[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY OF WAYNE STATE UNIVERSITY]

Epoxyethers. XVI. A Bicyclo Epoxyether[1,2]

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2,2,6-Trimethylcyclohexanone (III) was prepared in 69% over-all yield from carbethoxycyclohexanone. Halogenation of the ketone III gave the haloketones IV and V in excellent yield. The chloroketone IV was converted in 83% yield to the bicyclo epoxyether VII which was characterized by hydrolysis and reaction with *p*-nitrobenzoic acid to give the hydroxyketone IX and the ketobenzoate VIII. The structure of the hydroxyketone IX was proved by peracid oxidation to geronic acid.

Recently an investigation was initiated in this Laboratory to establish methods for the determination of the stereochemistry of the epoxyethers as well as the stereochemistry of the ring-opening reactions of them.[4] A bicyclo epoxyether such as VII has been sought for some time for this stereochemical investigation since the stereochemistry of this particular type of epoxyether would be known with certainty (the epoxide could only be fused *cis* to the cyclohexane ring). The present investigations resulted in the successful synthesis and characterization of such a bicyclo epoxyether (VII).

The most general method for preparation of epoxyethers is the reaction between an α-haloketone and a sodium alkoxide. However, this reaction, when applied to the α-halo derivatives of the more common cyclic ketones, led to a variety of products other than the desired epoxyethers. Thus depending on solvent and conditions, sodium methoxide reacted with the α-halo derivatives of cyclohexanone,[5] indanone,[6] tetralone[7] and alkyltetralones[7] to bring about variously, simple enolization, Favorski rearrangement, aromatization to phenols and the formation of α-hydroxyketals. Epoxyethers were presumed to be intermediates in the hydroxyketal formation, but could not be isolated. The alternate method for the preparation of epoxyethers, which involved epoxidation of an enol ether, has been shown not to be applicable for the synthesis of the simple bicyclo epoxyether from cyclohexanone enol ether.[8] All of these undesired reactions were circumvented in the present study by the use of the halo derivative of the highly substituted ketone, 2,2,6-trimethylcyclohexanone (III).

The trimethylcyclohexanone (III) reacted smoothly with chlorine and bromine in acetic acid to give the α-chloro (IV) and α-bromo (V) derivatives in 90 and 94% yields, respectively. A spectral analysis of each of these haloketones indicated that in alcohol solution the conformational isomer predominated in which the halogen was axially oriented. This form was considered to be the preferred form for reaction with methoxide ion to give epoxyether (*via* VI).

In alcohol solution the parent ketone III had $\lambda_{\max}$ at 292 mμ with log ϵ 1.44. The chloroketone IV had $\lambda_{\max}$ at 312 mμ (Δ 20 mμ) with log ϵ 1.60 (Δ 0.16 log ϵ). The bromoketone V had $\lambda_{\max}$ at 320 mμ (Δ 28 mμ) with log ϵ 2.01 (Δ 0.57 log ϵ). From these data the conformational structure of the bromoketone V is clear since Cookson[9] has shown from a number of steroid and triterpenoid α-bromoketones that an axial bromine of an α-bromocyclohexanone causes a shift in the ultraviolet absorption of about +28 mμ with the corresponding change of about +0.6 log ϵ.

Although the number of examples of α-chloroketones presented by Cookson was small, direct comparison of certain chloroketones with the corresponding bromo derivatives showed that neither the $\Delta\lambda_{\max}$ nor the Δ log ϵ is as great for the chloro compounds, which data support the axial conformation for the chlorine in IV. The infrared spectrum further supports IV since the parent ketone III had a carbonyl band at 5.83 μ (liquid film) and the chloroketone IV had identical absorption, 5.83 μ (liquid film). Axial α-halocyclohexanones are known to exhibit little shift of wave length of the infrared carbonyl absorption bands.[10] The solid bromoketone V was compared to the liquid chloroketone by means of spectra in chloroform solution. The fact that the absorption of V, 5.83 μ, was essentially identical with IV, 5.82 μ, supported the ultraviolet data for the conformational structure of the bromoketone V.

The bicyclo epoxyether VII was prepared in good yield (83%) from the chloroketone IV by reaction with sodium methoxide in methanol solution by allowing the temperature of the reaction to start at 0° and slowly rise to room temperature. The epoxyether was stable to alcoholysis under these conditions and the product did not show evidence of carbonyl or alcohol-containing impurities in the infrared spectrum.

