-Hydroxy-2-phenyl-3-endo-norbornylamine Hydrochloride

To a solution of 0.460 g (0.0056 moles) of sodium acetate dissolved in 13 ml (0.228 moles) of glacial acetic acid was added 0.216 g (0.00095 moles) of the amine hydrochloride. As the amine salt dissolved a precipitate occurred which was sodium chloride. During the course of the reaction the temperature remained at 23°. To this mixture was added in small quantities over a period of 3 days 0.660 g (0.0095 moles) of sodium nitrite. After addition was complete the reaction mixture was maintained at 23° for 2 additional days. During the 5-day period the mixture was continually stirred by a small magnetic stirring bar.

The reaction was worked up by pouring the mixture over approximately 40 g of ice. After the ice melted the organic material was extracted into chloroform. The extract was treated with cold 1 N hydrochloric acid to remove unreacted amine as the water soluble salt. The chloroform layer was then washed once with water and once with an aqueous sodium bicarbonate solution to insure the removal of the hydrochloric acid. The extract was dried over magnesium sulfate, then filtered. The chloroform was removed on a rotary evaporator without the application of heat which would have caused the acetates to rearrange. The residual oil (the acetates) were taken up in anhydrous

ether, and the major portion of the product was saved for analysis by vpc. A smaller portion was reduced to the corresponding alcohols by the dropwise addition of a slurry of freshly ground lithium aluminum hydride also in anhydrous ether. Hydride addition continued until its presence persisted after refluxing the reduction mixture for 30 min. Excess hydride was destroyed by the alternate addition of water and sodium hydroxide. The resulting alcohols were extracted with ether. The ether layer was dried over magnesium sulfate, filtered, then carefully evaporated to dryness on the rotatory evaporator. The alcohols were recovered in acetone for subsequent analysis by vpc.

D. PREPARATION OF KNOWN ACETATES FOR VPC COMPARISONS

The acetates of the corresponding alcohols of compounds 3 through 8 (Figure 4, page 26) were all prepared in identical fashion by the following procedure.

A small quantity of the alcohol (approximately 1 g, 0.005 moles) was dissolved in about 10 ml (0.123 moles) of pyridine. Then acetic anhydride, 1 mol equivalent of the alcohol (0.51 g, 0.005 moles), was added and the mixture was stirred overnight at room temperature. The reaction mixture was diluted with water and the organic material was extracted with ether. The ether extract was washed several

times with cold 1 N hydrochloric acid in order to remove the pyridine. To remove residual amounts of acid the ether layer was washed with water and a sodium bicarbonate solution. The extract was dried over magnesium sulfate, then filtered. Ether was removed in a rotatory evaporator without the application of heat. It appears that even a slight amount of heat (i.e., over 35^{o}) causes the acetate to rearrange. The acetate remains in the flask to be taken up in acetone for subsequent vpc analysis.

The alcohols were supplied by solvolysis reactions of the corresponding tosylates by Dr. Ben M. Benjamin. They were separated by elution chromatography on alumina.

E. VAPOR PHASE CHROMATOGRAPHY

The deamination of the 2-exo-hydroxy-2-phenyl-3-endo-aminonorbornane hydrochloride was previously described (page 42). Under the same conditions 0.216 g (0.00095 moles) of the 2-endo-hydroxy-2-phenyl-3-endo-aminonorbornane hydrochloride was deaminated. This compound is the same as that illustrated in Figure 5 (page 32) except where that had deuterium in the exo-3 position this has none and consequently was reduced by lithium aluminum hydride and not the deuteride. All other conditions were identical.

For each amine numerous spectra were obtained under various conditions. To determine the location of each

component the amine sample was diluted with a quantity of a known compound. Comparison then of the undiluted sample with the diluted sample provided an easy identification procedure. The known acetates and alcohols were placed on the chromatographic column individually under the same conditions employed to obtain the spectra of the mixture of products. At the conditions used no decomposition occurred.

The separation of alcohols was accomplished with a factory-packed column of 20 per cent Apiezon L on 60/70 mesh Anakrom ABS (acid washed, base washed, and silanized). The acetates were separated with the help of a laboratory-prepared column of 20 per cent Apiezon N on 60/70 mesh Anakrom ABS. The Apiezon N support was made by dissolving 7.0 g of the grease in benzene. The Anakrom material was added to the solution, and the mixture was swirled while being heated on the steam bath. The benzene was removed from the mixture by means of a rotatory evaporator.

Both the acetates and the alcohols were passed through temperature-programmed columns. The acetates were programmed from 170-230^{o} at a temperature rise of 0.5^{o}/min. The alcohols, after a 15-min delay from sample injection time, were programmed from 140-190^{o} at a rate of 0.5^{o}/min. A gas flow of argon was maintained at a flow of approximately 60 ml/min.

The order of retention of the alcohols was the same as that observed previously using elution chromatography (Figure 4, page 26) with alumina. The order for the acetates was slightly different. As a check to see if any peaks were being obscured the materials were also run on a column of 12 per cent silicone rubber, SE-30 on 60/70 mesh Anakrom ABS. The order of retention remained the same and no additional components were detected. The same experience was had when the components were placed on 0.2 per cent Versamid 900 on 80/100 mesh glass beads.

The calculation of the ratios of the components was determined by measuring the respective areas of the signals. The area measurement was based on the peak height of the signal times the width of the signal at one-half the peak height.

All of the major signal responses and most of the weak responses were identified in the spectra. There was one signal present in both the acetate and alcohol samples that was eluted directly after the tricyclic material (it was therefore the second component off the column) that could not be identified. It was not an acetate as it showed no change in position after reduction with hydride. It constituted less than 1 per cent of the total response of the spectra.

The acetates provided the best spectra to measure from. However, one compound was obscured. The acetate of the di-endo-diol (compound 8, Figure 4, page 26) was obscured by the acetate of the anti-7-diol (compound 7, Figure 4, page 26). However, the alcohol signals were very much separated. The anti-7 diol has a very distinct and well-formed response, but the signal due to the di-endo-diol is broad and difficult to measure. Therefore the following was done. The spectrum of the acetates from the deamination were measured. Then the ratio of the areas of the tricyclic material and the two compounds in question (one peak actually) were calculated. The same material after reduction with hydride was again measured and the ratio of the tricyclic material (reduction with hydride does not change this compound) to the anti-7-diol calculated. The loss in signal response was ascribed to the absence of the di-endo-diol and to a change in response factor. The response factors between the acetates and the alcohols were checked by preparing a synthetic mixture of just the tricyclic material and the acetate of the anti-7-diol and measuring the ratio. Reduction of this mixture with hydride to the corresponding alcohol gave the data necessary for calculation of the response factor between the acetate and the alcohol.

For the synthetic mixture the ratio of areas of the acetate of the anti-7-diol to the tricyclic material was 3.2; the same ratio after reduction was 2.96, a loss of 0.8 or 27 per cent which can be ascribed to the change in response factor. These same signals from the 2-exo-hydroxy amine (Figure 6, page 36) gave a ratio of 1.28 from the acetates and a ratio of 1.09 after reduction, a loss of 0.17 or 25 per cent. From the endo-hydroxy amine (Figure 3, page 17) the ratio from the acetates was 3.8 and from the reduction product 1.4, a loss of 2.4 or 37 per cent. The loss of 10-12 per cent is attributed to the presence of the di-endo-diol. The response factors between the alcohols was by experiment shown to be unity.

F. NMR SPECTRA OF PRODUCTS

1. Δ^3-Cyclohexenyl Phenyl Ketone

In the spectrum of the cyclohexenyl phenyl ketone (Figure 7) the signals at lowest field are assigned to the phenyl group. This group is split into two major portions and is centered at 7.7 ppm. The two olefinic hydrogens appear as a single response which is located at 5.7 ppm. Going upfield the next signal (3.5 ppm) is broad, integrates to one hydrogen, and is assigned to the C-1 carbon of the cyclohexenyl ring. At still higher field is series of unresolved signals from 1.5 to 2.5 ppm which are

attributed to the remaining six hydrogens on the cyclohexenyl ring.

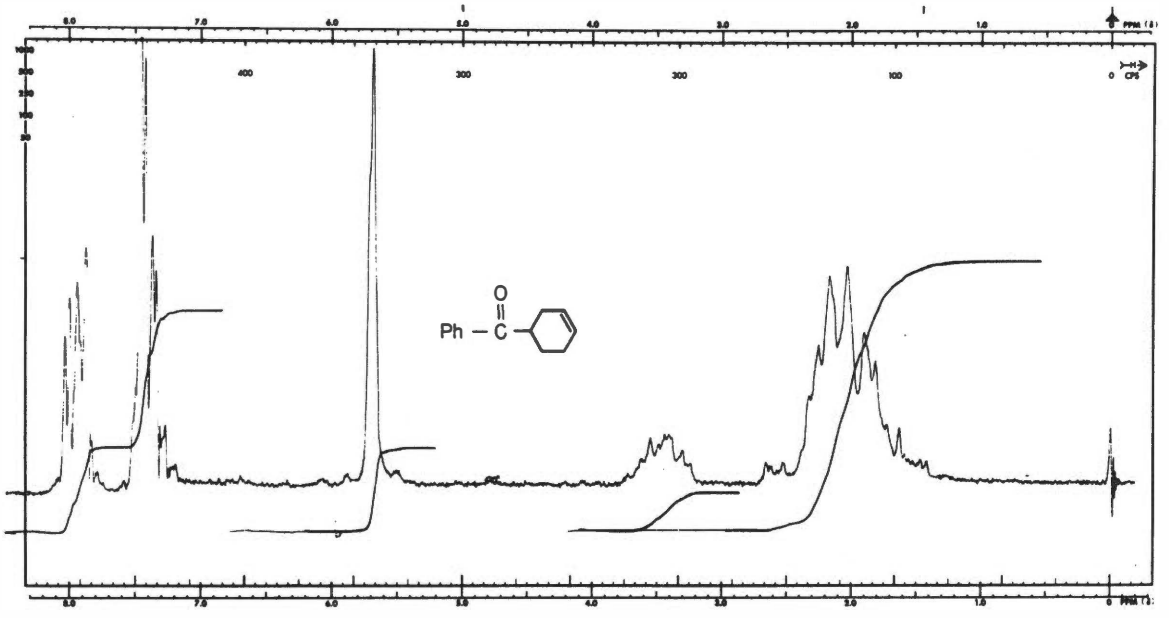


Figure 7. Δ^3-Cyclohexenyl phenyl ketone.
Solvent: Carbon tetrachloride.

2. Δ^3-(cis-5,6-Dideutero)-cyclohexenyl Phenyl Ketone

In the dideuterated compound (Figure 8) the responses attributed to both the phenyl group (7.7 ppm) and the olefinic hydrogens (5.7 ppm) remain unchanged as anticipated. There is a slight change in the shape of the latter signal though, as this signal now is beginning to split into a doublet and, therefore, is somewhat better resolved due to the removal of a coupling constant. The indication then is that a deuterium is on a carbon adjacent to the olefinic bond. Continuing upfield it is apparent that a coupling

constant has been removed from the signal which is assigned to the hydrogen at the C-1 (3.5 ppm) position of the cyclohexenyl ring. Therefore, a deuterium is present on the carbon atom adjacent to this position. The broad signal from 1.5 to 2.5 ppm upon integration shows a loss of two hydrogens. Unfortunately, the spectrum is not resolved well enough to make positive assignments. However, certain features are clear. Integration of the signals confirms that two deuterium atoms are still present in the molecule. These atoms are located neither at the olefinic carbons nor at the C-1 position of the cyclohexenyl ring. They are, however, located adjacent to these positions.

