Bicyclic Bases (1). Stereoselective Synthesis of *exo*- and *endo*-*N*-Benzyl-6-hydroxy-2-azabicyclo[2.2.1]heptane

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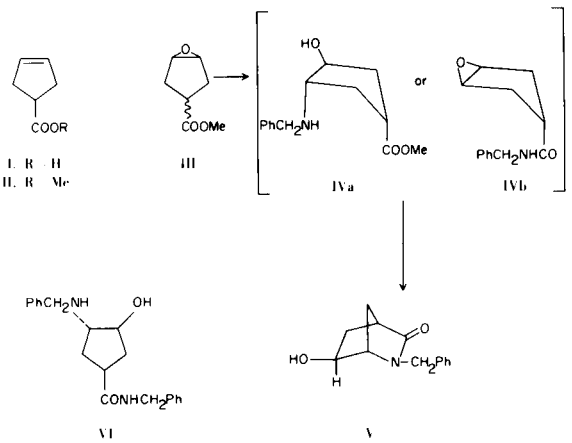
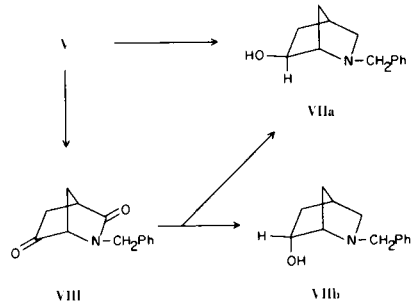
In connection with investigations of the stereochemical requirements of ligands acting at cholinergic receptors (2), we required the title bicyclic compounds as intermediates for the preparation of rigid acetylcholine analogs. We previously have reported (1,3) the synthesis of 5-substituted 2-azabicyclo[2.2.1]heptanes but there are no reports pertaining to the 6-substituted derivatives. We describe herein a synthetic approach to the title compounds starting from 4-carboxycyclopentene (I) (4).

Treatment of I with diazomethane afforded methyl ester II which was oxidized with *m*-chloroperbenzoic acid to a 4:1 mixture of diastereomeric epoxides, as determined by nmr and glc analyses. Attempts to separate the diastereomers were unsuccessful, and therefore the mixture was reacted with benzylamine to afford amide VI as the major product along with a low yield of the desired lactam V. Since the product ratio (VI:V = 3.4:1) is close to that of the isomeric ratio for III, the low yield might possibly be due to V originating from the isomer that is present in minor quantity. This would suggest that VI is formed from *cis*-III. On this basis the tentative stereochemical assignment of VI is as shown, assuming epoxide ring opening occurred in the normal way. As only the minor epoxide isomer (*trans*-III) could undergo cyclization to lactam V *via* intermediate IVa or IVb, the resulting OH group in the product should have an *exo* configuration.



LAH reduction of the lactam gave the *exo* amino-alcohol (VIIa). In order to obtain the *endo* isomer (VIIb), lactam V was oxidized with chromic oxide-sulfuric acid to the ketone (VIII) which was reduced with LAH. Tlc (basic alumina) of the oxalate salt of this product revealed that it was a mixture of VIIa and VIIb. It is noteworthy that VIIb had a much larger R_f value (0.8) than VIIa (0.4). This can be attributed to the reduction of polarity of VIIb due to intramolecular hydrogen bonding. Column chromatography separated the pure isomers in a ratio (VIIa:VIIb) of 1:2.



Ir studies further confirmed the stereochemistries of VIIa and VIIb. A 0.5 *M* solution (carbon tetrachloride) of VIIa revealed a weak absorption at 3625 cm^{-1} (free OH) and a broad absorption at 3375 cm^{-1} (bonded OH). Dilution to 0.005 *M* brought about a large increase in intensity of the absorption at 3625 cm^{-1} with a concomitant decrease in intensity and a shift of the bonded OH peak to 3200 cm^{-1}. At 0.5 *M*, VIIb possessed only one absorption (3375 cm^{-1}) in the hydroxyl region. Dilution (0.005 *M*) caused no change either in intensity or frequency of this absorption. These results indicate that VIIb is intramolecularly hydrogen bonded (5) and hence must possess the *endo* configuration at C-6. Compound VIIa exhibits no intramolecular hydrogen bonding because the *exo* orientation of the OH group renders internal hydrogen bonding impossible.

