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Highly Strained Bicyclic Systems. VIII. The Nitrous Acid Deamination of 5,5-Dimethylbicyclo[2.1.1]hexyl-2β-amine[1]

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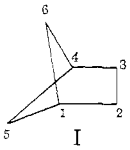
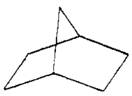
The deamination of 5,5-dimethylbicyclo[2.1.1]hexyl-2β-amine (III) gives a 66% yield of a mixture of four isomeric alcohols, identified as IV (56%), XV (21%), XIV (14%) and XIII (9%). The structures of XIII and XIV were confirmed by independent syntheses. The preference for displacement of nitrogen with retention of configuration (giving optically active IV), and the formation of optically active XV, lend support to the hypothesis that the bridged ion A (Chart 1) serves as an intermediate on the way to these products. The essentially complete retention of optical activity in the inverted alcohol XIV suggests that this product arises by direct solvent displacement of nitrogen from the corresponding diazonium salt, rather than from the alternate bridged ion C.

Introduction

Bicyclic systems involving small bridges are especially well suited for studies of reactions of molecules with well defined geometry. A number of bicyclo[2.1.1]hexanes (I) have recently become accessible as a result of the synthetic efforts of several laboratories,[4] and it is now possible to investigate the reactions of this simple, highly strained class of compounds. One of the objectives of our work in this area has been to examine the course of reactions which involve the development of positive charge at C_2 on the bicyclo[2.1.1]hexyl nucleus, and to relate the results to those available in the better known bicyclo[2.2.1]heptyl series (II). Syntheses of 5,5-dimethylbicyclo[2.1.1]hexyl-2β-amine (III) and of 5,5-dimethylbicyclo[2.1.1]hexan-2β-ol (IV)[5] recently have been completed, and we wish now to report the results of the nitrous acid deamination of III.[6]



I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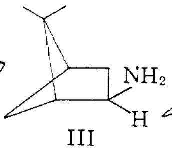
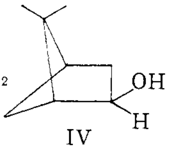


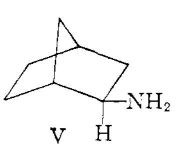
III



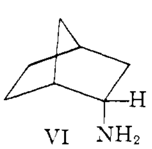
IV

Discussion

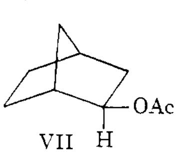
In considering the products that might be expected to arise from the deamination of III, it is relevant to review briefly some comparable reactions of bicyclo[2.2.1]heptylamines. In the case of the racemic *exo*- and *endo*-norbornylamines (V and VI), nitrous acid deamination carried out in acetic acid has been found to give chiefly *exo*-norbornyl acetate (VII). These results, as well as those obtained with the norbornyl-3C^{14}-amines, are compatible with the *bridged* ion VIII being the chief intermediate, with less than 20% of the product being derived from either rearranged bridged ions analogous to VIII, or the "nortricyclonium" ion IX.[7]



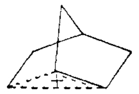
V

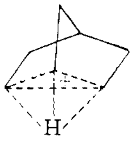


VI



VII

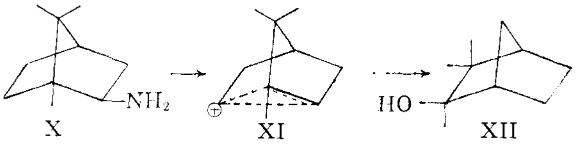

VIII



IX

A more recent, critical examination of the deamination of optically active *endo*-norbornylamine (VI) under similar reaction conditions confirmed the finding that the product was essentially free of *endo* substituted product.[8] In addition, it was observed that although the *exo*-norbornyl acetate (VII) formed was predominantly (77%) racemized, there was appreciable (23%) retention of optical activity. This partial retention of optical activity is most readily accounted for by assuming a small amount of direct solvent displacement of nitrogen (with Walden inversion) from the *endo*-diazonium salt.[8] Thus, even in the case of the *endo*-amine VI, where it is not possible for the corresponding diazonium ion to give rise *directly* to a bridged species (VIII or IX), the products are nevertheless derived largely from a non-classical intermediate which must form after the carbon to nitrogen bond is broken.