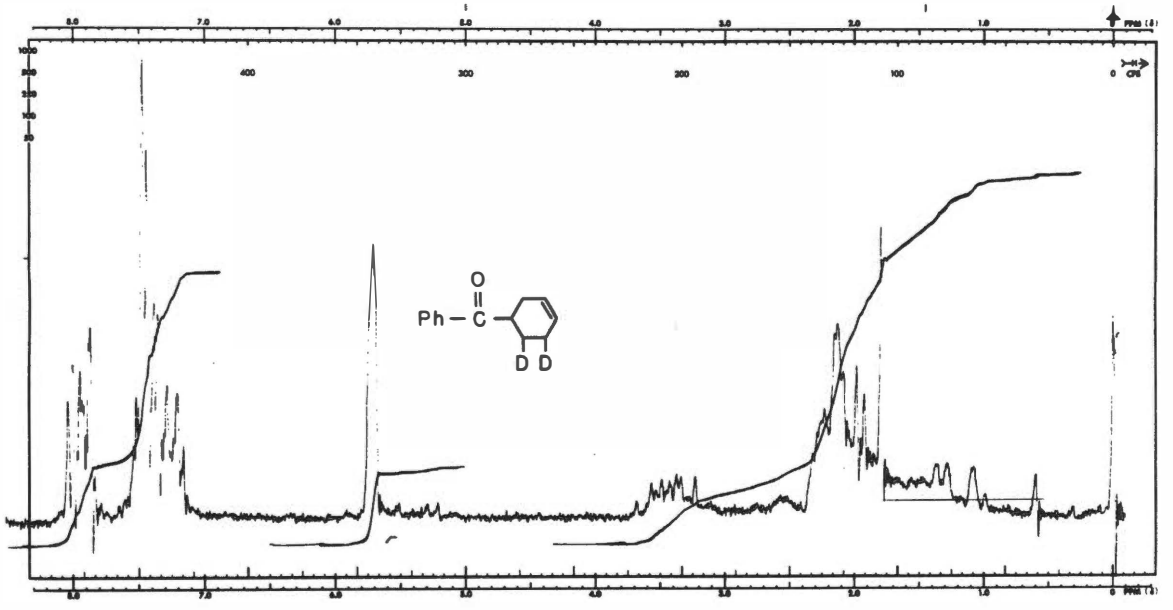


Figure 8. Δ^3-(cis-5,6-Dideutero)-cyclohexenyl phenyl ketone. Solvent: Carbon tetrachloride.

3. Δ^3-(4-Deutero)-cyclohexenyl Phenyl Ketone

The spectrum for the monodeuterated cyclohexenyl phenyl ketone (Figure 9) very closely resembles that of the undeuterated material except that only one olefinic hydrogen is present as determined by integration of the olefinic signal at 5.7 ppm. Irradiation of this signal (spin decoupling) collapses the small shoulder at 2.3 ppm. This small shoulder is also collapsed by irradiating the C-1 (3.5 ppm) hydrogen signal. Therefore, the shoulder peak is the response from the C-2 carbon position, and hydrogens are present on the carbons adjacent to it. This confirms the position of deuterium in the C-4 position.

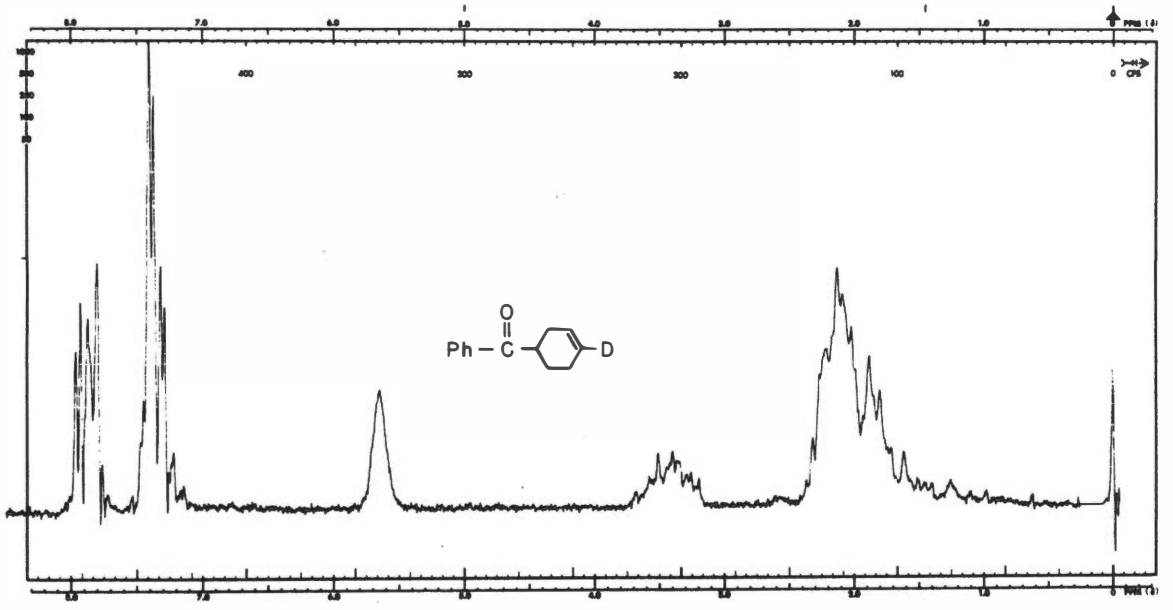


Figure 9. Δ^3-(4-Deutero)-cyclohexenyl phenyl ketone. Solvent: Carbon tetrachloride.

4. 3-Benzoyladipic Acid

In Figure 10 the signal at lowest field (7.7 ppm), the phenyl group, is split into two major portions. By analogy to the cyclohexenyl ring (maintaining the same carbon-numbering system) the hydrogen located at the C-1 position is assigned to the broad signal at 4.0 ppm. Continuing upfield there are three sets of distinct signals centered at 2.7, 2.3, and 1.7 ppm. These are assigned to the C-2, C-6, and C-5 hydrogens respectively. These assignments were confirmed by spin decoupling.

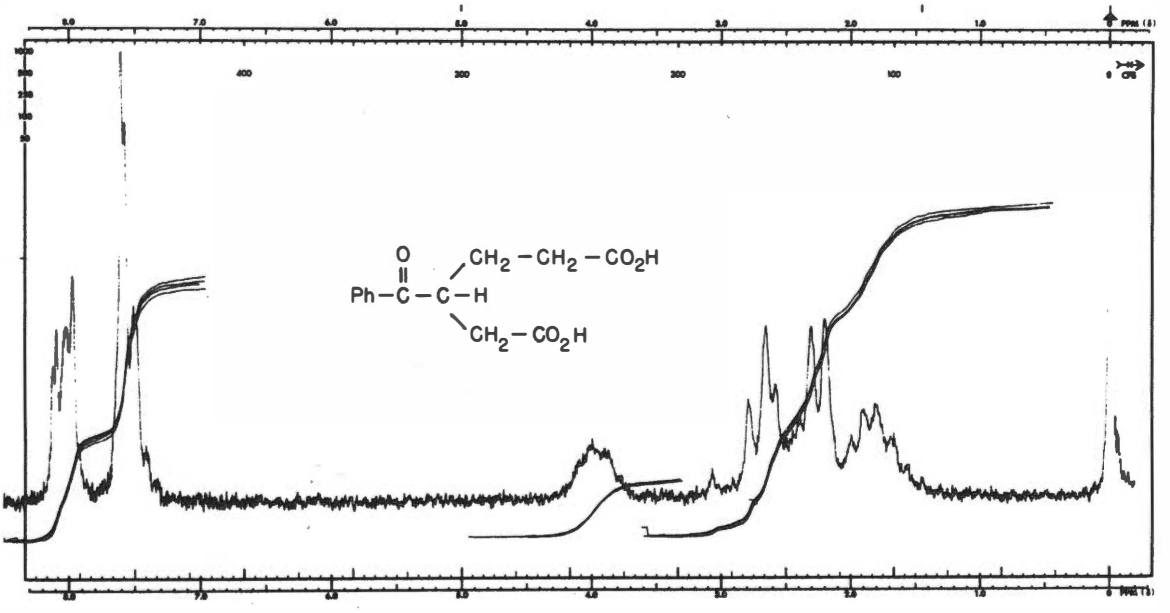


Figure 10. 3-Benzoyladipic acid.
$PhCOCH(CH_2CO_2H)(CH_2CH_2CO_2H)$
(1) (2) (6)(5) carbon-numbering system
Solvent: Deuterated dimethylsulfoxide.

5. 3-Benzoyl-4,5-dideuteroadipic Acid

In Figure 11 the signal assigned to the C-1 position (4.0 ppm) has been sharpened due to the loss of a coupling constant. This places deuterium on the carbon adjacent to this position. The signal at 2.7 ppm is unchanged and exhibits two hydrogens on integration; it is therefore the C-2 position. The signals at 2.3 and 1.7 ppm (C-5) both integrate to one hydrogen. The signal at 2.3 ppm (C-6) is coupled to the hydrogen at 4.0 ppm, and this was confirmed by spin decoupling experiments. Also the weak quartet at 1.7 ppm has collapsed to principally a doublet indicating that it is being split by only one hydrogen. This fixes the position of deuterium to the locations illustrated.

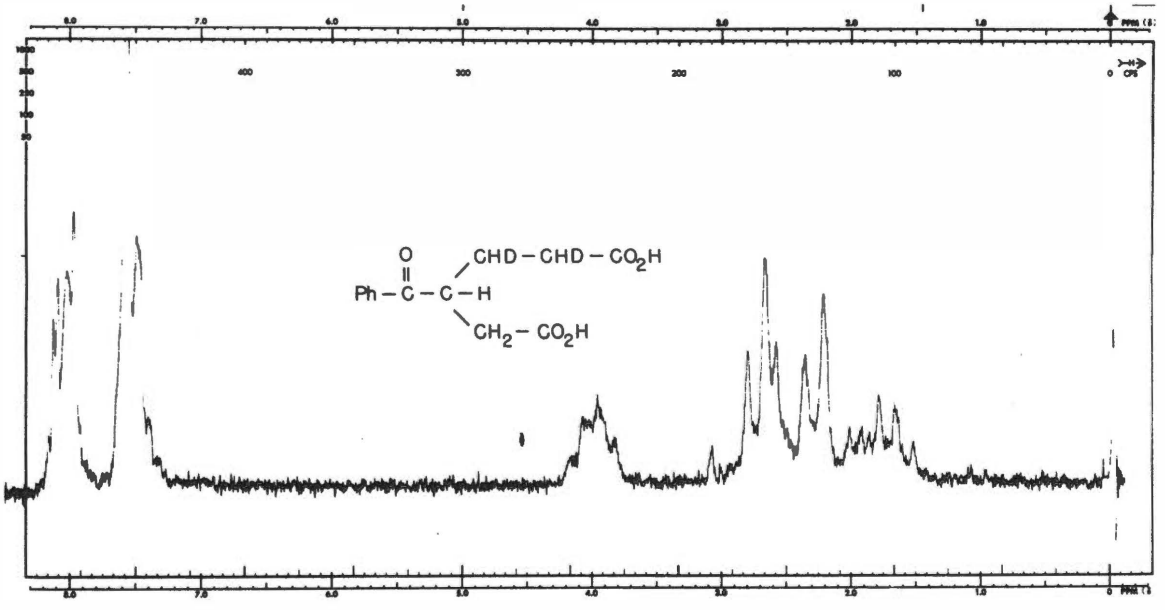


Figure 11. 3-Benzoyl-4,5-dideuteroadipic acid.
$PhCOCH(CH_2CO_2H)(CHDCHDCO_2H)$
(1)(2) (6)(5) carbon numbering system
Solvent: Deuterated dimethylsulfoxide.

6. 2-Phenyl-2-nortricyclenol

In the spectrum of the phenylnortricyclenol (Figure 12) the phenyl group is at low field and the hydroxyl hydrogen is located at 2.7 ppm. The doublet at 2.2 ppm is attributed to the syn-6 hydrogen (the syn is in reference to the hydroxyl group). Continuing to higher field the bridgehead hydrogen at the C-1 position is assigned to the response at 1.7 ppm. At 1.3 ppm is found a portion of the doublet attributed to the anti-6 hydrogen. The three hydrogens at C-3, C-4, and C-5 are assigned to the signal at 1.2 ppm. Since these hydrogens are equivalent, they produce a single response. Incorporated in this signal is the remaining portion of the doublet from the anti-C-6 hydrogen. At 1.1 ppm is the response assigned to the two C-7 hydrogens.

