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The Synthesis of 5- and 6-Hydroxy-2-methylisoquinclidine

Joseph I. DeGraw and Jill G. Kennedy

The reduction of the isomeric 5,6-epoxy-2-carboethoxyisoquinclidines with lithium aluminum hydride afforded 5- and 6-hydroxy-2-methylisoquinclidine. Contrary to expectation essentially single epimers were obtained for each alcohol.

In recent years the little investigated isoquinclidine ring system has received an increased amount of attention. This is mainly due to its occurrence in the natural products dioscorine and ibogaine. Morris and Pinder (1) obtained 2-methyl-5-isoquinclidinone (VI) as a degradation product of dioscorine and a synthesis of VI from cyclohexenone, methylamine and formaldehyde was later published (2). Cava, *et al.* (3,4) recently prepared both 2-methyl-5- and 6-isoquinclidinone (VI and VII) along with a variety of simple isoquinclidine derivatives. Their synthesis of VI and VII required a tedious separation of the intermediate 2-carbethoxy-5- and 6-isoquinclidinones by gas liquid chromatography. Since we wished to prepare, in quantity, both 5 and 6-hydroxy-2-methylisoquinclidine (IVa and Va), a synthetic approach independent of the above ketones was devised.

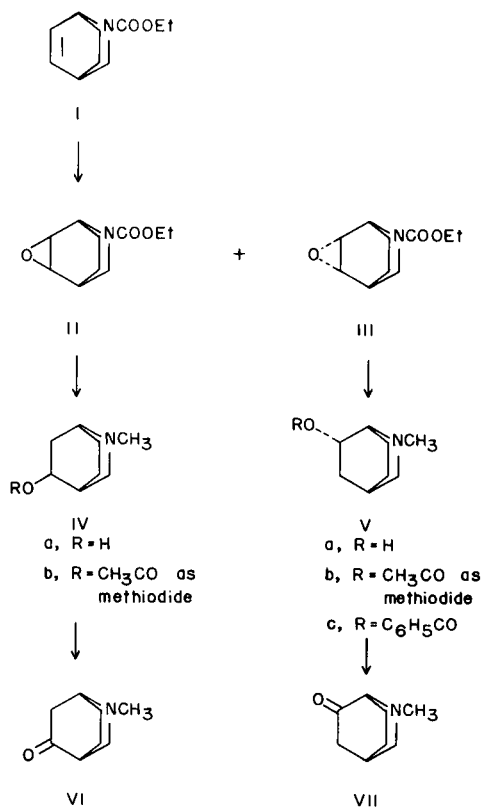
Treatment of 2-carbethoxy-2-azabicyclo[2.2.2]-oct-5-ene (3,4) (I) with *m*-chloroperbenzoic acid in chloroform afforded an equal mixture of epoxides (II and III) as shown by gas liquid chromatography (G. L. C.). These epoxides could be separated either by distillation or column chromatography and were identified on the basis of their N. M. R. spectra and reduction products. The fact that an equal mixture of epoxide isomers was found illustrates the essentially symmetrical steric environment of the double bond in I.

Reduction of the epoxide mixture afforded a mixture of 2-methyl-5- and 6-alcohols which were readily separated by fractional distillation. The 6-alcohol (Va) had the lower boiling point and shorter G. L. C. retention time; the infrared spectrum as a liquid film showed a hydroxyl band at 2.89μ , with tailing to 3.4μ , indicative of association. The higher boiling 5-alcohol (IVa) showed a broad, associated hydroxyl region (3.0 - 3.3μ) with poorly defined peaks at 3.04 and 3.20μ . The positions of the 5- and 6-hydroxyl groups were shown by oxidation to the respective ketones and consequent mixed melting point comparisons of the ketone picrates with authentic samples.

Gas liquid chromatography of the crude alcohol mixture showed only two significant peaks. Reduction of the more volatile epoxide (II) alone gave

only the 5-alcohol (IVa), while reduction of the epoxide (III) gave essentially the 6-alcohol (Va) along with a small amount of an unidentified component, possibly one of the other epimeric alcohols. It is difficult to explain why significant amounts of only two epimers were obtained in view of the aforementioned symmetrical nature of the isoquinclidine system. We are reluctant to speculate on the mechanism but it seems likely that a complex between the *N*-carbethoxy group and metal hydride, capable of interaction about the 5 and 6 positions, is somehow involved.