It is of interest that the stereoselectivity in the LAH reduction of VIII is considerably lower than that observed for the corresponding norbornanone (6,7). This may be

a consequence of less steric hindrance to *endo* attack of the hydride species due to the absence of *endo* protons at the 2- and 3-position.

EXPERIMENTAL

All melting points are uncorrected. A Perkin-Elmer Model 237B spectrophotometer was employed for the infrared spectra. The routine nmr spectra were obtained using a Varian A 60D spectrometer with tetramethylsilane as internal reference standard in deuteriochloroform solutions. Gas chromatographic analyses were obtained using a Perkin-Elmer Model 900 or a Varian Aerograph Model 700 gas chromatograph. The columns used were a six-foot OV-17/s (3%), a six-foot OV-210 (3%), and a 20-foot SE-30 (30%).

4-Carbomethoxycyclopentene (II).

4-Carboxycyclopentene (4) (20.00 g., 0.18 mole) in ether was cooled and treated with an excess of ethereal diazomethane. After heating on a steam bath to remove excess diazomethane, the ether was removed. Distillation afforded methyl ester II (18.00 g., 78%), b.p. 75-78° (37 mm Hg); ir (liquid film) 1740 cm^{-1} (ester C=O); nmr (neat) δ 5.62 (s, 2), 3.62 (s, 3), 2.98 (m, 1), 2.55 (m, 4). Preparative gc (SE 30, 150°) afforded an analytical sample.

Anal. Calcd. for $C_7H_{10}O_2$: C, 66.64; H, 7.99. Found: C, 66.51; H, 8.20.

exo-N-Benzyl-6-hydroxy-3-oxo-2-azabicyclo[2.2.1]heptane (V).

Methyl ester II (12.62 g., 0.1 mole) was added to a cold solution of 85% *m*-chloroperoxybenzoic acid (22.31 g., 0.11 mole) in chloroform (250 ml.) and the mixture was stirred in an ice bath for 1 hour and then at room temperature for 2 hours. The reaction mixture was filtered, extracted with 10% sodium bisulfite and then extracted with *N* sodium hydroxide. The chloroform solution was separated, dried (magnesium sulfate), and the solvent was removed to afford epoxide III (11.18 g., 79% crude yield); the ir spectrum lacked olefinic absorption; nmr (deuteriochloroform) δ 3.65 (s, 3), 3.49, 3.44 (two s, 2, 4:1 ratio) 1.6-2.8 (m, 5).

Crude III (5.00 g., 0.035 mole) and benzylamine (3.75 g., 0.035 mole) were dissolved in ethanol (20 ml.) and the mixture was allowed to reflux for 13 hours. The ethanol was removed and the residue was heated at 150-153° for 2 hours and then at 190° for 1 hour. The reaction mixture was cooled, ethanol (20 ml.) and 2 *N* sodium hydroxide (21 ml.) were added and the mixture was refluxed for 1 hour. The ethanol was removed and the aqueous mixture was filtered to afford compound VI (2.57 g.) which was recrystallized from ethyl acetate; m.p. 178-178.5°; ir (potassium bromide) 3400 (broad) 3300, 3225, 1640 (amide C=O), 1545 cm^{-1}.

Anal. Calcd. for $C_{20}H_{24}N_2O_2$: C, 74.04; H, 7.46; N, 8.64. Found: C, 74.15; H, 7.58; N, 8.65.

The above filtrate was extracted with methylene chloride and the extract washed with 10% hydrochloric acid, separated, and dried (magnesium sulfate). Removal of the methylene chloride afforded an oil (1.34 g.) which was chromatographed (silica gel, chloroform-ethyl acetate) and recrystallized (ethyl acetate) to give pure V (0.49 g., 6.7% yield), m.p. 105-107°; ir (potassium bromide) 3260 (bonded OH), 1675 (lactam C=O), 1455, 1425, 1365, 1235, 1140, 1085, 975 cm^{-1}; nmr (deuteriochloroform) δ 7.26 (m, 5, phenyl), 4.58 and 3.96 (d, 15 Hz, 1H each, benzyl CH_2), 3.96 (d of d, J = 2.8 and 7 Hz, HC-O), 3.50 (s, 1, OH), 3.48 (m, 1, bridgehead), 2.67 (s, 1, bridgehead), 1.3-2.2 (m, 2, *exo-endo* CH_2), 1.85 (m, 2, bridge).