7. 6-anti-Deutero-2-phenyl-2-nortricyclenol

In the deuterated phenyl-nortricyclenol (Figure 13) the doublet due to the syn-C-6 (2.2 ppm) hydrogen has almost collapsed because the other hydrogen on this carbon has been replaced by deuterium. A coupling constant has been removed from the bridgehead hydrogen response at 2.1 ppm as evidenced by the decrease in width at one-half the signal peak height. At 1.3 ppm there is still a small signal due to hydrogen in the anti-C-6 position. The doublet does not completely disappear as the initial

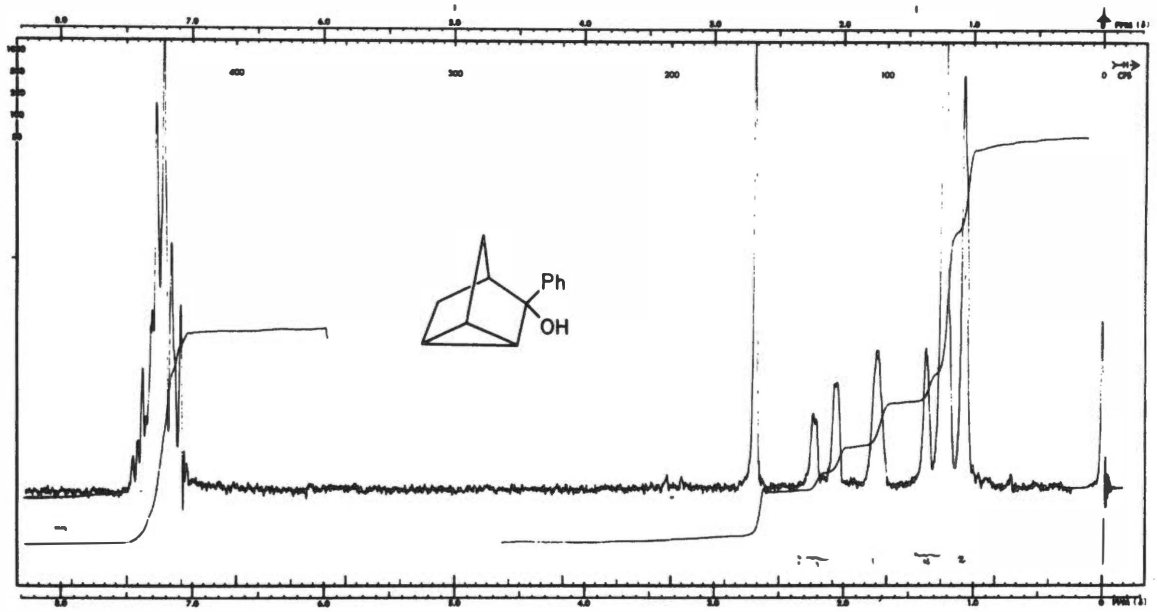


Figure 12. 2-Phenyl-2-nortricyclenol.
Solvent: Carbon tetrachloride.

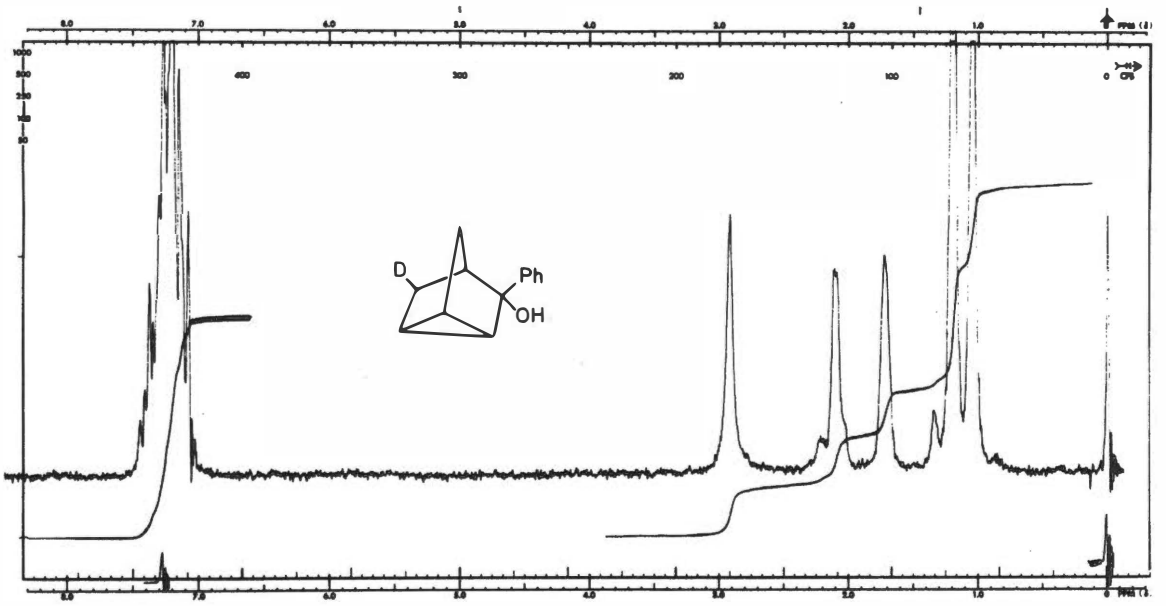


Figure 13. 6-anti-Deutero-2-phenylnortricyclenol.
Solvent: Carbon tetrachloride.

material was deuterated only to the extent of 92 per cent, the remaining 8 per cent is hydrogen and distributed between two positions. The assignment of the C-3, C-4, C-5 hydrogens and the C-7 hydrogens at 1.2 ppm and 1.0 ppm respectively remain unchanged.

8. 7-Hydroxy-7-syn-phenyl-2-exo-hydroxynorbornane

In Figure 14, a spectrum of the anti-diol, the hydroxyl hydrogens are located at 5.4 ppm while the triplet at 4.0 ppm is attributed to the endo-C-2 hydrogen. Continuing upfield the broad signal from 2.2-2.9 ppm can be resolved into two major portions. The portion from 2.6-2.9 ppm is assigned to the bridgeheads C-1 and C-4 with the C-4 hydrogen being the component at higher field. The other portion of the signal from 2.2-2.6 ppm is assigned to the exo-C-6 and exo-C-5 hydrogens. The apparent doublet at 1.8 ppm represents the two hydrogens located at the C-3 position. At highest field is found the endo-C-5 and endo-C-6 hydrogens. These are the most shielded hydrogens in the molecule.

9. endo-5,6-Dideutero-7-hydroxy-7-syn-phenyl-2-exo-hydroxynorbornane

In the deuterated anti-diol (Figure 15) the hydroxyl signals are broad due to a lack of hydrochloric acid which allows the rapid exchange of hydrogen necessary to produce

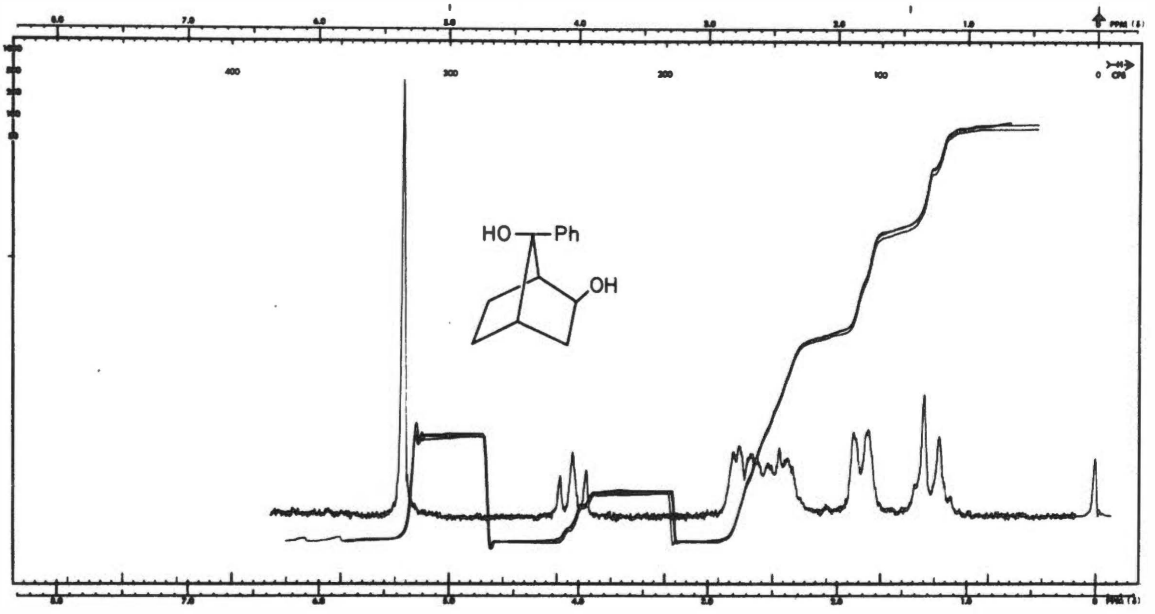


Figure 14. 7-Hydroxy-7-syn-phenyl-2-exo-hydroxynorbornane.
Solvent: Pyridine with a trace of hydrochloric acid.

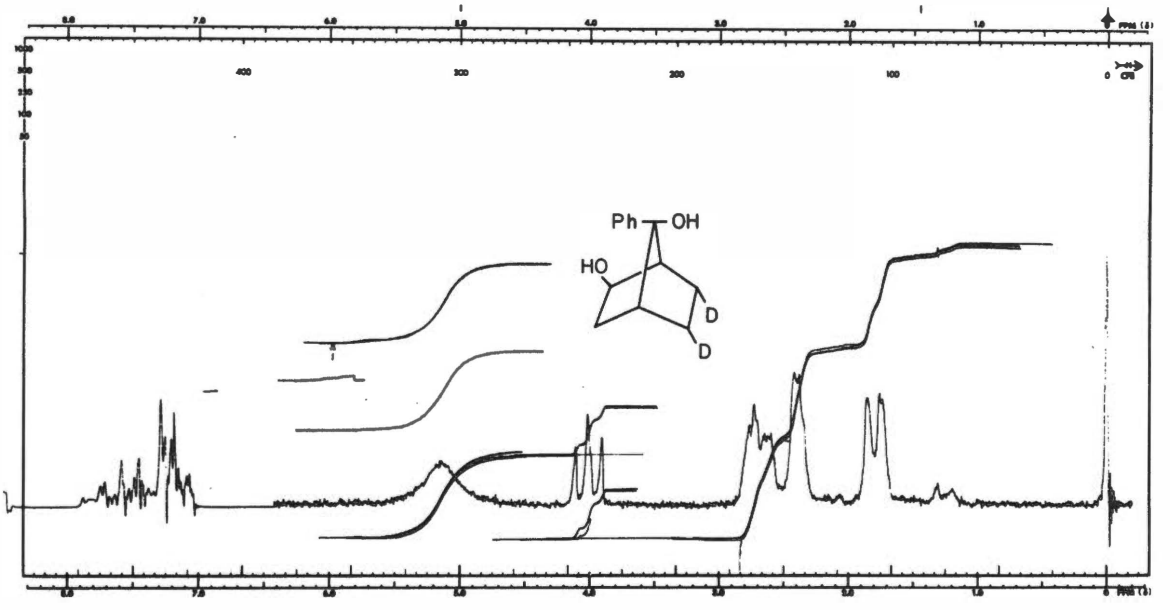


Figure 15. endo-5,6-Dideutero-7-hydroxy-7-syn-phenyl-2-exo-hydroxynorbornane.
Solvent: Pyridine.

a sharp hydroxyl hydrogen signal. As seen from the spectrum, coupling constants have been removed from the bridgehead hydrogen responses at 2.6 and 2.9 ppm and from the exo-C-5 and exo-C-6 hydrogens at 2.2 and 2.6 ppm. The signals for the endo-C-5 and endo-C-6 hydrogens at 1.4 and 1.2 ppm have virtually disappeared. The remainder of the spectrum remains unaffected.