Turning to the case of isobornylamine (X), the initially formed deamination product (*ca.* 90% yield) has been shown to be camphene hydrate (XII).[9] This result again fits in with expectations



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[1] For Part VII of this series see W. D. Kumler, A. Lewis and J. Meinwald, *J. Am. Chem. Soc.*, **83**, 4591 (1961). The work described in this paper was presented, in part, before the Division of Organic Chemistry of the American Chemical Society at the 139th National Meeting in St. Louis, Mo., March 21-30, 1961 (abstract page 39-O).

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[4] For a recent review of this subject see J. Meinwald, *Rec. Chem. Prog.*, **22**, 39 (1961).

[5] J. Meinwald and P. G. Gassman, *J. Am. Chem. Soc.*, **82**, 2857 (1960); **82**, 5445 (1960).

[6] A study of the solvolysis of the *p*-toluenesulfonate of IV will be presented in a subsequent paper.

[7] J. D. Roberts, C. C. Lee and W. H. Saunders, Jr., *J. Am. Chem. Soc.*, **76**, 4501 (1954); K. Alder and G. Stein, *Ann.*, **514**, 211 (1934); G. Komppa and S. Beckmann, *ibid.*, **512**, 172 (1934).

[8] J. A. Berson and D. A. Ben-Efraim, *J. Am. Chem. Soc.*, **81**, 4094 (1959). In a more exacting study, J. A. Berson and A. Remanick have detected 5% of *endo*-norborneol (private communication).

[9] W. Hückel and P. Rieckmann, *Ann.*, **625**, 1 (1959).

based on the intermediacy of a bridged ion XI. In this example, the preference for nucleophilic attack at the more heavily substituted center of the bridged ion fits in well with the pattern which Berson has recently pointed out to be characteristic for kinetically controlled reactions involving ions of this type.[10]

The deamination of the bicyclo[2.1.1]hexylamine (III) has shown itself to be somewhat more complex than the cases discussed above. The mixture of acetates, contaminated with a small amount of nitrate ester, was reductively cleaved with lithium aluminum hydride to give a 66% yield of alcohol mixture. Vapor phase chromatography of this mixture revealed the presence of four components, constituting 9, 21, 56 and 14% of the total product (percentages given in order of elution).

The 9% constituent seemed to be tertiary and unsaturated on the basis of its relatively low retention time on a polyethylene glycol column, its infrared spectrum and its n.m.r. spectrum (olefinic protons at 4.46 τ). An alcohol (XIII) meeting these specifications can be readily derived from III (see Chart 1). The ring opening would be favorable since (1) a tertiary carbonium ion (D) is generated and (2) the strain inherent in the bicyclic system is relieved. Although the corresponding ring opening reaction was not observed in the bicyclo[2.2.1]heptyl deaminations discussed above, it is apparent that the process becomes more likely for our more highly strained system. The structure of this product was confirmed by direct comparison with an authentic sample of XIII, prepared independently as outlined in Chart 2.[11] Probably the most remarkable point is that the deamination product does not go *entirely* to XIII, but that the ring opening is in fact relatively unimportant.

CHART 1

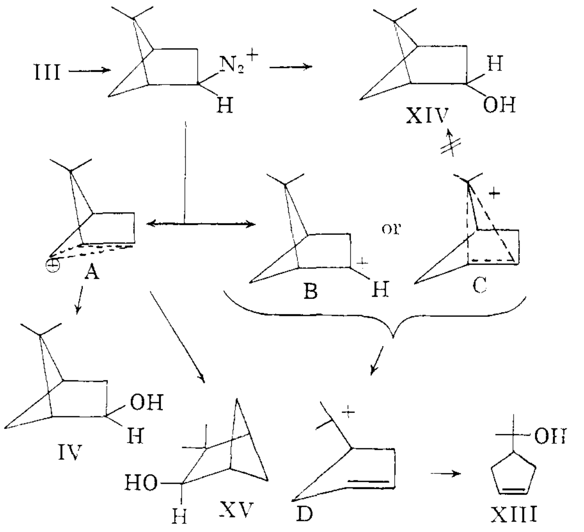
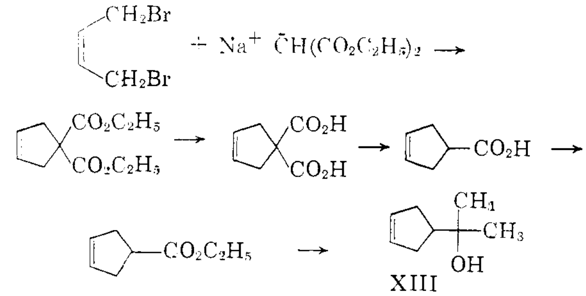
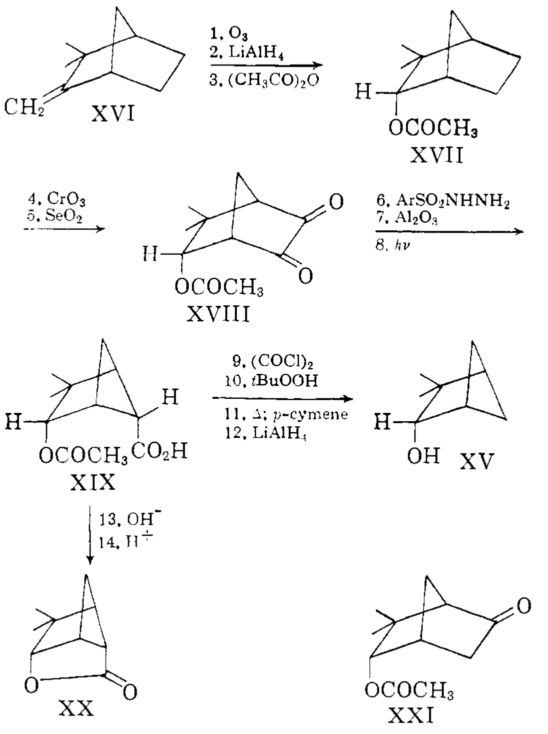


