Oxazolidine Formation in the Attempted Eschweiler-Clarke Reductive Methylation of *cis*-3-Aminobicyclo[2.2.2]octan-2-ol

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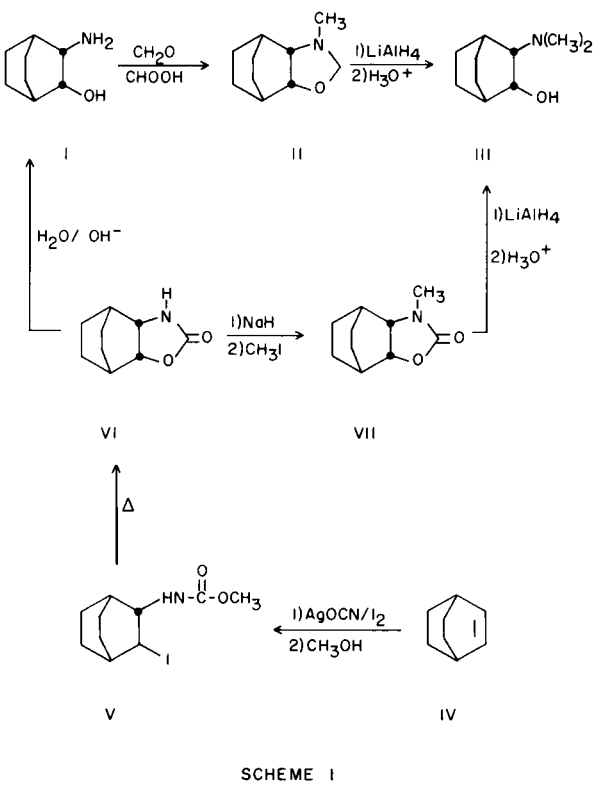
Evidence is presented confirming the formation of *N*-methyl-*cis*-bicyclo[2.2.2]octyl[2,3-*d*]-oxazolidine as the product of Eschweiler-Clarke reductive alkylation of *cis*-3-amino-bicyclo-[2.2.2]octan-2-ol.

In a study of certain bicyclic β-amino-alcohols, attempts were made to prepare *cis*-3-dimethylamino-bicyclo[2.2.2]octan-2-ol (III) from the corresponding primary amino-alcohol (I) by Eschweiler-Clarke modification of the Leuckart reaction (1). Only *N*-methyl-*cis*-bicyclo[2.2.2]octyl[2,3-*d*]oxazolidine (II) was isolated. Chemical and spectral evidence is presented to confirm the structure of II.



SCHEME I

The desired primary amino-alcohol (I) (2) was prepared from bicyclo[2.2.2]oct-2-ene (IV) by addition of iodo-isocyanate, Scheme I. The intermediate iodoisocyanate was not isolated but subjected to methanolysis to afford *trans*-3-iodo-2-carbomethoxyaminobicyclo[2.2.2]octane (V) in excellent yield. Pyrolysis (190°) afforded *cis*-bicyclo[2.2.2]octyl[2,3-*d*]oxazolidin-2-one (VI), although in poor yield. Considerable polymerization occurred during this reaction. Alkaline hydrolysis of the carbamate afforded I, which was subjected to Eschweiler-Clarke reductive alklation conditions.

The product of the Eschweiler-Clarke reaction, although acid soluble, showed no OH or NH stretching bands in the infra-red near 3.0 μ. Oxazolidine bands were noted in the 8.7-9.5 μ region (3). Three bands, 8.76, 9.21, 9.32 μ, characteristic of the oxazolidine ring were observed. The nmr spectrum showed, in addition to an *N*-methyl singlet at 2.27 δ, two AB doublets at 3.76 and 4.67 δ, J = 2.5 cps, characteristic of the C-2 protons of certain oxazolidines (4,5). This characteristic nmr pattern remained in the spectrum of the hydrochloride of II in deuterium oxide indicating considerable stability of this system to aqueous acid.