The 6-alcohol (Va) readily afforded a benzoate ester (Vc), characterized as the picrate, when



treated with benzoyl chloride at room temperature. Treatment with acetic anhydride and pyridine at room temperature yielded the liquid acetate ester (Vb) characterized as its crystalline methiodide. The 5-alcohol was unreactive toward benzoyl chloride and required a few hours reflux with acetic anhydride to form the acetate ester (IVb), again characterized as the methiodide.

We were unable to establish an unequivocal proof of stereochemistry for the alcohols and their corresponding epoxides. However, certain observations did allow us to give a tentative assignment. A series of papers by Aaron, *et al.*, (5-9) has dealt with the problem of hydroxyl configuration in epimeric azabicyclic alcohols. These authors have shown that the stereochemistry could be determined by a comparison of gas-liquid chromatographic retention times, pK_a , and intra versus intermolecular hydrogen bonding (N---H-O) in the hydroxyl region of the infrared spectrum. Since our problem concerned hydroxyl groups attached to two different carbon atoms (5 and 6) rather than epimers of a single carbon atom, the G.L.C. and pK_a data could not be given too much significance. However, the lower G.L.C. retention time and much lower boiling point along with the higher pK_a observed for the 6-alcohol favor an intramolecularly hydrogen bonded alcohol. The more important infrared measurements were inconclusive since no appreciable or reliable change in hydroxyl band wavelength was noted upon running the alcohols in progressively diluted carbon tetrachloride solutions. The peak positions were also unreliable due to the broadening caused by rapid carbonate formation. One might infer that the dual infrared peak seen in the OH region of the 5-alcohol is due to the free and bonded OH, characteristic of intermolecularly bonded alcohols.

The N.M.R. spectra of the isomeric epoxides were more definitive for the stereochemical assignment. Tori, *et al.* (10), have published the N.M.R. spectra for the epoxide derivatives of benzobicyclo-[2.2.2]octene. When the epoxy ring and the ethylene bridge were *trans* the bridge protons appeared as two doublets centered at 8.25 and 8.61 τ . When the bridge and epoxy ring were *cis* these protons again appeared as two doublets, but widely separated at 7.97 and 8.96 τ . In our epoxides (II and III) the ethylene bridge protons (C₇ and C₈) appeared as uninterpretable, complex multiplets in the 8.2-8.6 τ region. However, in the more volatile epoxide (II) the C₃ protons appeared as two doublets centered about 6.62 and 6.83 τ , while in III the doublets were shifted to 6.54 and 7.04 τ . These observations suggest that the epoxy ring is *trans* to the aza bridge in II and *cis* in III. It follows that the alcohols formed by hydride reduction would have the same stereochemistry as their epoxide precursors. The previously discussed physical data for the alcohols are in agreement with our stereochemical conclusion

based on the epoxides. We regret that our time commitments and funds would not allow us to pursue a more rigid chemical proof of the stereochemistry.

EXPERIMENTAL

5,6-Epoxy-2-carbomethoxyisoquinuclidines (II and III).

A solution of 0.93 g. (5.14 mmoles) of the 5,6-olefin (I), prepared by the procedure of Cava, *et al.* (4), and 1.34 g. of *m*-chloroperbenzoic acid (85% active oxygen, 6.7 mmoles) in 20 ml. of chloroform was allowed to stand 21 hours. Another 0.79 g. of peracid was added and the solution allowed to stand another 20 hours. The solution was washed with 15 ml. of 2% sodium sulfite, 5 ml. of 10% sodium hydroxide and two 30 ml. portions of water. The chloroform was dried over magnesium sulfate and evaporated *in vacuo* to leave 0.82 g. of a yellow syrup. G.L.C. analysis (10% XF-1150 on 45/60 mesh Chromasorb W at 190°) showed approximately 10% unreacted olefin and 45% each of the epoxides.

A 7.6 g. portion of a larger run was fractionally distilled at 1.3 mm. through a 30 cm. spinning band column to afford (1) 0.7 g. of liquid, b.p. 110-112°, (2) 1.3 g. at 112-123° and, (3) 1.5 g. at 123-124°. Thin layer chromatoplates (silica gel, chloroform-ethyl acetate, 3:2) showed fraction (1) to be pure II (R_f 0.8), fraction (2) was a mixture (R_f 0.7 and 0.8) and fraction (3) was pure III (R_f 0.7). The elemental analyses were not quite acceptable, possibly due to instability. A separation by column chromatography on silica gel again gave chromatographically pure isomers, but failed to improve upon the analyses.