CHART 2



The 21% constituent was a crystalline, saturated alcohol, not identical with any known compound. It gave analytical figures corresponding to the formula $C_8H_{14}O$. Since Wagner–Meerwein rearrangement of III, analogous to the transformation of isobornylamine (X) into camphene hydrate (XII), would give rise to XV, this structure was selected as a working hypothesis. As no easy method for degrading a product of this structure to a known compound presented itself, we undertook an independent synthesis of XV from *dl*-camphene (XVI), as outlined in Chart 3. Ozonolysis of XVI gave camphenilone, which was reduced with lithium aluminum hydride and acetylated to give *endo*-camphenilyl acetate (XVII). Chromic oxide oxidized XVII in about 30% yield to a crystalline keto-acetate, tentatively formulated as the 5-keto-2-*endo*-acetoxy compound XXI on the basis of the closely analogous oxidation of bornyl acetate to the corresponding 5-ketone under comparable conditions.[12] The oxidation of this intermediate by selenium dioxide to give the diketone XVIII removes this element of structural ambiguity, which is reintroduced, however, by the selective formation of one mono-*p*-toluenesulfonylhydrazone upon treatment of the diketone with *p*-toluenesulfonylhydrazide. Chromatography of this derivative on basic alumina resulted in the smooth

CHART 3



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(10) J. A. Berson, *Tetrahedron Letters*, **16**, 17 (1960).

(11) The details of this synthesis are being prepared for publication.

(12) J. Bredt and A. Goeb, *J. prakt. Chem.*, [2] **101**, 273 (1921).

elimination of *p*-toluenesulfinic acid, and the desired α-diazoketone was eluted as a bright yellow crystalline solid in almost 80% yield. Once more the question of whether this material was the 5-diazo-6-ketone or the 6-diazo-5-ketone was left unanswered. Irradiation of this intermediate gave the crystalline acid XIX in unusually good yield (77%). Formulation of XIX as the *endo* isomer is in accord with theoretical expectations, and is supported experimentally by its ready conversion to the corresponding γ-lactone XX (λ_{max} 5.63 μ).

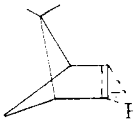
Removal of the carboxyl function from XIX would complete the synthesis, and this was carried out by treatment of the corresponding acid chloride with *t*-butyl hydroperoxide to give a perester as described by Bartlett and Simons,[13] followed by pyrolysis in *p*-cymene.[14] Lithium aluminum hydride reduction of the resultant acetate gave a crystalline alcohol (XV) which was readily proved to be the racemic form of the optically active, 21% product from the deamination of III.