The epoxyether was characterized by acid-catalyzed hydrolysis to the α-hydroxyketone IX and by reaction with *p*-nitrobenzoic acid to give the α-ketobenzoate VIII. To show that no carbon skeleton rearrangement had occurred in these reactions the α-ketobenzoate was hydrolyzed to the α-hydroxyketone IX and the structure of this

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(1) Number XV in this series is in THIS JOURNAL, **80**, 2276 (1958). A preliminary announcement of this work was made at the 130th Meeting of the American Chemical Society in Atlantic City, N. J., September, 1956.

(2) Sponsored in part by the Office of Ordnance Research, U. S. Army.

(3) Public Health Service Post-doctoral Research Fellow of the National Cancer Institute, 1955–1956.

(4) C. L. Stevens and T. H. Coffield, *J. Org. Chem.*, **23**, 336 (1958).

(5) C. L. Stevens and J. Tazuma, THIS JOURNAL, **76**, 715 (1954).

(6) K. G. Rutherford and C. L. Stevens, *ibid.*, **77**, 3278 (1955).

(7) C. L. Stevens, J. J. Beereboom, Jr., and K. G. Rutherford, *ibid.*, **77**, 4590 (1955).

(8) This simple bicyclo epoxyether from cyclohexanone enol ether has been claimed previously and the claims have been discussed in detail in ref. 5.

(9) R. C. Cookson, *J. Chem. Soc.*, 282 (1954).

(10) R. N. Jones, D. A. Ramsey, F. Herling and K. Dobriner, THIS JOURNAL, **74**, 2828 (1952); E. J. Corey, *ibid.*, **75**, 2301 (1953).

ketone proved by peracid oxidation to geronic acid.[11]

In an initial exploration of the rates of reaction of the haloketones with alcoholic sodium methoxide, the bromoketone was found to consume one equivalent of base instantly in methanol at the reflux temperature at about 1 molar concentrations. Under the same conditions the chloroketone required about 5 minutes for the consumption of one equivalent of base.

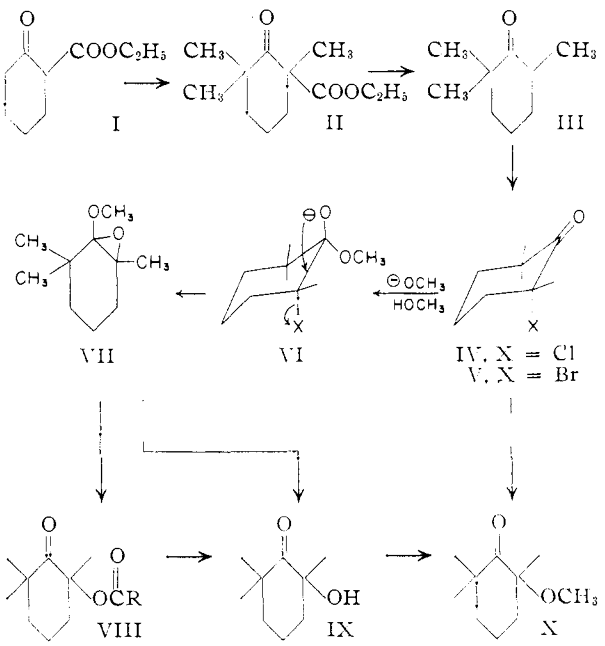
No pure product was obtained from either haloketone in the fast reaction at the boiling point. The infrared spectra of crude products showed two carbonyl bands, one for a saturated (methoxyketone) and one for an α,β-unsaturated ketone, and these same products probably also contained epoxyether.

Under conditions which gave 83% of epoxyether from the chloroketone, the bromoketone still gave serious by-products and only 59% of epoxyether was formed, as judged by conversion to the ketoester VIII. However, using the liquid ammonia procedure in the absence of methanol,[12] the bromoketone reacted smoothly with sodium methoxide to give the α-methoxyketone X as the only product. The structure of the α-methoxyketone was established by independent synthesis from the α-hydroxyketone IX.