10. 2,5-exo-Dihydroxy-2-phenylnorbornane

In the spectrum (Figure 16) of the 2,5-exo-hydroxy-2-phenylnorbornane the hydroxyl signal is found at low field, 6.0 ppm. The isolated multiple signal at 4.0 ppm is attributed to the endo-C-5 hydrogen. The next signal encountered, 2.7 ppm, results from the unresolved bridgehead hydrogens with the C-1 hydrogen being at slightly higher field. The two hydrogens at C-7 are assigned to the responses at 2.6 and 2.3 ppm. The signal attributed to the C-3 hydrogens is partially split and is located at 2.1 ppm. The broad multiple signal centered at 1.6 ppm is assigned to the C-6 hydrogens.

11. 4,7-Dideutero-2,5-exo-dihydroxy-2-phenylnorbornane

In Figure 17 the spectrum of the deuterated exo-2,5-dihydroxy-2-phenylnorbornane hydrogen has been lost from the broad signal at 2.7 ppm attributed to the bridgehead hydrogens. The missing hydrogen is identified as the C-4

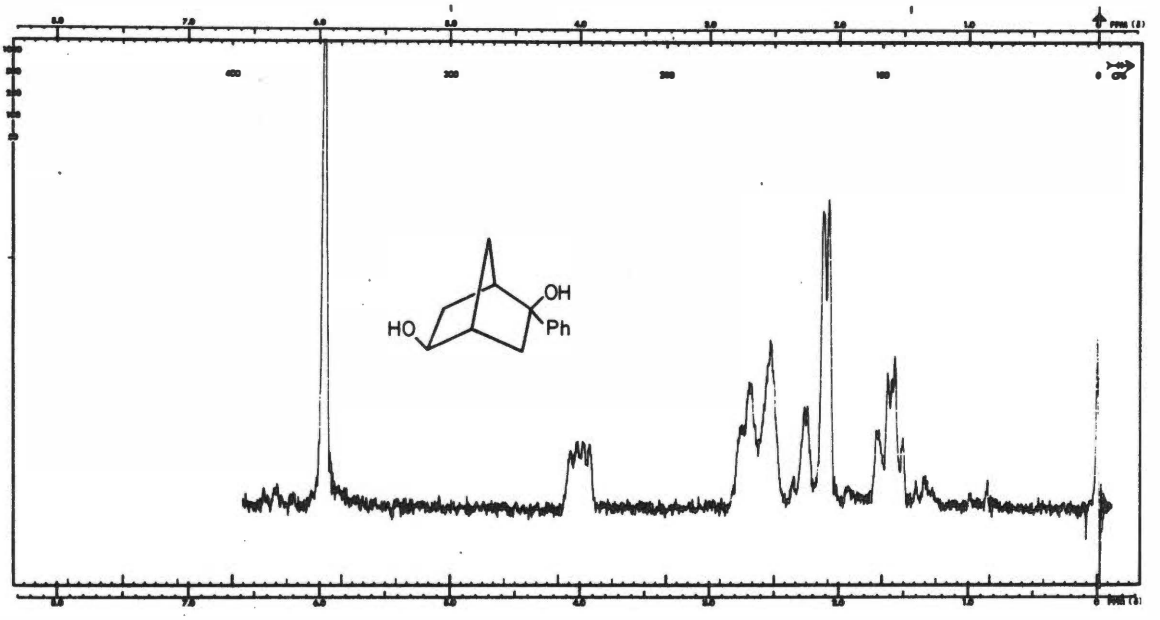


Figure 16. 2,5-exo-Dihydroxy-2-phenylnorbornane.
Solvent: Pyridine.

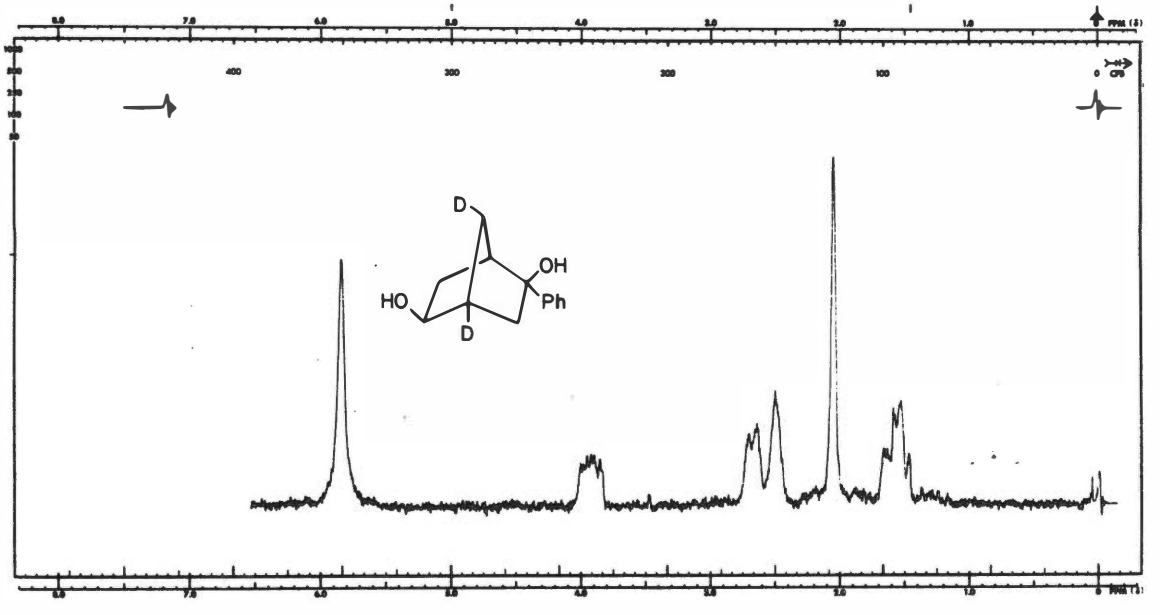


Figure 17. 4,7-Dideutero-2,5-exo-dihydroxy-2-phenyl-norbornane.
Solvent: Pyridine.

hydrogen because the coupling constant has disappeared from the signal at 2.1 ppm which is assigned to the C-3 hydrogens. Integration of the endo-C-5 (4.0 ppm) hydrogen shows the presence of only 0.96 hydrogens instead of the expected 1.0 hydrogens. The bridgehead hydrogens integrate to approximately 1.20 hydrogens versus the expected value of 1.08 hydrogens which would be expected if the initial deuteration was only 92 per cent complete. Therefore, approximately 12 per cent of the hydrogens at the endo-C-5 position are deuterium. A hydrogen at the C-7 position has also been replaced by deuterium. The response at 2.3 ppm (attributed to the hydrogen anti to the hydroxyl phenyl grouping) has virtually disappeared.

12. 2,6-endo-cis-Dihydroxy-2-phenyl-bicyclo[3.1.1]heptane

The bicyclo[3.1.1]heptane compound is shown in Figure 18. The response at 4.6 ppm is attributed to the exo-C-6 hydrogen. The two hydrogens at the C-7 position are centered at 2.9 ppm, and both the exo and the endo hydrogens on the C-4 position are assigned to the broad signal from 2.4-2.8 ppm. The two hydrogens on the C-5 carbon are adjacent to this signal and are at a higher field strength, 1.8-2.3 ppm. The bridgehead hydrogens C-1 and C-3 are assigned to the multiple splitting pattern from 1.0-1.7 ppm.

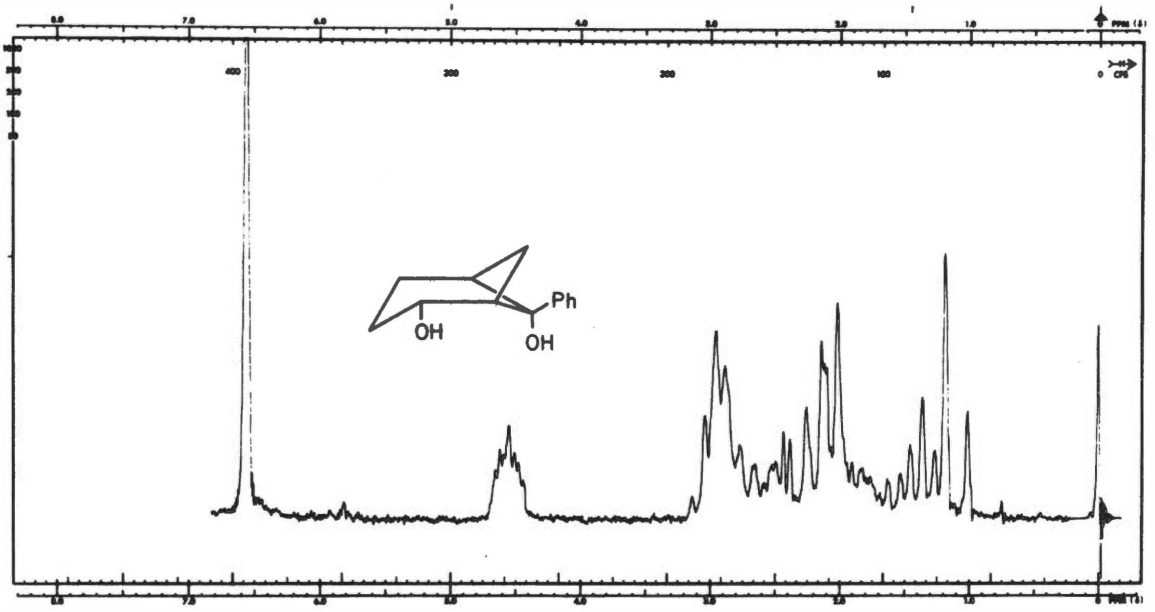


Figure 18. 2,6-endo-cis-Dihydroxy-2-phenylbicyclo[3.1.1]-heptane.
Solvent: Pyridine.

13. 4,5-cis-exo-Dideutero-2,6-endo-cis-dihydroxy-2-phenyl-bicyclo[3.1.1]heptane

In the deuterated bicyclo[3.1.1]heptane compound (Figure 19) the exo-C-6 hydrogen at 4.6 ppm now appears as a doublet, each portion of which is itself an unresolved doublet. Spin decoupling experiments show it is coupled primarily with the C-1 bridgehead. If the functional groups are considered to be on the same cyclohexane ring system then this system can have two conformations, either a boat or a chair form. In the boat position the exo-C-6 hydrogen would be close to a 90^{o} angle with the bridgehead hydrogen whereas in the chair conformation this angle would

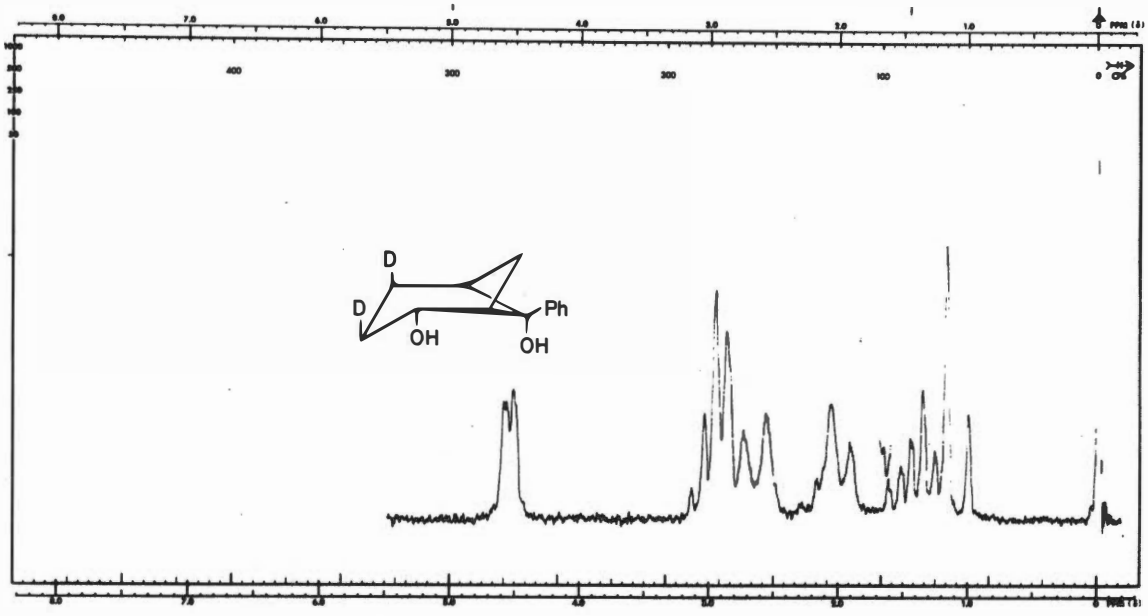


Figure 19. 4,5-cis-exo-Dideutero-2,6-endo-cis-dihydroxy-phenyl-bicyclo[3.1.1]heptane.
Solvent: Pyridine.

approximate 30^{o}. Since these two hydrogens are strongly coupled, the favored conformation is the chair form. The responses at 2.6 and 1.9 ppm are assigned to the endo-C-5 and endo-C-4 hydrogens respectively. The C-4 hydrogen is at lower field due to the close proximity of the hydroxyl groups. The bridgehead hydrogen at C-3 forms an angle of approximately 90^{o} with the C-4 hydrogen when the molecule is in the chair conformation and thus does not couple to any appreciable extent with this hydrogen. The primary source of coupling with the C-3 hydrogen is with a C-7 hydrogen. The syn-C-7 hydrogen appears to be the one at lowest field as this is the set of signals that is collapsed

when irradiated by the C-3 hydrogen. The syn-hydrogen angle with respect to the bridgehead hydrogens is about 30^{o} while the anti-hydrogen is very close to 90^{o}. The C-1 bridgehead hydrogen shares a similar relationship. Integration shows that two hydrogens were lost from the C-4 (2.4-2.8 ppm) and C-5 (1.8-2.3 ppm) positions. The deuterium in these positions must be in the exo-configuration due to the loss of the coupling constant with the C-6 position and a similar loss with the C-3 (1.0-1.7 ppm) position.