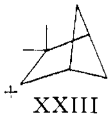
The third and fourth deamination products, obtained in 56% and 14% yields, were recognized as the known alcohol IV and its epimer XIV, respectively. *We regard the preferred formation of IV, involving retention of configuration, as the single most striking and significant aspect of this reaction.* In particular, the route to the 2β-alcohol IV can involve *neither* a direct S_N2 type of solvent displacement of nitrogen from the intermediate diazonium salt, *nor* solvent uptake by the simple 2-carbonium ion (B in Chart 1), since both of these mechanisms would be expected to give the 2α-epimer XIV. A convenient explanation of this predominant configurational retention is provided by the hypothesis that IV arises from the bridged ion A (Chart 1), analogous to ions VIII and XI, in which the α-side of the molecule is shielded by the bridging C_6-methylene group. Nucleophilic opening of this ion would be expected to give IV and XV, which are, in fact, the two main reaction products isolated.

Some additional conclusions can be drawn on the basis of the possible optical activity of the alcohols IV, XIV and XV. In order to get the desired data, it was necessary to develop preparative gas chromatographic techniques for the separation of these isomers; the separation of the epimeric pair, IV and XIV, was particularly difficult. After considerable exploratory work a suitable system was found, and it became possible to determine that all three alcohols were optically active.

In the case of the 2β-alcohol IV, the deamination product had an activity identical, within experimental error, with that of an authentic sample of (−)-IV. This result is in accord with expectations based on the formulation involving A, as given in Chart 1, and serves to exclude the participation of an ion such as XXII, which would have a plane of symmetry due to hydrogen bridging.

In the case of XV, we do not know the maximum possible rotation for an optically pure sample. However, the fact that XV has any optical activity at all ($[\alpha]^{25}\text{D}$ − 43.4°) points to its formation *via* a concerted rather than stepwise pathway, since stepwise rearrangement (B → XXIII → XV) would necessarily give racemic XV, due to the plane of symmetry in XXIII.


XXII


XXIII

Finally, examination of the 2α-alcohol XIV revealed it to be between 0 and 7.5% racemized. This observation excludes the possible derivation of XIV from the symmetrical bridged ion C, since C would have given racemic XIV. It therefore seems most likely that XIV arises from the initial diazonium salt without the intervention of a bridged ion, by direct solvent displacement of nitrogen analogous to that encountered by Berson in the case of *endo*-norbornylamine.

The question of whether the intermediate diazonium salt goes directly to bridged ion A or to B (which then goes to A) remains open. However, when the above results are considered along with those obtained in the solvolysis of the *p*-toluenesulfonate of IV,[6] the direct formation of the bridged bicyclo[2.1.1]hexyl cation appears to be an attractive possibility.

Acknowledgments.—The support of this work by research grants from the National Science Foundation and the National Institutes of Health is acknowledged with pleasure.

Experimental

Nitrous Acid Deamination of (−)-2β-Amino-5,5-dimethylbicyclo[2.1.1]hexane.—To 1.00 g. of (−)-III[5] in 10 ml. of glacial acetic acid at 0°, 0.88 g. of sodium nitrite was added over a 1-hour period. When the reaction mixture started to solidify, it was allowed to warm to about 10° and was then recooled to 0°. After the addition was complete, the mixture was stirred for 1 hour at 0° and allowed to stand at room temperature overnight. An additional 0.12 g. of sodium nitrite was then added. The solution was stirred for 1 hour and poured into 40 ml. of ice-cold 20% aqueous sodium hydroxide. The basic solution was extracted thoroughly with ether. The ethereal solution was washed with dilute hydrochloric acid and water, followed by drying over anhydrous magnesium sulfate. Removal of the drying agent and solvent gave 1.14 g. of a sweet smelling, light yellow liquid, whose infrared spectrum corresponded to that of an acetate (5.78 μ) contaminated with a small amount of nitrate ester absorbing at 6.10 μ.

The total product was dissolved in 20 ml. of anhydrous ether and added dropwise to a stirred suspension of 1.14 g. of lithium aluminum hydride in 20 ml. of anhydrous ether. The slurry was stirred at room temperature for 4 hours, cooled to 0°, and hydrolyzed by dropwise addition of 4.6 g. of water over a 30-minute period. The reaction mixture was stirred for 1 hour at room temperature and the inorganic salts were removed by filtration. The filtrate was dried over anhydrous magnesium sulfate, filtered, and the solvent removed under reduced pressure. The residue was distilled to give 0.66 g. (66%) of alcoholic product.

Vapor phase chromatography (0.25″ × 6′ column of 0.5% polyethylene glycol 400 on glass beads at 107°) showed that the mixture consisted of four components, which constituted 9, 21, 56 and 14% of the product in order of elution.