Anal. Calcd. for $C_{13}H_{15}NO_2$: C, 71.86; H, 6.96; N, 6.45. Found: C, 72.04; H, 6.99; N, 6.41.

exo-N-Benzyl-6-hydroxy-2-azabicyclo[2.2.1]heptane (VIIa).

Lithium aluminum hydride (0.095 g., 0.0025 mole) was added to a solution of V (0.250 g., 0.0012 mole) in dry, freshly distilled THF (20 ml.). This was refluxed for 8 hours and treated with 1 ml. of water, 1.5 ml. of 10% of sodium hydroxide, and finally with 2.1 ml. of water. The mixture was filtered, saturated with sodium chloride, and extracted with chloroform. The chloroform solution was extracted with 1% hydrochloric acid. The chloroform phase was separated, the aqueous solution was made alkaline with 10% sodium hydroxide and extracted with chloroform. After drying (sodium sulfate), removal of chloroform afforded VIIa (0.161 g.) as an oil; nmr (deuteriochloroform) δ 7.30 (s, 5), 4.03 (m, 1), 3.80-3.40 (m, 3), 2.92 (m, 2), 2.35 (m, 2), 2.22-1.03 (m, 4). Gas chromatography (OV-210, 150°) indicated a single isomer. The oxalate salt was prepared and twice recrystallized (methanol-ethyl acetate), m.p. 134-137°.

Anal. Calcd. for $C_{15}H_{19}NO_5$: C, 61.42; H, 6.53; N, 4.78. Found: C, 61.26; H, 6.57; N, 4.62.

endo-N-Benzyl-6-hydroxy-2-azabicyclo[2.2.1]heptane (VIIb).

Lactam V (0.218 g., 0.001 mole) and 0.4 ml. of Jones' reagent (8) in 10 ml. of acetone were maintained at room temperature for 1 hour after which time gc (OV-210, 200°) revealed the absence of V and the presence of a new compound (VIII). The reaction mixture was diluted with water and thoroughly extracted with chloroform. The chloroform solution was washed with water, dried (sodium sulfate) and solvent was removed to afford 0.231 g. of an oil (VIII) which was reduced with LAH (0.163 g., 0.004 mole) as described earlier. This afforded 0.144 g. of an oil which was converted to the oxalate salt (0.173 g.), m.p. 96-127°. Thin-layer chromatography (basic alumina, chloroform) of this oxalate salt revealed that it was a mixture of VIIa (R_f = 0.4) and VIIb (R_f = 0.8). Column chromatography (basic alumina, chloroform) of the mixture of oxalate salts afforded 0.054 g. of VIIb, 0.008 g. of a mixture of VIIa and VIIb, and 0.024 g. of VIIa as the free amines which are oils. The nmr spectrum (deuteriochloroform) of VIIb exhibited: δ 7.32 (s, 5), 4.27 (s, 1), 3.98 (m, 1), 3.95-3.47 (m, 2), 3.15 (m, 1), 2.78 (m, 1), 2.38 (m, 2), 2.12-0.77 (m, 5).

Anal. Calcd. for $C_{15}H_{19}NO_5$ (VIIb oxalate): C, 61.42; H, 6.53; N, 4.78. Found: C, 61.27; H, 6.24; N, 4.50.

Hydrogen Bonding Studies of VIIa and VIIb.

Solutions of VIIa and VIIb (0.5 *M*) in spectral grade carbon tetrachloride were placed in 0.1 mm cells and the ir spectra were recorded between 4000 and 3000 cm^{-1}; both solutions were diluted (0.005 *M*), placed in 1.0 cm cells and the ir spectra were again recorded.

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