The preparation of the chloroketone IV, reaction of IV with sodium methoxide and preparation of the hydroxy and methoxyketones IX and X, respectively, have been subjects of part of recent reports of Wright and co-workers[13] and Meinwald and Cornwall.[11] The preparation of the IV by treatment of the parent ketone with chlorine as reported in this paper appears to be the method of choice. The present work also indicates that the 6-methoxy-2,2,6-trimethylcyclohexanone isolated by Bharucha, Cohen and Wright,[13] and which formed the semicarbazone and 2,4-dinitrophenylhydrazone of the corresponding hydroxyketone, actually was mostly epoxyether, as suggested by Meinwald and Cornwall, and not the hydroxyketal, which the latter authors also considered as a possibility.

The starting 2,2,6-trimethylcyclohexanone (III) has been prepared previously by polymethylation of 2-methylcyclohexanone followed by fractionation.[14] The ketone III also was made by methylation of 2-methylcyclohexanone, conversion of the 2,2-substituted derivative in the mixture to the 6-hydroxymethylene derivative and then final methylation of that derivative followed by removal of the 6-formyl group. The over-all yield from 2-methylcyclohexanone[15] was 22.3%.

In this work the trimethylketone III was made by direct trimethylation of the readily available carbethoxycyclohexanone followed by removal of the carbethoxy group to give the pure ketone III in 69% over-all yield.



Experimental

6-Carbethoxy-2,2,6-trimethylcyclohexanone (II).—Redistilled 2-carbethoxycyclohexanone[16] (187 g., 1.1 moles) was added dropwise over a 30-minute period to a stirred, ice-cooled suspension of 131 g. (5.5 moles) of sodium hydride in 700 ml. of dry benzene. Methyl iodide (465 g., 3.3 moles) was added after hydrogen evolution had moderated and the cold mixture was stirred one hour before heating to reflux. Shortly after the reflux temperature was reached, stirring temporarily became extremely difficult because the mixture thickened with precipitated salts. Reflux was maintained for four hours, then interrupted briefly for the addition of 232 g. (1.64 moles) of methyl iodide, and resumed for an additional 36 hours after which time hydrogen evolution had ceased. The reaction mixture was cooled in ice and decomposed by the slow addition of 30 ml. of alcohol, followed by 50 ml. of water. After standing several hours, one liter of water was added, the layers separated, and the aqueous phase extracted with three portions of ether. The organic layers were dried, concentrated and distilled to give 179.6 g. (77%) of the alkylated ketoester, b.p. 118–126° (15 mm.), $n^{25}\text{D}$ 1.4512–1.4526. The analytical sample, obtained as a center fraction from a similar preparation, had the following properties: b.p. 123° (15 mm.), $n^{25}\text{D}$ 1.4530, $d^{25}{}_4$ 1.0064.

Anal. Calcd. for $C_{12}H_{20}O_3$: C, 67.89; H, 9.50. Found: C, 68.21; H, 9.45.

2,2,6-Trimethylcyclohexanone (III).—A variety of acidic and basic catalysts effected the single step hydrolysis and decarboxylation of II. The method described was found to be the most satisfactory of those investigated on the basis of purity of product, yield and convenience.

A solution containing 179.6 g. of β-ketoester, 110 g. of *p*-toluenesulfonic acid monohydrate, 190 ml. of acetic acid and 85 ml. of water was heated to reflux for a period of 48 hours. The cooled reaction mixture was diluted with one liter of water and then extracted three times with pentane. The combined pentane extracts were washed with 10% sodium hydroxide, water, and then dried over sodium sulfate. After removal of the solvent, distillation of the residue at atmospheric pressure afforded 105.8 g. (89%) of pure 2,2,6-trimethylcyclohexanone,[14] b.p. 176.5–178°, $n^{25}\text{D}$ 1.4454–1.4457, $d^{25}{}_4$ 0.8977.

The 2,4-dinitrophenylhydrazone crystallized from ethanol as orange plates, m.p. 140.5–141° (reported[14] m.p. 141°).

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[11] J. Meinwald and C. C. Cornwall, THIS JOURNAL, **77**, 5991 (1955).

[12] C. L. Stevens, R. L. McLean and A. J. Weinheimer, *ibid.*, **80**, 2276 (1958).

[13] A. Bell, T. H. Strickland and G. F. Wright, *J. Org. Chem.*, **16**, 1742 (1951); K. R. Bharucha, H. L. Cohen and G. F. Wright, *ibid.*, **19**, 1097 (1954).