Isomer (II) higher volatility and R_f: I.R. λ max (film), (μ) 5.92 (C=O), 9.05 (urethane C-O) and unidentified strong bands at 10.30, 11.70, 12.40, 13.00; N.M.R. (100 m.c., in CCl₄) 5.65 τ doublet (C₁ H), 5.95 quartet (CH₂ of urethane), 6.72 (C₅ and C₈ H's), 6.62 and 6.83 doublets (C₃ H's), 7.68 (C₄ H), 8.2-8.6 (C₇ and C₈ H's), 8.76 triplet (CH₃).

Anal. Calcd. for C₁₀H₁₅NO₃: C, 60.9; H, 7.67; N, 7.10. Found: C, 60.2; H, 7.74; N, 7.42.

Isomer (III), lower volatility and R_f: I.R. λ max (film), (μ) 5.92 (C=O), 9.05 (urethane C-O) and unidentified strong band at 13.00; N.M.R. 6.83 τ (C₅ and C₈ H's), 6.54 and 7.04 doublets (C₃ H's), other signals the same as in isomer II.

Anal. Calcd. for C₁₀H₁₅NO₃: C, 60.9; H, 7.67; N, 7.10. Found: C, 60.0; H, 7.45; N, 6.89.

Reduction of Epoxides.

To 20.0 g. of lithium aluminum hydride in 500 ml. of tetrahydrofuran at 0-5° was slowly added 31.0 g. of crude 5,6-epoxy-2-carbomethoxyisoquinuclidine (II-III) in 200 ml. of tetrahydrofuran. The mixture was stirred at reflux for 16 hours, chilled in ice and the excess hydride destroyed with ethanol and a little water. The solvent was evaporated *in vacuo* and the residue suspended in 300 ml. of ether. Water was added until the salts deposited as a white, pasty mass. The ether was decanted and another three 100-ml. ether extractions were performed. The ether extract was dried over magnesium sulfate and evaporated to leave 12.5 g. (52%) of a syrup whose infrared spectrum was devoid of carbonyl absorption. G.L.C. (20% DC-550 on 45/60 mesh Chromasorb W at 150°) showed two significant peaks in a 65:35 ratio.

The mixture was fractionally distilled through a spinning band column at 10 mm. to give 4.34 g. of a mobile liquid at 84-86°, an intermediate fraction of 2.00 g. at 87-116° and 2.80 g. of a viscous liquid at 116-117°. The intermediate fraction was mainly composed of the lower boiling liquid. Reduction of the epoxide (II) alone gave the higher boiling alcohol exclusively and reduction of the epoxide (III) gave mostly the lower boiling alcohol along with a small amount of an unidentified component as shown by G.L.C.

6-Hydroxy-2-methylisoquinuclidine (Va); lower boiling alcohol: I.R. λ max (film), (μ) 2.89, tailing to 3.4 (OH, associated). A 5% carbon tetrachloride solution also showed 2.89 μ and was not significantly changed on further dilution (broadening of peaks from carbonate formation was observed in both alcohols); pK_a 10.30 (measured as pH at 1/2 neutralization by titration with 0.1 N HCl); G.L.C. retention time, 11.8 minutes.

The picrate, m.p. 269-271°, was prepared in and recrystallized from ethanol as yellow needles.

Anal. Calcd. for C₁₄H₁₈N₄O₈: C, 45.4; H, 4.90; N, 15.1. Found: C, 45.1; H, 4.98; N, 15.4.

The methiodide, m.p. > 300°, was prepared by treatment with an

excess of methyl iodide, followed by recrystallization from methanol.

Anal. Calcd. for $C_9H_{13}NO$: C, 38.2; H, 6.41; N, 4.95. Found: C, 38.2; H, 6.24; N, 4.72.

5-Hydroxy-2-methylisoquinclidine (IVa); higher boiling alcohol. I.R. λ max (film), (μ) 3.04, 3.20 (OH, strongly associated), not significantly changed in 5% carbon tetrachloride solution nor in more dilute solutions; pK_a 9.85; G.L.C. retention time, 15.7 minutes.

Picrate, m.p. 260-262°, yellow needles from ethanol.

Anal. Calcd. for $C_{14}H_{18}N_4O_5$: C, 45.4; H, 4.90; N, 15.1. Found: C, 45.3; H, 5.00; N, 15.4.

Methodide, m.p. > 300°, white crystals from ethanol-2-propanol.

Anal. Calcd. for $C_9H_{13}NO$: C, 38.2; H, 6.41; N, 4.95. Found: C, 37.9; H, 6.31; N, 4.79.

2-Methyl-5-isoquinclidinone Picrate (VI).