Identification of Alcoholic Deamination Products.—(a) The 9% component was isolated by preparative vapor phase chromatography. It was shown by its retention times on two columns (0.3% polyethylene glycol 400 on glass beads and 10% Carbowax 4000 on firebrick) and by infrared

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[13] P. D. Bartlett and D. M. Simons, *J. Am. Chem. Soc.*, **82**, 1753 (1960).

[14] This reaction sequence has been used recently by K. Wiberg, B. R. Lowry and T. H. Colby, *ibid.*, **83**, 3998 (1961), to effect some similar decarboxylations.

analysis to be identical with an authentic sample of XIII which was synthesized independently for comparison purposes.[11]

(b) The 21% component was also isolated by preparative vapor phase chromatography. Recrystallization from 30–60° petroleum ether, followed by sublimation, gave an analytical sample, m.p. 106–107°. Gas chromatography on two columns and infrared analysis showed this component to be one enantiomorph of (+)-XV.

Anal. Calcd. for $C_8H_{14}O$: C, 76.14; H, 11.18. Found: C, 75.93; H, 11.41.

(c) The 56 and 14% components were shown by v.p.c. on two columns to be identical with IV and XIV, respectively. These epimers were not separated on a preparative vapor phase chromatograph in our initial experiments, but they were collected as a single sample. Infrared comparison with an authentic 56:14 mixture of IV and XIV gave superimposable infrared spectra.

Camphenilone.—Camphenilone was prepared from commercial (±)-camphene by ozonolysis according to the procedure of Bailey.[15]

Camphenilyl Acetate (XVII).—Lithium aluminum hydride reduction of camphenilone gave a quantitative yield of the corresponding alcohol, m.p. 66–69° (lit.[16] m.p. 76°).

The crude alcohol was acetylated with acetic anhydride in dry pyridine at 100°. The acetate XVII, b.p. 97–99° (14 mm), infrared spectrum (neat) 5.78, 8.00 and 9.50 μ, was obtained in 88% yield.

2-Acetoxy-3,3-dimethylbicyclo[2.2.1]heptan-5-one (XXI).—Seventy-five grams of chromium trioxide suspended in 150 ml. of glacial acetic acid was added over a 45-minute period to a refluxing solution of 30 g. of camphenilyl acetate (XVII) in 50 ml. of glacial acetic acid. After the addition was completed, the reaction mixture was refluxed for 15 minutes, cooled, and poured into an ice-cold solution of 140 g. of sodium hydroxide in 1.2 l. of water. The product was extracted with ether and dried over anhydrous magnesium sulfate. The drying agent was removed by filtration and the solvent was taken off on a flash evaporator. The residue was fractionally distilled to give 9.6 g. (30%) of XXI, b.p. 91–100° (1.2 mm). This material crystallized slowly on standing. Three recrystallizations from 30–60° petroleum ether, then sublimation, gave an analytical sample, m.p. 65.0–65.5°, whose infrared spectrum was identical with the spectrum of the liquid distillate (5.75, 8.00, 9.42 and 10.78 μ).

Anal. Calcd. for $C_{11}H_{16}O_3$: C, 67.32; H, 8.22. Found: C, 67.44; H, 8.28.

2-Acetoxy-3,3-dimethylbicyclo[2.2.1]heptan-5,6-dione (XVIII).—A solution of 4.40 g. of XXI, 4.90 g. of selenium dioxide and 6 ml. of acetic anhydride was refluxed for 4 hours. The reaction mixture was cooled, diluted with ether and filtered. The filtrate was cooled in a Dry Ice–acetone-bath and the precipitate which formed was collected by filtration and air-dried to give 1.50 g. of XVIII, m.p. 115–117°. Chromatography of the filtrate on Florisil and recrystallization of the eluted product from ether gave an additional 0.65 g. of XVIII, m.p. 115–118°. This gave a total yield of 2.15 g. (46%).

Recrystallization from ether followed by sublimation gave an analytical sample, m.p. 121–122°.

Anal. Calcd. for $C_{11}H_{14}O_4$: C, 62.84; H, 6.71. Found: C, 62.89; H, 6.62.

2-Acetoxy-3,3-dimethylbicyclo[2.2.1]heptan-5,6-dione Monotosylhydrazone.—*p*-Toluenesulfonylhydrazine (1.75 g.) in 5 ml. of hot glacial acetic acid was added to a hot solution of 1.84 g. of XVIII in 3 ml. of acetic acid. The solution was allowed to stand for 0.5 hr. and poured onto 200 g. of ice. The resulting white precipitate was collected by filtration and air-dried to give 2.85 g. (86%) of tosylhydrazone, m.p. 153–155°. Three recrystallizations from ethanol–water gave an analytical sample as colorless prisms, m.p. 161–162°.