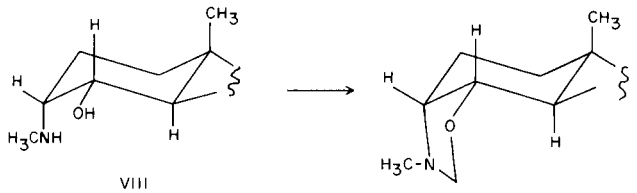
To confirm its structure, II was treated with lithium aluminum hydride which afforded III. To preclude possible skeletal rearrangements of the bicyclo[2.2.2]-octane system under the acidic conditions of the reductive alkylation, III was also prepared by an unambiguous route.

Compound VI was converted to its *N*-methyl derivative utilizing sodium hydride in DMF followed by treatment with methyl iodide. Lithium aluminum hydride reduction of *N*-methyl-*cis*-bicyclo[2.2.2]octyl[2,3-*d*]oxazolidin-2-one (VII) afforded III, which was identical in all respects with the tertiary amino-alcohol prepared from oxazolidine II.

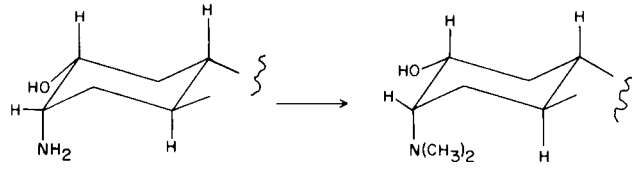
These results may be explained using a combination of steric and structural arguments. The amino and hydroxyl moieties in I, and in other intermediates to II, are located in such proximity that formation of the oxazolidine is sterically favorable, and the geometry of the bicyclic system may preclude further reduction.

Similar, although somewhat inconsistent, results, have been observed in steroidal systems. In a 3α-methylamino-4α-hydroxy-5α-pregnane derivative (VIII) the oxazolidine is the product of the attempted Eschweiler-Clarke reduction (4). In a geometrically similar system, 3a-amino-2e-*trans*-decalol (IX) reductive alkylation led to the desired tertiary amino-alcohol (6). Similar results are reported in the 3e-amino-2e-*trans*-decalol system.

Further experiments to investigate the geometric requirements of oxazolidine formation in similar systems are underway.



VIII



IX

EXPERIMENTAL

Melting points were obtained on a calibrated Thomas-Hoover Unimelt and are corrected. Infrared data were recorded on a Beckman IR5A spectrophotometer. Nmr spectra were determined with a Varian A-60 spectrometer using tetramethylsilane or 3-(trimethylsilyl)-1-propanesulfonic acid sodium salt as internal standard. Microanalyses were conducted by Drs. G. Weiler and F. B. Strauss, Oxford, England.

trans-3-Iodo-2-carbomethoxyaminobicyclo[2.2.2]octane (V).

To a cold (−15°) solution of 10.0 g. (0.093 mole) of bicyclo[2.2.2]oct-2-ene (IV) in 500 ml. of anhydrous ether was added 25.6 g. (0.17 mole) of freshly prepared silver cyanate and 23.8 g. (0.093 mole) of iodine. The stirred mixture was allowed to warm to room temperature over a period of six hours. The inorganic salts (silver iodide and excess silver cyanate) were removed by filtration and 200 ml. of anhydrous methanol added to the filtrate. The resulting solution was refluxed overnight and the organic solvents removed utilizing a rotary evaporator. The residual oil was dissolved in ether, washed with 5% aqueous sodium bisulfite, with water, dried (magnesium sulfate) and evaporated, affording a yellow oil which was chromatographed over 150 g. of silicic acid (Mallinckrodt) using chloroform as eluent. In the first 1500 ml. eluted, 24.6 g. (89%) of the slightly oily iodocarbamate was obtained suitable for pyrolysis. A sample was crystallized for analysis from hexane-ether, m.p. 97.5-98.5°; infrared (potassium bromide), 3.00, 3.40, 3.48, 5.89, 6.45, 6.89, 7.48, 7.78, 8.00, 8.35, 9.35, 9.42, 9.60, 9.75, 10.70, 11.48, 11.97, 12.81, 13.94 μ; nmr (deuteriochloroform), δ 5.58 (H-N, broad unresolved multiplet), 4.08 (H-2 and H-3, unsymmetrical multiplets, 3.65 (H_3CO-, singlet), 1.50-2.1 (methylene-methine envelope, ten protons).