[14] H. Sobotka and J. D. Chanley, THIS JOURNAL, **71**, 4136 (1949); Attenburrow, *et al.*, *J. Chem. Soc.*, 1094 (1952).

[15] F. E. King, T. J. King and J. G. Topliss, *ibid.*, 919 (1957).

[16] H. R. Snyder, L. A. Brooks and S. H. Shapiro, "Organic Syntheses," Coll. Vol. II, John Wiley and Sons, Inc., New York, N. Y., p. 531.

The oxime, prepared in ethanolic potassium hydroxide, melted at 102.5–103° (reported[17] m.p. 102.5–103°).

6-Chloro-2,2,6-trimethylcyclohexanone (IV).—A quantity of chlorine sufficient to impart a yellow coloration was bubbled into a solution of 93.7 g. of III in 350 ml. of acetic acid. After the disappearance of this color, the solution was surrounded by an ice-bath, and chlorine addition was resumed until the yellow color persisted. The reaction mixture was then diluted with one liter of water and extracted with four portions of methylene chloride, which were combined and dried. Removal of the solvent and distillation gave 104.9 g. (90%) of the chloroketone, b.p. 98–100° (25 mm.), n^{25}_{D} 1.4637–1.4645, d^{25}_{4} 1.0385 (reported[13] b.p. 82° at 12 mm., n^{20}_{D} 1.4683, d^{20}_{4} 1.039).

6-Bromo-2,2,6-trimethylcyclohexanone (V).—To an ice-cooled, stirred solution of 65.9 g. (0.47 mole) of ketone III in 75 ml. of acetic acid containing one drop of a 25% solution of hydrogen bromide in acetic acid, was added dropwise over a 15-minute period a solution of 75.4 g. (0.47 mole) of bromine in 75 ml. of acetic acid. The addition was interrupted short of completion when the coloration due to unreacted bromine persisted. With continued stirring and cooling, 600 ml. of water was added slowly, which caused the crystallization of the bromoketone. After filtration and thorough washing with water the bromoketone was obtained as a colorless, highly volatile solid; yield 97.5 g. (94%), m.p. 38–38.5°. Sublimation or recrystallization from aqueous acetic acid at 0° raised the melting point to 38.5–39.5° (reported m.p. 37–39°[18] and 41°[19]).

1-Methoxy-2,2,6-trimethyl-7-oxabicyclo[4.1.0]heptane (**VII**).—To an ice-cold solution of 9.2 g. (0.4 g. atom) of sodium in 200 ml. of absolute methanol was added 34.9 g. (0.2 mole) of chloroketone IV in 25 ml. of methanol. The mixture immediately became cloudy with precipitated sodium chloride and was allowed to stand at room temperature for 24 hours to complete the reaction. The mixture was then diluted with one liter of cold water and extracted with four portions of hexane which were combined and dried over anhydrous potassium carbonate. Removal of the solvent at atmospheric pressure and distillation of the residue gave 28.4 g. (83%) of the epoxyether, b.p. 80.5–82.5° (25 mm.), n^{25}_{D} 1.4398–1.4403, d^{25}_{4} 0.9417.

Anal. Calcd. for $C_{10}H_{18}O_2$: C, 70.55; H, 10.66. Found: C, 70.50; H, 10.70.

6-Methoxy-2,2,5-trimethylcyclohexanone (X).—A suspension of methanol-free sodium methoxide in ammonia was prepared by the addition of 6.4 g. (0.2 mole) of anhydrous methanol dissolved in 10 ml. of ether to a suspension of 0.2 mole of sodium amide in 200 ml. of liquid ammonia, after which a solution of 21.9 g. (0.1 mole) of bromoketone V in 50 ml. of ether was added. The ammonia was replaced with ether, water was added and the ether layer was separated and dried. Removal of the solvent and distillation gave 15.4 g. (90%) of the colorless methoxyketone, b.p. 90–92° (25 mm.), n^{25}_{D} 1.4462–1.4464. On redistillation, this material boiled at 91–92° (25 mm.), n^{25}_{D} 1.4463, d^{25}_{4} 0.9541.

Anal. Calcd. for $C_{10}H_{18}O_2$: C, 70.55; H, 10.66. Found: C, 70.50; H, 10.69.