Anal. Calcd. for $C_{18}H_{22}N_2SO_5$: C, 57.09; H, 5.86; S, 8.47. Found: C, 57.01; H, 5.81; S, 8.51.

Diazoketone from 2-Acetoxy-3,3-dimethylbicyclo[2.2.1]-heptan-5,6-dione Monotosylhydrazone.—The monotosylhydrazone (7.77 g.) was chromatographed on a 5″ × 1″ column of basic alumina (Merck) using benzene as solvent. Evaporation of the eluent gave 3.62 g. (79%) of product, m.p. 70–71°. Two recrystallizations from hexane gave the diazoketone as chunky yellow crystals, m.p. 72–72.5°; infrared spectrum (KBr) 4.80, 5.79 and 5.89 μ.

Anal. Calcd. for $C_{11}H_{14}N_2O_3$: C, 59.45; H, 6.35; N, 12.60. Found: C, 59.61; H, 6.48; N, 12.83.

3β-Acetoxy-2,2-dimethylbicyclo[2.1.1]hexane-*endo*-5-carboxylic Acid (XIX).—A solution of 691 mg. of diazoketone in 80 ml. of 25% aqueous dioxane was irradiated in a Pyrex vessel using a bank of eight 15 watt Sylvania "black-lite" fluorescent tubes as light source. The dioxane–water was removed on a flash evaporator and the residue made basic with sodium bicarbonate solution. The basic solution was extracted thoroughly with ether and acidified with dilute hydrochloric acid. The acidic solution was extracted with ether and the ethereal extract was dried over anhydrous magnesium sulfate. Filtration and evaporation of the solvent gave 509 mg. (77%) of XIX, m.p. 121–124°. Recrystallization from water and sublimation gave an analytical sample, m.p. 134.0–134.5°.

Anal. Calcd. for $C_{11}H_{16}O_4$: C, 62.25; H, 7.60. Found: C, 62.53; H, 7.90.

3β-Hydroxy-2,2-dimethylbicyclo[2.1.1]hexane-*endo*-5-carboxylic Acid and Lactone (XX).—A solution of 60 mg. of XIX in 2 ml. of 10% aqueous sodium hydroxide solution was heated on a steam-bath for 1.5 hours. The reaction mixture was cooled, diluted with water, acidified with dilute hydrochloric acid, and immediately extracted with ether. Evaporation of the solvent after drying over anhydrous magnesium sulfate gave 45 mg. (94%) of the corresponding hydroxy acid, m.p. 159–160°. Sublimation at low temperature gave a sample, m.p. 159–160.5°.

The 3β-hydroxy-2,2-dimethylbicyclo[2.1.1]hexane-*endo*-5-carboxylic acid prepared above (42 mg.) was heated on a steam-bath for 15 minutes in a 5% sulfuric acid solution. The solution was cooled, made basic with sodium bicarbonate solution, and extracted with ether. The ethereal solution was dried over anhydrous magnesium sulfate, filtered, and the solvent removed to give 36 mg. (96%) of crude lactone. The crystalline lactone was sublimed to give an analytical sample of XX, m.p. 46–48°, infrared spectrum (neat) 5.63 μ.

Anal. Calcd. for $C_9H_{12}O_2$: C, 71.02; H, 7.95. Found: C, 70.70; H, 7.99.

2,2-Dimethylbicyclo[2.1.1]hexan-3-ol (XV).—Oxalyl chloride (1.00 g.) was added dropwise to a stirred solution of 500 mg. of XIX in 10 ml. of benzene. Evolution of gas ceased in about 15 minutes. The reaction mixture was allowed to stand 3 hours and the benzene and excess oxalyl chloride were removed under reduced pressure to give the crude acid chloride (infrared spectrum 5.55 and 5.78 μ).

The acid chloride was dissolved in 1 ml. of *p*-cymene and added dropwise at ice temperature to a stirred solution of 0.40 g. of *tert*-butyl hydroperoxide, 1 ml. of pyridine and 3 ml. of *p*-cymene. After stirring at 0° for 1 hr. the reaction mixture was poured onto 10 g. of ice and washed with 10 ml. of 5% sulfuric acid, 10 ml. of water and 10 ml. of 5% sodium bicarbonate solution. The organic material was dried over anhydrous magnesium sulfate. Removal of the drying agent by filtration gave a solution of crude perester in *p*-cymene.