14. 2,7-syn-Dihydroxy-7-phenylnorbornane

In the undeuterated syn-7-diol (Figure 20) the response at 4.0 ppm is assigned to the two hydroxyl hydrogens. This signal is partially superimposed on the triplet of the endo-C-3 hydrogen which is centered at 3.8 ppm. Continuing upfield the C-1 and C-4 bridgehead hydrogens are located at 2.6 and 2.4 ppm respectively. The two hydrogens at the C-2 position are assigned to the major doublet at 2.0 ppm while the hydrogens on the C-5 and C-6 positions form a quartet that is centered at 1.1 ppm. The endo-C-5 and endo-C-6 hydrogens are attributed to the two observable signals of the quartet at higher field while the exo hydrogens are assigned to the two signals at lower field. The exo signals are broader because they are coupled with the bridgehead hydrogens.

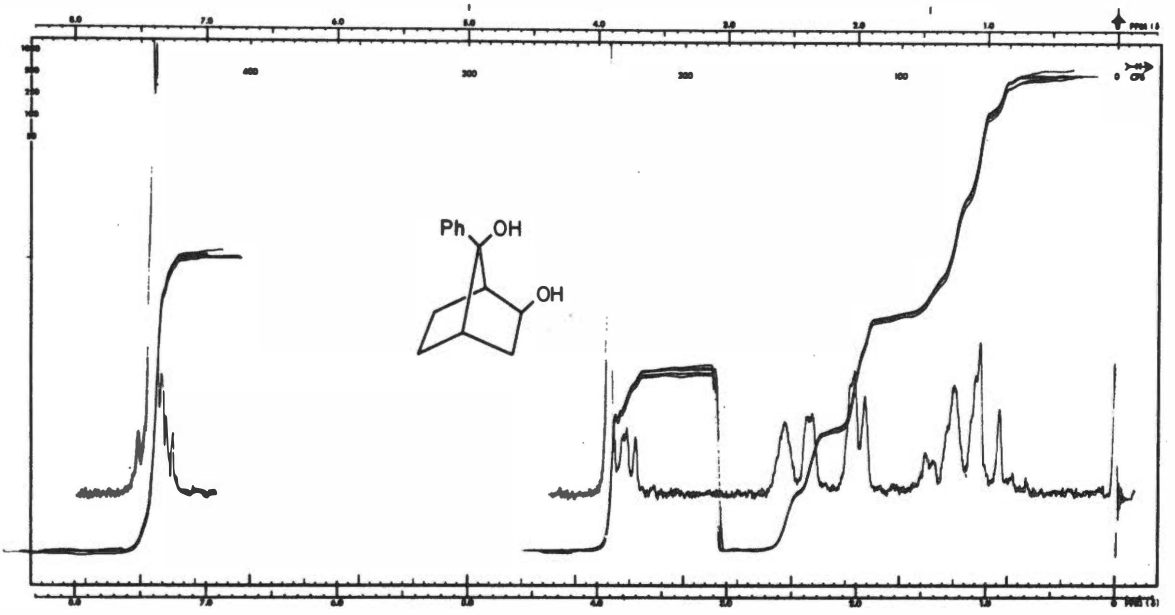


Figure 20. 2,7-syn-Dihydroxy-7-phenylnorbornane.
Solvent: Deuterochloroform.

15. 3,6-endo-Dideutero-2,7-syn-dihydroxy-7-phenylnorbornane

In the deuterated form of the syn-7-diol (Figure 21) the major triplet of the endo-C-3 hydrogen is not present in the deuterated compound. Both bridgehead positions continue to integrate to one hydrogen each but the C-2 position shows a loss of one hydrogen. A hydrogen has also been lost from the C-5 and C-6 positions. The hydrogen here was lost from the endo position, i.e., from the portion of the quartet at higher field. Such an interpretation is consistent with having deuterium atoms located at the endo-C-5 and endo-C-2 positions.

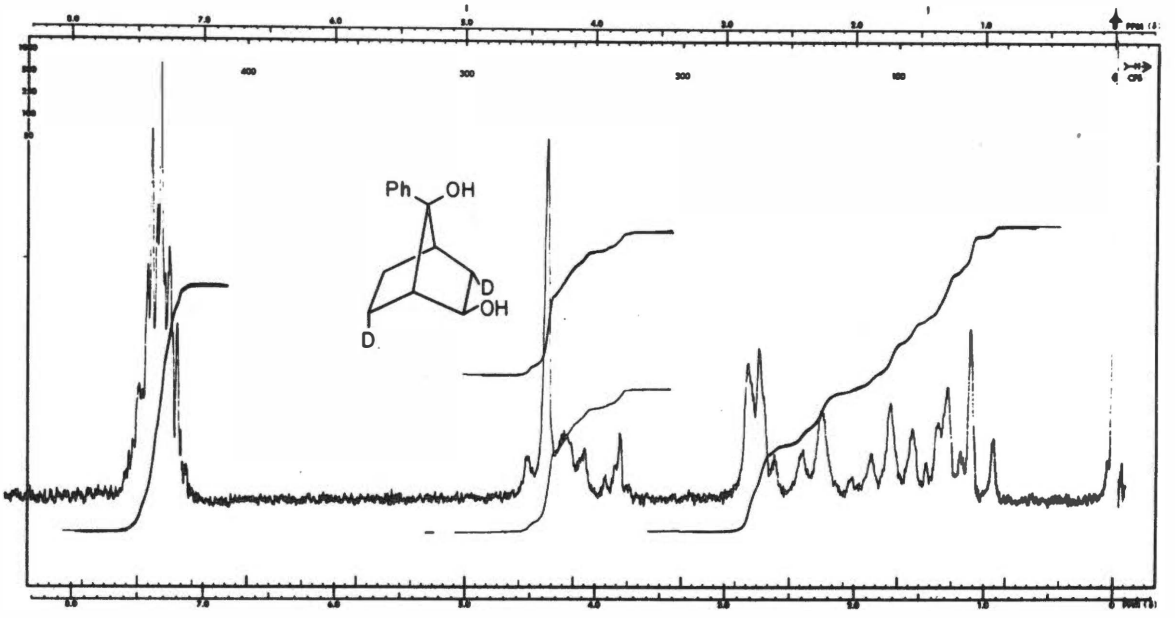


Figure 21. 3,6-endo-Dideutero-2,7-syn-dihydroxy-7-phenyl-norbornane.
Solvent: Deuterochloroform.

16. 2-exo-Phenyl-2-hydroxy-5-exo-hydroxynorbornane

In the compound depicted in Figure 22 the apparent doublet at 4.4 ppm is attributed to the endo-C-5 hydrogen, and the endo-C-6 hydrogen signal is assigned to the large quartet that is centered at 3.2 ppm. The C-4 and C-1 bridgehead hydrogens lie close together at 2.6 and 2.7 ppm with the C-1 hydrogen being at higher field. Continuing upfield the exo-C-3 hydrogen signal is located at 2.4 ppm, and the syn-C-7 hydrogen is found at 2.0 ppm. The endo-C-3 hydrogen is at 1.7 ppm while the anti-C-7 and exo-C-6 hydrogens are assigned to the response at 1.5 ppm. The two broad signals at 6.0 ppm are the hydroxyl hydrogens. They

are broad because no hydrochloric acid was added to permit the rapid exchange of hydrogen necessary to produce a sharp response.

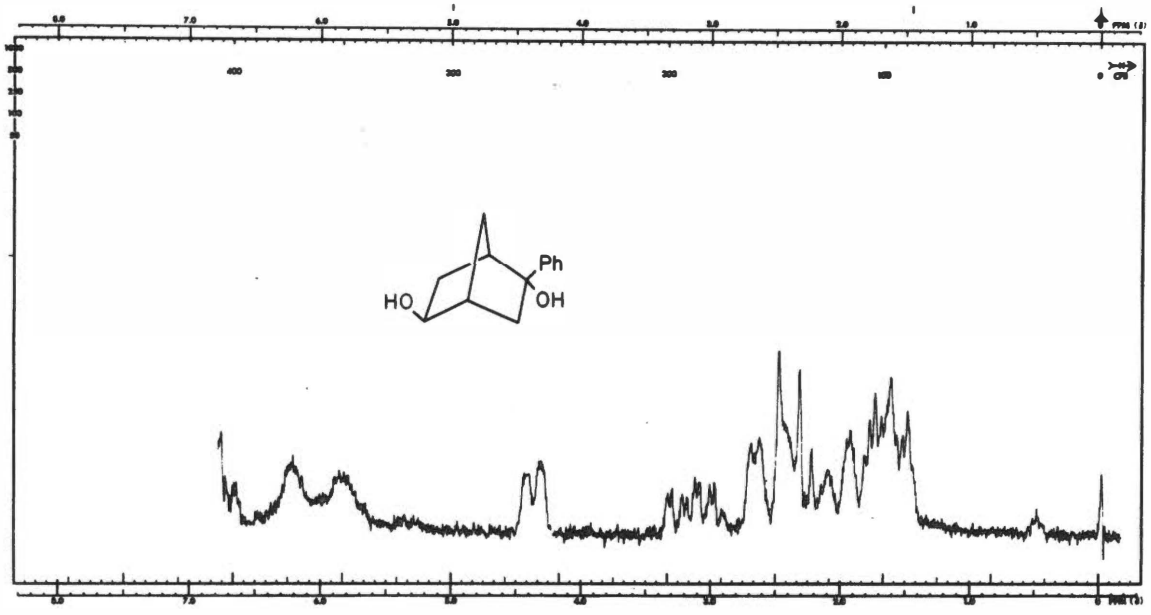


Figure 22. 2-exo-Phenyl-2-hydroxy-5-exo-hydroxynorbornane. Solvent: Pyridine.

17. 5-endo-6-exo-Dideutero-2-endo-5-exo-dihydroxy-2-phenylnorbornane

The deuterated compound is illustrated in Figure 23. The signal at 4.4 ppm exhibited by hydrogen at C-5 in the undeuterated compound (Figure 22, above) is virtually absent in the present spectrum. The residual signal integrates to 0.14 hydrogens. The expected value is 0.08 hydrogens due to incomplete deuteration of the starting compound, 5-norbornene-2-ol. The "extra" hydrogens can be

attributed to a displacement of deuterium from this position to the bridgehead C-4 position at 2.6 ppm, the only position available to it. Unfortunately, because of the complexity of the signal, the integration is not accurate enough to permit a rigorous examination of this area. The large quartet centered at 3.2 ppm and assigned to the endo-C-6 hydrogen in the undeuterated compound (page 66) is an apparent singlet in the deuterated compound because of the loss of coupling with the exo-C-6 hydrogen and the endo-C-5 hydrogen. Integration shows that a hydrogen, as expected, has been lost from exo-C-6 and the anti-C-7 hydrogen group centered at 1.5 ppm.