The 2,4-dinitrophenylhydrazone was prepared using a 5% excess of the reagent dissolved in methanol containing aqueous hydrochloric acid. It was obtained as yellow needles which melted at 127–127.5° after three recrystallizations from ethanol (reported[13] m.p. 126–127.5°).

The same derivative, identified in each case by melting point and mixed melting point, was obtained from the α-haloketones IV and V when treated with 2,4-dinitrophenylhydrazine under identical conditions, and also from the methoxyketone in a similar preparation using ethanol as solvent.

6-Hydroxy-2,2,6-trimethylcyclohexanone from Epoxyether VII.—Hydrolysis was carried out by the dropwise addition (15 minutes) of 29.6 g. of VII to 75 ml. of 65% methanol containing 5 drops of sulfuric acid. Fifty ml. of water was added and the solution allowed to stand at room temperature for one hour before further dilution with 250 ml. of water. The mixture was made slightly basic with potassium hydroxide solution, saturated with sodium chloride and extracted with several portions of ether, which were dried over sodium sulfate. From this solution there was obtained 22.3 g. (84%) of the hydroxyketone IX, b.p. 92–94° (15 mm.), n^{28}_{D} 1.4583–1.4590, d^{25}_{4} 0.9991.

Anal. Calcd. for $C_9H_{16}O_2$: C, 69.19; H, 10.32. Found: C, 69.14; H, 10.32.

The 2,4-dinitrophenylhydrazone was obtained as orange needles, m.p. 224–225° (reported[13] m.p. 224–225°).

Reaction of Epoxyether VII with *p*-Nitrobenzoic Acid. *p*-Nitrobenzoate Ester of 6-Hydroxy-2,2,6-trimethylcyclohexanone (**VIII**).—A mixture of 1.0 g. of VII and 1.5 g. (50% molar excess) of *p*-nitrobenzoic acid in 25 ml. of dry benzene was refluxed for 24 hours. Unreacted acid, 0.47 g., was filtered from the cooled solution which was then washed with saturated sodium bicarbonate solution, water and dried. Evaporation of the solvent left a nearly quantitative yield of the crude ester as a pale yellow solid having m.p. 105–108°, raised to 108–109° by recrystallization from ethanol at 0°. Another recrystallization gave material having m.p. 108.5–109°.

Anal. Calcd. for $C_{16}H_{19}NO_5$: C, 62.94; H, 6.27. Found: C, 63.03; H, 6.21.

6-Hydroxy-2,2,6-trimethylcyclohexanone from Ketoester VIII.—Steam was passed through a solution of 18.45 g. (0.06 mole) of VIII in 100 ml. of ethylene glycol during the dropwise addition of a solution of 7.8 g. (0.12 mole) of potassium hydroxide in 50 ml. of water. Steam distillation was continued until 200 ml. of distillate was collected. The distillate was saturated with sodium chloride and extracted several times with ether. Distillation of the dried extract gave 7.73 g. (82%) of the hydroxyketone, b.p. 93° (15 mm.), n^{28}_{D} 1.4585–1.4587, n^{25}_{D} 1.4599. The infrared spectrum was identical with that of the hydroxyketone obtained previously.

The pure 2,4-dinitrophenylhydrazone was obtained after three recrystallizations from ethyl acetate; m.p. and m.m.p. with the derivative obtained previously 224–225°.

Reaction of 6-Bromo-2,2,6-trimethylcyclohexanone (V) **with Methanolic Sodium Methoxide.**—This reaction was performed on a 0.1-mole scale in essentially the same way as described for the chloroketone. The material isolated boiled over the range 71–86° (25 mm.), and had n^{25}_{D} 1.4423–1.4528. On the basis of infrared spectra, epoxyether was present in several fractions, but was apparently contaminated with lower boiling α,β-unsaturated ketone and with higher boiling methoxyketone. The total reaction product was heated at reflux for 24 hours with excess *p*-nitrobenzoic acid in benzene, and the resulting neutral fraction was evaporated to dryness *in vacuo*, leaving a residue of 18.0 g. (59%) of VIII, m.p. 107–109°.