Anal. Calcd. for $C_{10}H_{16}INO_2$: C, 38.85; H, 5.22; N, 4.53. Found: C, 39.02; H, 5.09; N, 4.53.

cis-Bicyclo[2.2.2]octyl[2,3-*d*]oxazolidin-2-one (VI).

trans-3-Iodo-2-carbomethoxyaminobicyclo[2.2.2]octane (V) (24.6 g., 0.083 mole) was heated at 190-200° for one hour while passing a stream of dry nitrogen over the reaction mixture. The methyl iodide was trapped by passing all gases evolved through a cold solution of pyridine in benzene. The black reaction residue was dissolved in the minimum amount of chloroform and placed on a column prepared from 200 g. silicic acid (Mallinckrodt) packed with 25:75 chloroform-hexane. Elution was accomplished with 2000 ml. of 25:75 chloroform-hexane, 2000 ml. of 50:50 chloroform-hexane, 2000 ml. of 75:25 chloroform-hexane and finally with chloroform. The oxazolidinone was in the final 300-ml. portion of 50:50 chloroform-hexane in all fractions of 75:25 chloroform-hexane. No additional material was obtained in 100% chloroform, yielding 5.5 g. (40%) of slightly tan-colored crystals. An analytical sample was crystallized from ether-hexane, m.p. 125-126°; infrared (potassium bromide), 3.08, 3.49, 5.78, 6.80, 6.90(w), 7.20, 7.43, 8.05, 9.05, 9.53, 9.78, 10.42, 13.09 μ; nmr (deuteriochloroform), 6.62 (H-N, broad unresolved multiplet), 4.60 (H-C-O, doublet of doublets, J_{23} = 9.7 cps, J_{21} = 3.2 cps), 3.78 (H-C-NH, broadened doublet, J_{32} = 9.7 cps), 1.4-2.1 (methylene-methine envelope, ten protons).

Anal. Calcd. for $C_9H_{13}NO_2$: C, 64.65; H, 7.83; N, 8.39. Found: C, 64.79; H, 7.91; N, 8.58.

N-Methyl-*cis*-bicyclo[2.2.2]octyl[2,3-*d*]oxazolidine (II).

To a solution of 450 mg. (3.2 mmoles) of *cis*-3-aminobicyclo-[2.2.2]octan-2-ol (I) in 5 ml. of formic acid was added 5 ml. of 37% formalin and the mixture heated on a steam bath overnight. The reaction mixture was poured into 20% aqueous sodium hydroxide, extracted twice with ethyl acetate; the organic layer was washed with water, saturated brine, and dried (magnesium sulfate) and the solvent removed utilizing a rotary evaporator affording 354 mg. (70%) of II, as a yellow oil, infrared (neat): 3.40, 3.48, 3.51, 3.59 (w), 6.90, 8.10, 8.51, 8.76, 9.21, 9.32, 9.63, 10.06, 10.16 μ, nmr (deuteriochloroform), δ 3.76 and 4.67 (2′-methylene protons, doublets, J = −2.5 cps), 3.97 (5′-proton, doublet of doublets, J = 9 cps, J = 3 cps), 2.27 (H_3C-N, singlet), 1.4-2.1 (methylene-methine envelope, including 4′-proton, eleven protons).

Hydrochloride, m.p. 240-241° dec. (methanol-ethyl acetate).

Anal. Calcd. for $C_{10}H_{18}ClNO$: C, 58.96; H, 8.91; N, 6.88; Cl, 17.41. Found: C, 58.78; H, 8.91; N, 6.85; Cl, 17.41.

Picrate, m.p. 219° dec. (methanol).

Anal. Calcd. for $C_{16}H_{20}N_4O_8$: C, 48.48; H, 5.09; N, 14.14. Found: C, 48.33; H, 4.97; N, 13.95.

N-Methyl-*cis*-bicyclo[2.2.2]octyl[2,3-*d*]oxazolidine-2-one (VII).