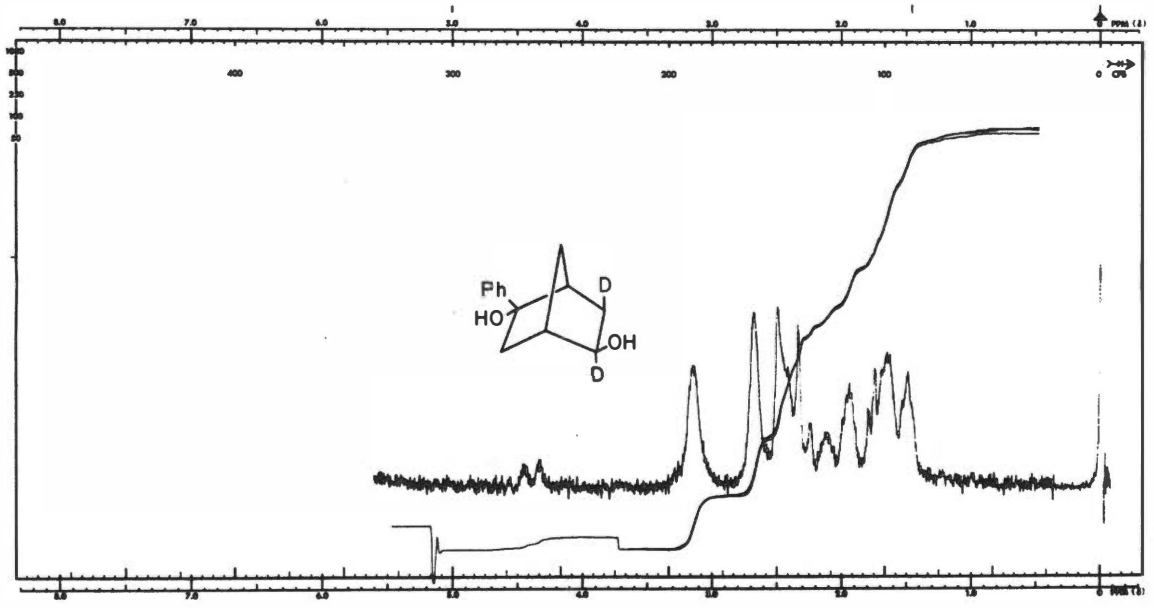


Figure 23. 5-endo-6-exo-Dideutero-2-endo-5-exo-dihydroxy-2-phenylnorbornane.
Solvent: Pyridine.

18. 2,3-endo-Dihydroxy-2-phenylnorbornane

The spectrum of the di-endo-diol is shown in Figure 24. The doublet at 4.2 ppm is assigned to the exo-C-3 hydrogen. It is split by the bridgehead hydrogen and is weakly coupled with the exo-C-5 hydrogen. At 2.6-3.0 ppm is a broad signal attributed to the bridgehead hydrogens with the C-4 hydrogen being at lower field. The endo-C-5 and endo-C-6 hydrogens are located at 2.3 ppm. They are deshielded by the close proximity of the hydroxyl groups and thus are at lower field than usually expected. The signal at 1.4 ppm represents four hydrogens, namely the exo-C-5 and exo-C-6 hydrogens, and both of the hydrogens at the C-7 position.

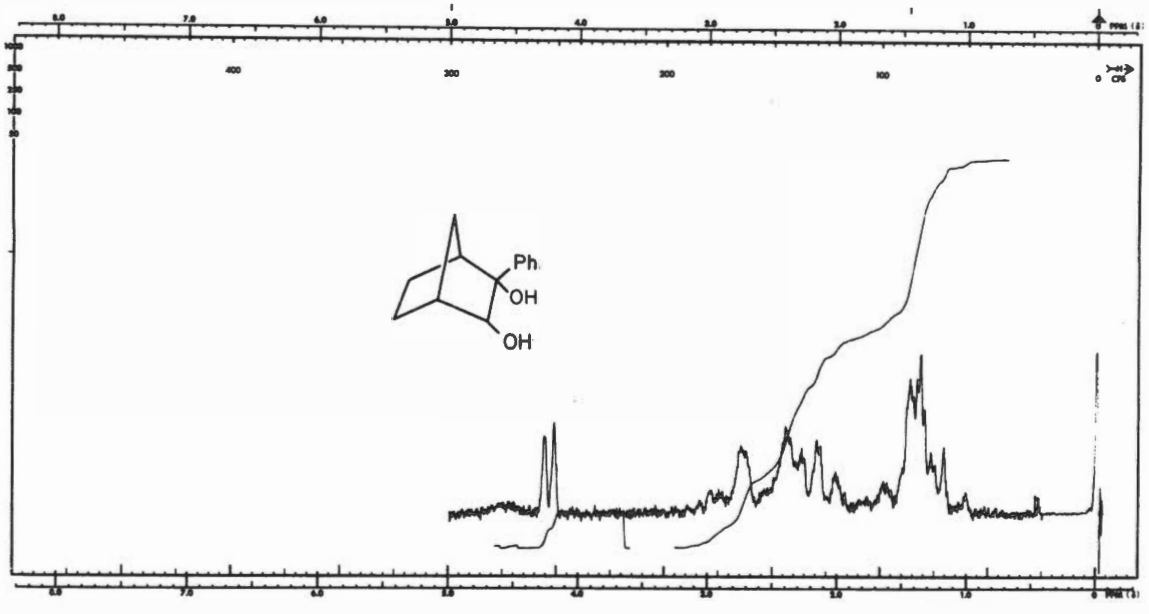


Figure 24. 2,3-endo-dihydroxy-2-phenylnorbornane. Solvent: Pyridine.

19. 5,6-exo-Dideutero-2,3-endo-dihydroxy-2-phenylnorbornane

In Figure 25 is illustrated the deuterated di-endo-diol. The effects of deuterium in the compound are evident by the decrease in width of the signals at one-half peak height when compared to the corresponding signals in the undeuterated compound (Figure 24). In each case mentioned the narrowing of the response signal is due to the loss of a coupling constant.

The exo-C-3 hydrogen at 4.2 ppm, the C-1 hydrogen at 2.75 ppm, and the endo-C-5 and endo-C-6 hydrogen responses at 2.3 ppm have all lost coupling constants due to replacement of the exo-C-5 and exo-C-6 positions with deuterium. Proton integration confirms the loss of two hydrogens from the response at 1.4 ppm which contains the exo-C-5 and exo-C-6 hydrogens.

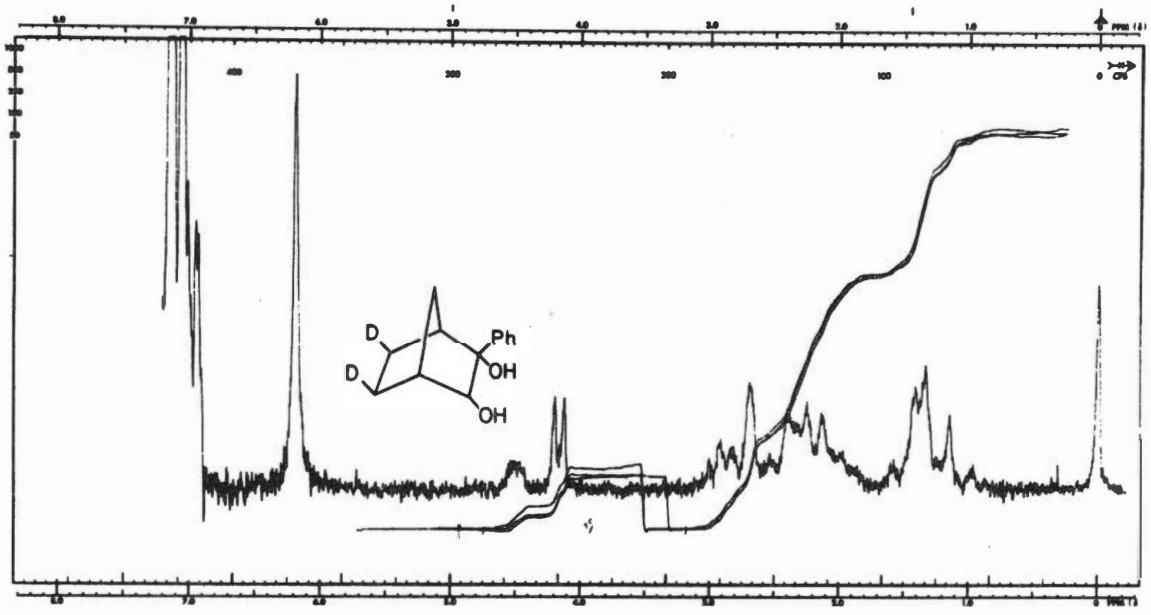


Figure 25. 5,6-exo-Dideutero-2,3-endo-dihydroxy-2-phenyl-norbornane.
Solvent: Pyridine

CHAPTER IV

RESULTS

A. PRODUCT YIELDS

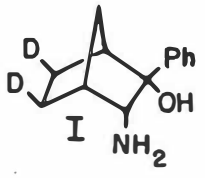
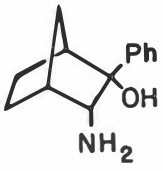
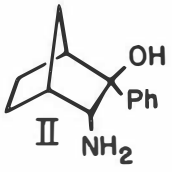
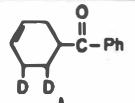
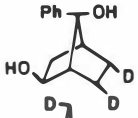
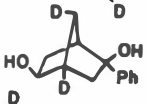
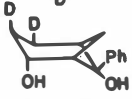
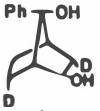
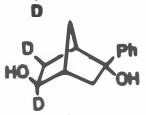
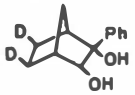
The yields of products, both acetates and alcohols, obtained from the two different amines are shown in Table I. The figures recorded for the results of liquid chromatography are presented in mole percentages based upon the number of moles of the original amine. Recovery is only 85.5 per cent. The almost 15 per cent loss can be attributed to:

1. The method of recovery of product. The method used consisted of passing a stream of air into an Erlenmeyer flask to remove solvent while heating the flask on the steam bath.
2. Incomplete reaction of the amine. All water-soluble components would have been lost prior to placing the material on the column of alumina.

The method of recovery accounted for no measurable loss of product in the alcohols as column yield was 100 per cent. It is also doubtful that any loss occurred when the products were in the acetate form. This is based on the observation that from a given deamination sample the ratios of acetates

TABLE I

PRODUCT YIELDS

	 I		 II	
	Liquid Elution (normalized)		Acetates (vpc)	Acetates (vpc)
	18.8	22.2	18.4	0.4
	6.4	7.6	8.1	22.3
	20.8	23.5	22.1	29.2
	3.0	3.6	3.0	1.7
	18.9	22.2	22.3	2.9
	4.8	5.7	9.7	37.2
	4.0	4.8	5.5	6.3
	8.8	10.4	10.4	?
	85.5*			

*Mole per cent recovered from starting amine.

as analyzed by vpc are the same ratios that one obtains after the same sample has been reduced with lithium aluminum hydride. However, there are fewer minor components in the alcohol spectrum. The differences in the spectra are attributed to the loss of components that are water soluble and are not reduced to alcohols by lithium aluminum hydride. Therefore, incomplete conversion of the amine to the desired acetate products represents the major loss.

B. REACTION PATHWAYS BASED ON NMR INTERPRETATIONS

1. Formation of the Cyclohexenyl Phenyl Ketone

Since the cyclohexenyl phenyl ketone (compound 1, Figure 4, page 26) presumably can arise from both ions M and N (Figure 26), there was some question as to what route actually was involved. With deuterium in the exo-5,6 positions of the amine the product would have the same deuterium distribution irrespective of whether the compound was formed from ion M or ion N.