The *p*-cymene–perester mixture was heated under nitrogen to 140–150° for 20 minutes, during which the initial vigorous evolution of gas ceased. The reaction mixture was cooled, diluted with ether and added dropwise to a stirred suspension of 0.50 g. of lithium aluminum hydride in 20 ml. of anhydrous ether at 0°. The reaction mixture was stirred for 3 hours at 0° and hydrolyzed by dropwise addition of 2.00 g. of water. The reaction mixture was then stirred for 1 hour and the inorganic salts were removed by filtration. The filtrate was dried over anhydrous magnesium sulfate, filtered, and the ether distilled off under reduced pressure. Isolation of the product by preparative vapor phase chromatography gave 96 mg. (32%) of (±)-XV, m.p. 77–78°. This was shown by v.p.c. on two columns and by infrared analysis to be the racemic mixture corresponding to the optically active XV isolated from the deamination of III.

Isolation of α- and β-Alcohols from Deamination of β-Amine.—A larger scale deamination reaction was carried out with the intention of isolating the α- and β-alcohols

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(15) P. S. Bailey, *Chem. Ber.*, **88**, 795 (1955).

(16) S. Beckmann and R. Mezger, *ibid.*, **89**, 2738 (1956).

XIV and IV in a pure state in order to determine their optical purities.

A solution of 6 g. of (−)-amine III in 60 ml. of glacial acetic acid was stirred at 10° and 5.28 g. of sodium nitrite was added over a period of 1 hour. After stirring for a further hour at 0–10°, the mixture was allowed to stand at room temperature overnight.

After adding another 0.72 g. of sodium nitrite, the mixture was poured into iced aqueous sodium carbonate and the basic solution was extracted several times with ether. The combined extracts were washed with dilute hydrochloric acid and water before drying over anhydrous magnesium sulfate. Evaporation of the filtered solution yielded *ca.* 8 g. of a sweet smelling orange oil. (A thin layer chromatoplate run on silica gel G in benzene and sprayed with 50% methanol–sulfuric acid showed four spots in two pairs.)

The mixture of acetate and nitrate esters was dissolved in dry ether (70 ml.) and this solution was added dropwise to a stirred slurry of 2.5 g. of lithium aluminum hydride in 100 ml. of dried ether. After stirring for 2 hours at room temperature, the mixture was allowed to stand overnight and then refluxed for 0.5 hours. After the dropwise addition of 10 ml. of water to the cooled mixture, stirring was continued for a further hour. The inorganic salts were removed by filtration on a sinter, where they were triturated with ether. The combined filtrate and washings were dried over anhydrous magnesium sulfate, filtered and the solvent removed through a short column, to yield a pale yellow liquid (*ca.* 5.7 g.).

Infrared spectra indicated that this was a mixture of alcohols and a thin layer chromatoplate on silica gel G in chloroform showed two main spots (identical in migration behavior with the α- and β-alcohols) separated by a diffuse area (corresponding to the rearranged and ring-opened alcohols).

At this stage, a series of preliminary investigations was carried out in order to find a suitable v.p.c. packing for the separation of the α- and β-alcohols in the mixture. These can be reviewed as: analytical columns: (i) 15% Carbowax on firebrick, 162°, good separation of first two components but no separation of α- and β-alcohols; (ii) 3% neopentyl glycol succinate, 112°, partially separated the α-alcohol as a shoulder; (iii) Ucon, 125°, no separation of α- and β-alcohols; (iv) Craig polyester, 94°, partial separation of α- and β-alcohols; (v) 20% LAC 446 on firebrick, 126°, quite good separation of α- and β-alcohols.

The α- and β-alcohols were successfully separated preparatively on a 5-ft. column of 20% LAC 446 on firebrick at a temperature of 126°. By recycling the fractions first collected, pure samples were obtained of both these alcohols.

The α-alcohol showed $[\alpha]^{25}\text{D}$ −4.9° (*c* 7.9 in ethanol) whilst a synthetic sample had $[\alpha]^{25}\text{D}$ −5.3° (*c* 8.0 in ethanol), indicating that racemization could have occurred only to an extent of 7.5% and this is almost within the experimental error in readings from the polarimeter.[17]

A thin layer chromatoplate of the synthetic and deamination α-alcohols showed them to be identical and in a high state of purity.