Conversion of 6-Hydroxy-2,2,6-trimethylcyclohexanone (IX) to the Methyl Ether X.—The sodium salt of the hydroxyketone was formed by the addition of 28.7 g. (0.184 mole) of IX dissolved in 50 ml. of ether to a suspension of 0.25 mole of sodium amide in 250 ml. of liquid ammonia. The salt precipitated as a gummy solid which collected in a single mass on the stirrer. A solution of 35.5 g. (0.25 mole) of methyl iodide in 25 ml. of ether was added and with continued stirring the gum gradually disintegrated and was replaced by a finely divided precipitate of sodium iodide. After 30 minutes, an additional 10-g. quantity of methyl iodide was added. Stirring was continued for another 30 minutes and then the ammonia was replaced by ether and the mixture heated briefly to reflux. After decomposition by the addition of water, distillation of the material isolated from the ether indicated that the product was contaminated with unchanged hydroxyketone.

The total crude mixture was submitted to a second methylation process, identical with that just described. From this reaction, there was obtained 24.5 g. (78%) of the methoxyketone, b.p. 92–94° (25 mm.), n^{25}_{D} 1.4473–1.4487, still slightly contaminated with the starting hydroxyketone. The identity of this product with the methoxyketone prepared previously from 6-bromo-2,2,6-trimethylcyclohexanone and sodium methoxide was established by comparison of their dinitrophenylhydrazones. The derivative of the methylation product melted at 125–125.5°, and the mixture melting point with the derivative obtained above was 125.5–126.5°.

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[17] M. S. Newman, 1. Waltcher and H. F. Ginsberg, *J. Org. Chem.*, **17**, 962 (1952).

[18] A. N. Newmayanov, K. A. Pecherskaya and T. P. Tolstaya, *Uchenye Zapiski Moskov. Gosudarst. Univ. im. M. V. Lomonozova No.* 132, *Org. Khim.* **7**, 66 (1950); *C. A.*, **49**, 3853 (1955).

[19] R. N. Chakravarti, *J. Chem. Soc.*, 1505 (1947).

Oxidation of Hydroxyketone IX to Geronic Acid.—A solution of 20.0 g. of hydroxyketone in 175 ml. of acetic acid containing 85 ml. of 30% hydrogen peroxide was maintained at 60° for nine hours, after which time complete oxidation was indicated by complete solubility of a portion of the reaction mixture in saturated potassium carbonate solution. The cooled reaction mixture was poured into an aqueous solution of excess sodium carbonate which was extracted twice with ether, acidified with hydrochloric acid and then extracted four times with ether. The latter ether extract was dried over sodium sulfate and distilled to give 17.22 g. (78%) of geronic acid, b.p. 147–150° (3.3 mm.), $n^{25}D$ 1.4472–1.4477; semicarbazone, m.p. 164.5–165° (reported[20] m.p. 165°); 2,4-dinitrophenylhydrazone, recrystallized from ethyl acetate–hexane, m.p. 139.5–140° (reported[21] m.p. 135.5–137°).

Acknowledgment.—The authors wish to thank Dr. J. M. Vandenbelt, R. B. Scott and their associates at Parke, Davis and Co. for the ultraviolet and infrared spectral determinations.

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[21] H. H. Strain, THIS JOURNAL, **57**, 758 (1935).

DETROIT 2, MICHIGAN

[CONTRIBUTION FROM THE PHARMACEUTICAL INSTITUTE, MEDICAL FACULTY, UNIVERSITY OF KYUSHU]

Thermal Behavior of *dl-trans-* and *dl-cis-*2-Iodo-N,N-dimethylcyclohexylamines[1]

BY TANEZO TAGUCHI AND MORIFUSA ETO[2]

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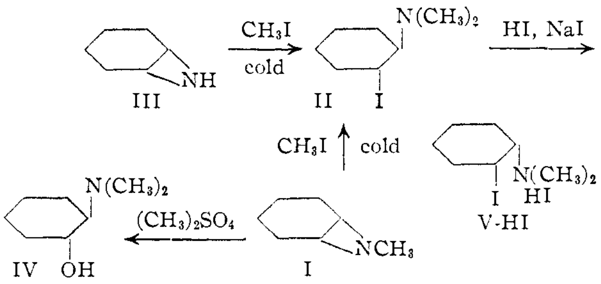
dl-trans-2-Iodo-N,N-dimethylcyclohexylamine (II) was obtained by the reaction of methyl iodide with either *meso-cis*-N-methylcyclohexenimine (I) or *meso-cis*-cyclohexenimine (III). The *cis* epimer V was prepared from II-hydroiodide. The configurations assigned to II and V were confirmed by a number of reactions on stereochemical grounds. Under pyrolytic conditions the *trans* epimer II gave cyclopentanecarboxaldehyde (VI) and cyclohexanone (VII), while the *cis* epimer V gave only cyclohexanone (VII). The thermal behavior was not governed by *cis* elimination, which is generally accepted for pyrolysis, but by heterolytic reaction rules. This was attributed to the reactivity of the dimethylamino group, since in the case of the *trans* epimer II hydrochloride destruction of the reactivity of the dimethylamino group by salt formation altered the reaction mechanism to *cis* elimination.