However, with deuterium in the exo-2 position of the amine it is possible to differentiate. If formed through ion M, the deuterium would be the olefinic hydrogen in the C_3 position of the cyclohexenyl ring. Whereas if the ion proceeded from ion N, the deuterium would be in the C_4 position of the ring. As discussed in the experimental portion of the dissertation, the deuterium was found in the

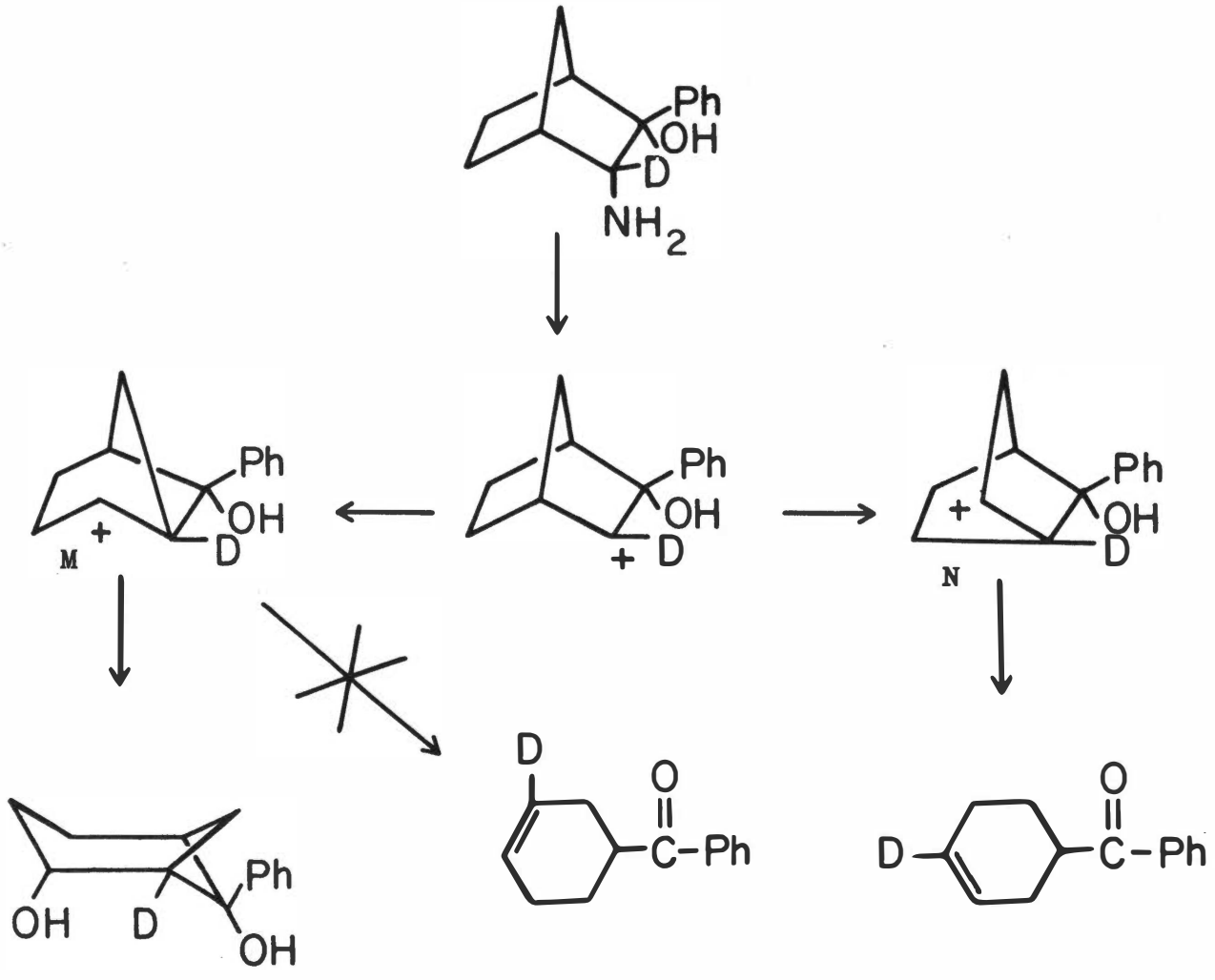


Figure 26. Formation of cyclohexenyl phenyl ketone.

C_4 position with no evidence for any deuterium in the C_3 position.

2. Deamination of the 2-endo-Hydroxy-2-phenyl-3-endo-amino-norbornane-5,6-d_2

The deuterium distributions resulting from the deamination of this compound are summarized and illustrated in Figure 27.

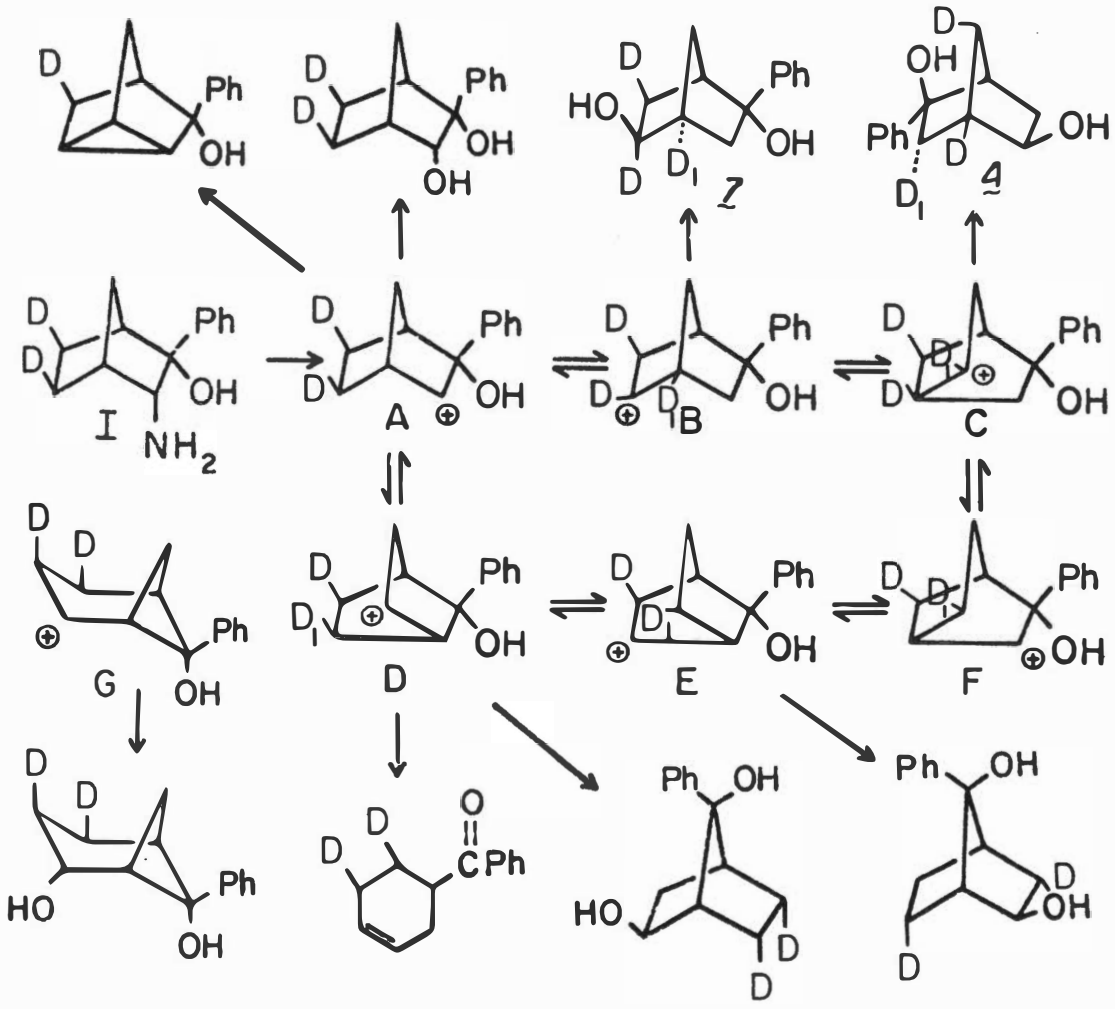


Figure 27. Deamination of 2-endo-hydroxy-2-phenyl-3-endo-aminonorbornane-5,6-exo-d_2.

CHAPTER V

DISCUSSION OF RESULTS

Following is an explanation of the products obtained and of the yields listed in Table I (page 72). In the nitrous acid deamination of an amine in glacial acetic acid buffered with sodium acetate, the diazonium acetate (or the diazonium cation and the acetate anion) decomposes with evolution of nitrogen, leaving a positive charge on the bicyclic fragment and a negative charge on the acetoxyl ion, the latter being referred to as the counter ion. Referring to amine I as depicted in Figure 28, we see that if the exo-phenyl group is considered to be oriented upward (i.e., "above" the cyclohexane ring as represented in Figure 28), then the diazonium group and subsequently the counter ion will be located "below" the cyclohexane ring. When amine I ionizes by way of the diazonium salt, the initial carbonium ion is an open ion.* Ion A, formed directly from amine I, must be classical in character because it undergoes all four of the following reactions:

---

*An open or classical ion can be defined as an ion which in its ground state does not have seriously delocalized bonding sigma electrons. Conversely, a nonclassical ion may be defined as an ion that in its ground state has considerably delocalized sigma-bonding electrons.

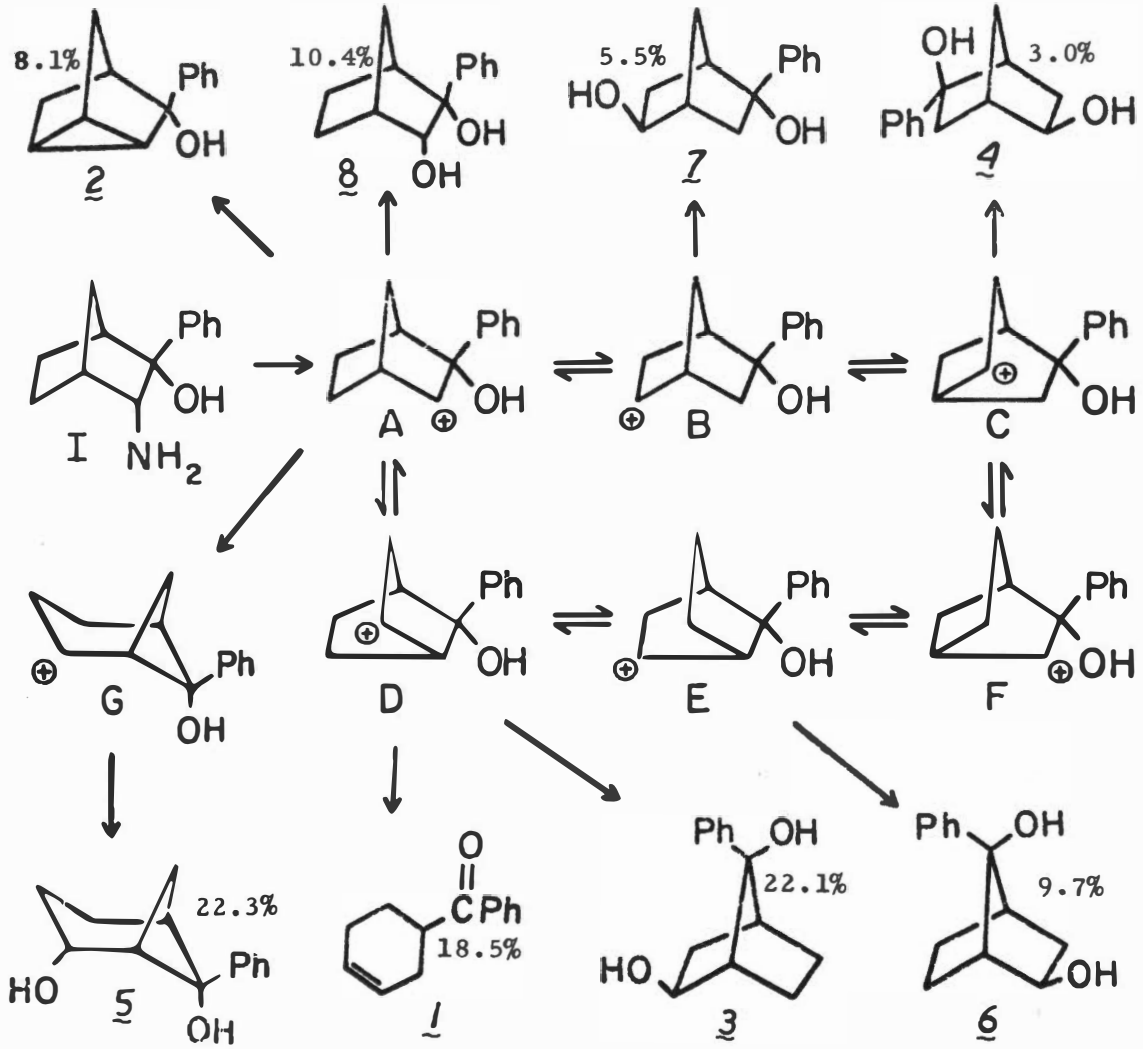


Figure 28. Yields from amine I; 2-endo-hydroxy-2-phenyl-3-endo-aminonorbornane.