(+)-5,5-Dimethylbicyclo[2.1.1.]hexan-2-one.—The pure α-alcohol (70 mg.) was recovered from the ethanolic solution which was used to determine its rotation. The alcohol then was dissolved in 5 ml. of A.R. acetone and the solution cooled in ice whilst 0.2 ml. of 6 *N* chromic acid was added dropwise with stirring. The mixture was allowed to stand for 15 min. at room temperature with occasional shaking. After pouring the mixture into water, it was extracted several times with ether. The combined extracts were washed with aqueous sodium carbonate and then dried over anhydrous magnesium sulfate. Evaporation of the solvent yielded 40 mg. of the ketone (infrared spectrum identical with that of previous samples).

Without further purification, this ketone showed $[\alpha]^{25}\text{D}$ +73° (*c* 1.67 in ethanol) [optically pure material, $[\alpha]^{25}\text{D}$ +120.5° (*c* 1.8 in ethanol)]. The crude ketone therefore shows *ca.* 60% of the expected optical activity. Considering the state of purity of the sample, this confirms the previous result that the α-alcohol from the deamination cannot be far from optical purity.

A sample of pure β-alcohol collected after a second pass through the v.p.c. showed $[\alpha]^{25}\text{D}$ −7.5° (*c* 8.7 in ethanol) [optically pure material, $[\alpha]^{25}\text{D}$ −7.7° (*c* 10 in ethanol)]. This confirms that no racemization has taken place.

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(17) The previously reported (ref. 5) value for the specific rotation of XIV was erroneously given as −3.0°.

[CONTRIBUTION FROM THE NATIONAL INSTITUTE OF ARTHRITIS AND METABOLIC DISEASES, NATIONAL INSTITUTES OF HEALTH, PUBLIC HEALTH SERVICE, BETHESDA, MD.]

Behavior of Esters in Liquid Hydrogen Fluoride. Facile Inversions in the Cyclitol Series[1]

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A number of cyclitol esters have been found to undergo rearrangement when dissolved in liquid hydrogen fluoride. In these rearrangements, the configuration of the middle carbon atom of a *cis–trans* sequence is inverted. Mechanisms to rationalize these transformations are proposed and a simple method for the preparation of *muco*-inositol from *myo*-inositol is described.

In earlier work in this Laboratory[3] it has been shown that β-L-arabinopyranose tetrabenzoate and 2,3,4-tri-*O*-benzoyl-β-L-arabinosyl fluoride are readily converted to 3,4-di-*O*-benzoyl-β-L-ribosyl fluoride through the action of liquid hydrogen fluoride at room temperature. Much earlier, Brauns[4] had reported a similar conversion of cellobiose octaacetate to what was probably 3,6-di-*O*-acetyl-4-*O*-(tetra-*O*-acetyl-β-D-glucopyranosyl)-α-D-mannopyranosyl fluoride. These Walden inversions, readily carried out with accessible derivatives under mild conditions, are comparatively rare in the carbohydrate field[5] and are obviously of

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(1) The nomenclature used here is that of H. G. Fletcher, Jr., L. Anderson and H. A. Lardy [*J. Org. Chem.*, **16**, 1238 (1951)]. The numbering of the carbon atoms in the cyclitol field presents unique difficulties and the reader should be warned that in the system used here (as well as in others) the numbering depends not only on the configuration of the cyclitol but also, at times, on the position of substituents. Thus, for instance, corresponding carbon atoms in *myo*-inositol (I) and *muco*-inositol (III) are assigned different numbers. For a discussion of the nomenclature of the cyclitols as well as an excellent comprehensive review of this field see S. J. Angyal and L. Anderson, *Adv. Carbohydrate Chem.*, **14**, 135 (1959).

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(3) C. Pedersen and H. G. Fletcher, Jr., *J. Am. Chem. Soc.*, **82**, 945 (1960).

(4) D. H. Brauns, *ibid.*, **48**, 2776 (1926).

(5) The rearrangements which are induced by a mixture of aluminum chloride and phosphorus pentachloride [*cf.* N. K. Richtmyer, *Adv. Carbohydrate Chem.*, **1**, 37 (1945)] present some features which suggest that the mechanism involved may closely resemble the transformations caused by hydrogen fluoride. The racemizations of some sugar derivatives, recently reported by F. Micheel and R. Böhm [*Tetrahedron Letters*, 107 (1962)], have been rationalized by mechanisms similar to some of those proposed here.