The reaction of *meso-cis*-N-methylcyclohexenimine (I) with methyl iodide at room temperature gave mainly *dl-trans*-2-iodo-N,N-dimethylcyclohexylamine (II) accompanied by a small amount of the methiodide of II; II was also prepared from *meso-cis*-cyclohexenimine (III) and excess methyl iodide. The configuration assigned to II is based on the known *trans* opening of the imine ring[3] and on the fact that treatment of the N-methylimine (I) with dimethyl sulfate gave *dl-trans*-2-dimethylaminocyclohexanol (IV) (see Scheme 1). The work of Winternitz and Mousseron,[4] who concluded that the reaction of I with methyl iodide with heat yields *dl-trans*-2-iodo-N,N,N-trimethylcyclohexylammonium iodide, supports this configuration for II. The following observations supply even stronger evidence for the configuration of II: boiling of the *trans* epimer hydroiodide II-HI with anhydrous sodium iodide in dry ethanol–acetone for many hours yielded the hydroiodide of *dl-cis*-2-iodo-N,N-dimethylcyclohexylamine (V), while all attempts to prepare V from esters of *dl-trans*-2-dimethylaminocyclohexanol failed.

The *trans* epimer II reacted with silver nitrate at room temperature to yield *dl-trans*-2-dimethylaminocyclohexanol (IV) and cyclopentanecarboxaldehyde[5] (VI), while the *cis* epimer V yielded only cyclohexanone (VII).[5] These results are stereochemically similar to those of Mousseron[4,6] obtained by analogous treatment of *dl-trans*-2-iodocyclohexylamine and *dl*-2-chlorocyclohexanols. Treatment of the epimers with water gave almost the same results. When II was warmed with water, *dl-trans*-2-dimethylaminocyclohexanol (IV) was obtained, and when it was heated with water at 140° in a sealed tube, IV and cyclopentanecarboxaldehyde (VI) were formed; V gave cyclohexanone (VII). Analogously, ethanolysis of II at 140–150° gave *dl-trans*-2-ethoxy-N,N-dimethylcyclohexylamine (IV′), a small amount of crude VII and a trace of crude VI, whereas V gave VII.

SCHEME 1



The similarity of these results suggests that the mechanism for the formation of a particular product is the same under all these conditions. For details see Scheme 2. One would expect that II in the preferred diequatorial conformation would yield VI *via* the N,N-dimethylcyclopentylmethylideneammonium (VIII), and that IV (or IV′) would be formed through the transition state with the migrating groups in axial positions followed by the formation of an intermediate, the *meso-cis*-N,N-dimethylcyclohexeniminium ion (IX).[7] With the *cis* epimer V, cyclohexanone would be expected

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[1] Studies in Stereochemistry. XVI.

[2] The Department of Agricultural Chemistry, Agricultural Faculty, University of Kyushu.

[3] (a) F. H. Dickey, W. Fickett and H. J. Lucas, THIS JOURNAL, **74**, 944 (1952); (b) R. Ghiradelli and H. J. Lucas, *ibid.*, **77**, 106 (1955); **79**, 734 (1957).

[4] F. Winternitz, M. Mousseron and R. Dennilauler, *Bull. soc. chim. France*, 382 (1956).

[5] G. E. McCasland obtained essentially the same rearrangement products from epimeric *dl*-2-aminocyclohexanols on treatment with nitrous acid in the cold; THIS JOURNAL, **73**, 2293 (1951).

[6] M. Mousseron and R. Jaquier, *Compt. rend.*, **229**, 216 (1949).

[7] For details of the original mechanistic explanation adapted for this case, see D. Y. Curtin and S. Schmukler, THIS JOURNAL, **77**, 1105 (1955).