1. Collapse with the acetoxyl counter ion. This results in the formation of the di-endo-diol (compound 8).
2. Hydride shift to form ion B, which then goes to product 7.
3. A Wagner-Meerwein rearrangement (6,2-carbon shift), which results in the formation of ion D, leading to products 1 and 3, and to ion E.
4. A Wagner-Meerwein rearrangement (1,2-carbon shift) yielding ion G and compound 5.

Since ion A can undergo attack from both the exo- and endo-positions, it must be considered an open classical ion. The situation in ion D, however, is not so clear. In the initially formed ion, A, the acetoxyl counter ion is located beneath the charge center (as the structure is shown in Figure 28) and must be reasonably close to the cation, because the ionization proceeded by way of the diazonium salt, and the departing nitrogen left without charge. In ion D, however, this counter ion is considerably removed from the charge center. The ion has suffered a carbon shift, and the counter ion has been removed so that any stabilization of charge received because of its proximity has been decreased. Ion D then avails itself of all three of its possible reaction pathways: (1) carbon-carbon

cleavage, Δ^3-cyclohexenyl phenyl ketone, compound 1;
(2) solvent attack, the anti-diol, compound 3; and
(3) hydride shift, ion E.

Ion E is prone to attack by the counter ion which yields the syn-7-diol, compound 6, in substantial quantity. The alternative to solvent attack on E is a Wagner-Meerwein rearrangement to form ion F. If ion E were nonclassical this shift would be infinitely fast, or, to rephrase it, $\Delta F^{\ddagger}$ for the shift would be zero, and the transition state to the nonclassical ion would have a lower $\Delta F^{\ddagger}$ than for the classical ion.

Ion F has two reaction paths available. One path involves attack on the ion by solvent to yield exo-diol--none of which was detected--or it may undergo a hydride shift to form ion C. Ion C can react with solvent to yield 4. Analysis by nmr of the positions of the deuterium atoms in the sample of compound 4 which was obtained on the deamination of deuterated reactant (Figure 28, page 78) confirms the route F to C to 4, and it can be calculated that about 12 per cent of 4 is formed this way, placing deuterium (D_1) at the endo-C-5 position in compound 4 and at the bridgehead position (C_4) in compound 7. Although it appears impossible to determine from the available spectra the exact amount of D_1 at each

minority position in the two compounds, it is quite clear that the amount of deuterium (D_1) is not the same in each. If ion B and C were one nonclassical ion instead of two equilibrating classical species, then the distribution of deuterium (D_1) would have to be the same in both 7 and 4. Since the distribution is not the same, these ions must be classical in nature.

Consider next the products arising on deamination of amine II (Figure 29). Here both the leaving group and the counter ion with respect to ion F are in different positions than they are when F is generated by a circuitous route from amine I. That is, the counter ion now is next to the phenyl group and above the charge center as F is oriented in Figure 29. From ion F four reaction paths are possible: (1) proton loss to form 2-phenyl-2-nortricyclenol, 2,; (2) hydride shift to form ion C; (3) Wagner-Meerwein rearrangement to produce E; or (4) attack by solvent to yield diol. This last-mentioned diol was not detected, but it should be mentioned as a possibility. The acetoxyl counter ion must be next to the phenyl group of ion C and close to the charge center. However, the major portion of the reaction does not proceed through C, but rather by way of ion E. This is not too surprising since norbornyl and substituted norbornyl cations are notoriously reluctant to react from an endo direction.[29] The counter ion for ion E

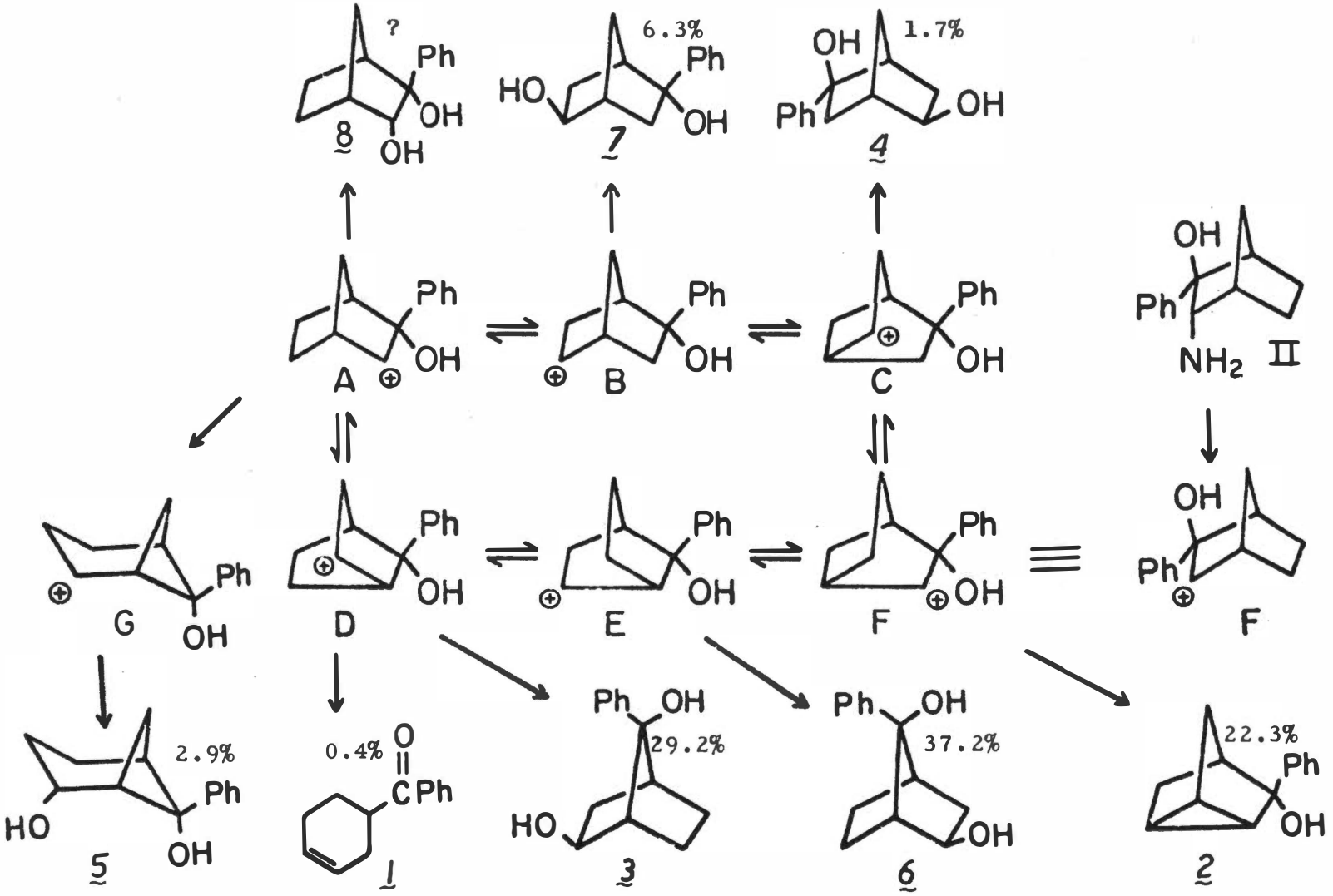


Figure 29. Yields from amine II; 2-exo-hydroxy-2-phenyl-3-endo-aminonorbornane.

is removed from the charge center, and E is thus in a favorable position to react with solvent; in fact, a large amount of material (6) resulting from solvent capture of ion E is found among the products. A hydride shift converts E to D. In ion D--derived from amine II--the counter ion is in a position for exo attack and is located next to the charge center. Steric hindrance by the phenyl group must not be of much importance here as a considerable amount of compound 3 was detected. However, there was only a trace of cyclohexenyl phenyl ketone (compound 1) isolated. A possible explanation for this is that the counter ion, being favorably situated, helps to stabilize the charge, whereas such stabilization is not possible when D is generated from amine I.

Following the foregoing sequence, ion A is produced by a Wagner-Meerwein rearrangement. The counter ion should be located adjacent to the phenyl group and exo or above the charge center as structure A is oriented in Figure 29. No product of exo-attack on ion A was detected. Since the charge center is located on a carbon adjacent to the phenyl group, both steric and inductive effects should be responsible for the low susceptibility to nucleophilic attack exhibited by ion A. Further, little of the 2,6-endo-dihydroxy-2-phenylbicyclo[3.1.1]heptane product, 5, formed by Wagner-Meerwein rearrangement, was detected, which can

also be ascribed to the position of the counter ion above and adjacent to carbon no. 7 here, but below and opposite from carbon no. 7 when generated from amine I. The preferred direction for ion A appears to be the formation of B through hydride shift. Ion B has the charge center located on the opposite side of the bridge from the counter ion (which is in an unfavorable exo-position) and should thus be in an excellent situation for attack by solvent. In fact, a substantial amount of product 7 resulting from solvent attack on B was detected. Ion B, however, can also undergo Wagner-Meerwein rearrangement to yield ion C. The comments made earlier regarding this ion still apply.

From both amine I and amine II the ratio of products 7:4 is greater than one. From amine I the ratio is 1.3 ± 0.3:1, and from amine II the ratio is 5.6 ± 1.1:1. The intermediate ions B and C from both amines I and II, if they are regarded as nonclassical ions, should yield the same ratios of products 4 and 7. The product ratios, however, are markedly different, and the discrepancy cannot be explained if the ions are nonclassical, although a rational explanation can be contrived if the counter-ions can control the reactivities of the intermediate classical ions.

One of the major conclusions of this dissertation is based upon the unequal deuterium (D_1) distribution in the minority positions of products 4 and 7 and the unequal

ratios of their products from two different amines. The conclusion is that the ions which are the immediate precursors (B and C) of these two products are classical ions. It then seems highly likely that all of the ions (Figures 28 and 29, pages 78 and 82, respectively) must also be classical in nature. It has often been stated that one of the properties of nonclassical norbornyl cations is extreme resistance to endo-attack to yield endo-products.[29] In the deaminations of I and II, however, no endo-products were observed. Therefore, it becomes important to search for minute quantities of these products using a very sensitive technique, for it has never been established to what extent endo-attack must take place in order for the intermediate to be a classical ion. One way to determine the yields of endo-products formed would be to repeat the deaminations discussed here with reactants (I and II) labeled with carbon-14. By isotope-dilution technique it should then be possible to detect extremely small quantities of the suspected products.[30]

CHAPTER VI

CONCLUSION

Based on the product analysis of the two different amines, I and II, that must pass through similar intermediates, it is difficult to presume that these intermediate cations are anything but classical in nature and unsymmetrically solvated. Nonclassical ions cannot be invoked here, since certain of the products are incompatible with nonclassical precursors.

Figure 26 (page 74) illustrates the reaction sequence leading to the cyclohexenyl phenyl ketone. Figures 27 (page 76) and 28 (page 78) represent schematically the accepted deamination pathway for the norbornylamines.

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VITA

Michael D. Eckart was born in Tampa, Florida, on June 20, 1938. He obtained his elementary and secondary education in Tampa. Following high school, he served in the armed forces. In 1957, he entered the University of Florida and received the Bachelor of Science in chemistry and a Bachelor of Science with a major in physics in 1961.

After two years in a position with the Celanese Corporation of America, the author enrolled as a graduate student at the University of Tennessee in 1963. While at the University he held a graduate teaching assistantship and an Oak Ridge Associated Universities predoctoral fellowship.

Mr. Eckart is married to the former Marie Inez Houle, and they have two children.