All equipment was dried at 120° overnight. To a slurry of 480

mg. (10 mmoles) of 50% sodium hydride in mineral oil in 20 ml. of 25:75 dry dimethylformamide-benzene over which a slow stream of dry nitrogen was passed, was added a solution of 1.68 g. (10 mmoles) of *cis*-bicyclo[2.2.2]octyl[2,3-*d*]oxazolidine-2-one (VI) in dimethylformamide. The mixture was heated at 70° for 2.5 hours to form the sodium salt of the carbamate. A solution of 5 ml. of methyl iodide in 20 ml. of dimethylformamide was added over twenty minutes and the mixture allowed to stir at room temperature for two hours. Sufficient ethanol was added to destroy any hydride remaining and the mixture partitioned between benzene and water. The benzene layer was washed with two additional portions of water, with saturated brine, dried (magnesium sulfate) and removed on a rotary evaporator affording a mixture of mineral oil and product. In order to remove the mineral oil, the crude product was dissolved in 20 ml. of 25:75 chloroform-hexane, adsorbed to a column of 60 g. of silicic acid packed with hexane. Elution with 600 ml. of hexane removed the mineral oil followed by 1200 ml. of chloroform to remove the product. The combined chloroform fractions were evaporated affording 1.60 g. (88%) of slightly yellow crystals, m.p. 85-87°. An analytical sample was prepared by crystallization from hexane-acetone, m.p. 87.5-89°; infrared (potassium bromide), 3.40, 3.47, 5.76, 6.72, 6.95, 7.12, 7.28, 7.46, 7.50, 7.70, 7.79, 7.92, 8.70, 8.80, 8.98, 9.19, 9.5, 9.7, 11.35, 13.07, 13.48 μ; nmr (deuteriochloroform) δ 4.65 (H-C-O-, doublet of doublets, J_{23} = 9.5 cps, J_{21} = 3.5 cps), 3.75 (H-C-N-, doublet of doublets, J_{32} = 9.5 cps, J_{34} = 3.0 cps), 2.88 (H_3C-N-, singlet), 1.4-2.1 (methylene-methine envelope, ten protons).

Anal. Calcd. for $C_{10}H_{15}NO_2$: C, 66.27; H, 8.34; N, 7.73. Found: C, 66.55; H, 8.33; N, 7.88.

cis-3-Dimethylaminobicyclo[2.2.2]octan-2-ol (III).

A. Lithium Aluminum Hydride Reduction of II.

All equipment was dried at 120° overnight. A stream of nitrogen was passed over a suspension of 1.0 g. (26 mmoles) of lithium aluminum hydride in 150 ml. of anhydrous ether. One gram (6.0 mmoles) of crude II in 30 ml. of ether was added dropwise over a period of ten minutes and the resulting slurry refluxed overnight. Excess hydride was destroyed by the addition of small amounts of ethyl acetate. Water, 10 ml., was added and the white precipitate removed by suction filtration using a Celite pad. The ether was evaporated affording 820 mg. (81%) of a colorless oil, *cis*-3-dimethylaminobicyclo[2.2.2]octan-2-ol (III); infrared (neat), 3.0, 3.40, 3.48, 3.58, 6.9, 7.41, 8.0, 8.70, 9.25, 9.60, 9.69, 9.87, 10.64, 11.26 μ.

Hydrochloride, m.p. 239-240° dec. (ethyl acetate-methanol).

Anal. Calcd. for $C_{10}H_{20}ClNO$: C, 58.38; H, 9.80; N, 6.81; Cl, 17.23. Found: C, 58.00; H, 9.66; N, 6.63; Cl, 17.38.

B. Lithium Aluminum Hydride Reduction of VII.

An ether solution of oxazolidinone VII, 2.0 g. (5.53 mmoles), was added dropwise to an ether suspension of 2.0 g. (53 mmoles) of powdered lithium aluminum hydride in 300 ml. of anhydrous ether. After refluxing overnight the mixture was treated as described for reduction of the oxazolidine. Evaporation of the ether afforded 720 mg. (77%) of a colorless oil, III. Comparison of the infrared and nmr spectra of the products of these two reactions, and the melting points and mixed melting points of their hydrochlorides, showed them to be identical.

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