To a solution of 1.70 g. (12.0 mmoles) of the higher boiling alcohol (IVa) in 17 ml. of acetic acid at 70° was added, dropwise over 10 minutes, 0.91 g. (9.1 mmoles) of chromic acid in 5 ml. of 80% acetic acid. The mixture was heated 1.5 hours at 70° and cooled to 0-5°. Water (50 ml.) was added followed by sodium hydroxide pellets until a pH of 11-12 was attained. Continuous extraction with ether for 48 hours yielded 0.86 g. (51%) of syrup. The material was converted to the picrate in ethanol and recrystallized from 90% ethanol until the infrared spectrum was free of hydroxyl absorption. The yellow crystals so obtained had m.p. 192-194° (dec.). Admixture with a sample of racemic 2-methyl-5-isoquinclidinone (m.p. 190-191°, dec.), provided by Prof. A. R. Pinder, showed m.p. 190-191° (dec.). The infrared spectra of the picrates as Nujol mulls were similar, but not quite identical.

2-Methyl-6-isoquinclidinone Picrate (VII).

The lower boiling alcohol was similarly oxidized as above and the ketone-alcohol mixture separated by G.L.C. (20% DC-550 on 45/60 mesh Chromasorb W at 153°). The ketone was converted to the picrate, m.p. 229-231°, after recrystallization from ethanol. Mixed melting point comparison with 2-methyl-6-isoquinclidinone picrate, m.p. 230-232°, prepared by the method of Cava, *et al.* (4), showed m.p. 229-232°. The infrared spectra of the picrates as Nujol mulls were identical.

5-Acetoxy-2-methylisoquinclidine Methiodide (IVb).

A solution of 0.50 g. of 5-hydroxy-2-methylisoquinclidine (IVa) in 2.5 ml. of acetic anhydride was heated at reflux for 2.5 hours and evaporated *in vacuo*. The residue was dissolved in 10 ml. of water and washed twice with 10 ml. portions of ether. The aqueous portion was adjusted to pH 8 with saturated sodium bicarbonate and extracted with five 20-ml. portions of ether. The ether extract was dried over magnesium sulfate and evaporated to leave 0.31 g. of syrup; λ max (film), (μ) 5.75 (C=O of ester). A 0.14 g. portion in 2 ml. of ether was treated with 1 ml. of methyl iodide for one hour at ambient temperature. The solid was collected to afford 0.22 g. of slightly hygroscopic, yellow crystals which were recrystallized from ethyl acetate to yield 0.10 g. of yellow crystals, m.p. 170-173° (evacuated capillary).

Anal. Calcd. for $C_{11}H_{20}INO_2$: C, 40.6; H, 6.20; N, 4.31. Found: C, 40.4; H, 6.42; N, 3.97.

6-Acetoxy-2-methylisoquinclidine Methiodide (Vb).

A 216 mg. portion of 6-hydroxy-2-methylisoquinclidine (Va) was treated with 1.5 ml. of acetic anhydride at room temperature for 2 hours. The reaction was worked up and converted to the methiodide as above to yield yellow crystals, m.p. 176-179° (evacuated capillary), after recrystallization from ethanol.

Anal. Calcd. for $C_{11}H_{20}INO_2$: C, 40.6; H, 6.20; N, 4.31. Found: C, 40.6; H, 6.24; N, 4.05.

6-Benzoyloxy-2-methylisoquinclidine (Vc).

To an ice cold solution of 0.92 g. (6.55 mmoles) of 6-hydroxy-2-methylisoquinclidine (Va) in 20 ml. of ether was added 0.77 ml. (6.66 mmoles) of benzoyl chloride, dropwise with stirring. The mixture was stirred 15 hours at room temperature and treated with 10 ml. of water, followed by solid potassium carbonate until strongly basic. The mixture was extracted with four 20-ml. portions of ether, which was dried over magnesium sulfate and evaporated to leave 0.85 g. of syrup. The syrup in a little ethanol was added to a warm solution of 0.69 g. of picric acid in 70 ml. of water. The resulting yellow, crystalline precipitate was collected, washed with water and dried to leave 0.95 g., m.p. 203-210°. Recrystallization from 2-propanol-acetone yielded 0.61 g. of yellow crystals, m.p. 216-219° and a second crop of 0.10 g., m.p. 220-222°. An analytical sample similarly obtained from another run showed m.p. 214-216°.

Anal. Calcd. for $C_{21}H_{22}N_4O_5$: C, 53.2; H, 4.67; N, 11.8. Found: C, 53.2; H, 4.94; N, 12.1.

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Menlo Park, California 94025