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ON THE STEREOCHEMISTRY OF PIPERIDINE QUATERNIZATIONS[1]

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Seemingly contradictory conclusions were reached recently by two groups who studied the stereochemistry of quaternizations of 4-substituted piperidines. For example, House, Tefertiller, and Pitt[2] reported that quaternization of 4-_t_-butyl-1-ethylpiperidine with methyl tosylate in acetonitrile gave a 4:1 ratio of diastereomeric products, and they concluded that the major product was formed from the more stable equatorial-1-ethyl conformer. On the other hand, Imbach, Katritzky, and Kolinski[3] reported that quaternization of 4-phenyl-1-ethylpiperidine with methyl iodide gave a 12.5:1 product ratio, and they concluded that the major product was formed from the less stable axial-1-ethyl conformer. Similar stereoselectivity has been observed for quaternization reactions in methanol of 1,2,3-trialkylaziridines with deuteriomethyl benzenesulfonate and deuteriomethyl iodide;[4,5] it seemed most unlikely to us that change of leaving group from tosylate to iodide would affect markedly the stereochemistry of piperidine quaternizations. It also seemed unlikely to us that an aryl or alkyl substituent in the 4-position could be capable of exerting a field effect that would drastically affect the stereochemistry of piperidine quaternizations. Therefore, we decided to relate the stereochemistry of the quaternization reactions of 4-cyclohexyl- and 4-phenyl-1-ethylpiperidine with methyl benzenesulfonate and methyl iodide

in acetonitrile. We report here results that show conclusively that these quaternizations are stereoselective in the same manner. Additional results are reported that give support to the belief that the major products are formed from the equatorial-1-ethyl conformers.

4-Phenyl-1-ethylpiperidine, b.p. 120-122°/6.5 mm., n_D^{21} 1.5247, lit.[6] b.p. 137°/11 mm., as a 0.5 M solution in 20 ml. of dry acetonitrile, was treated with a 10% excess of methyl iodide. After 60 hr. at 30°, the solvent was removed at reduced pressure from a 1-ml. aliquot, and the residue was taken up in deuteriochloroform. Present in the 60-Mc. NMR spectrum * were singlets at τ 6.62 and 6.70 ppm, the latter being the more intense, which are assigned to the N-methyl hydrogens of the two diastereomers. The intensity ratio of these bands, which is taken as equal to the product ratio, was 2.51:1.[7] Note that Imbach, Katritzky, and Kolinski reported that this reaction gave a product ratio of 12.5:1.[5] These workers examined the 40-Mc. spectrum of the product in deuterium oxide; at 60 Mc., in deuterium oxide, there is no discernible chemical shift between the N-methyl resonances.[8]

The solvent was removed from 15 ml. of the reaction mixture. The residue was taken up in 80 ml. of ethanol and shaken in the presence of 0.70 g. of Adams' catalyst under 4.3-4.6 atm. of hydrogen for 12 hr. Present in the NMR spectrum of the deuteriochloroform solution of the resulting 4-cyclohexylpiperidinium iodides were singlets at τ 6.62 and 6.78 ppm, the latter being the more intense, with an intensity ratio of 2.43:1.[7]

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* All NMR spectra were determined with a Varian Associates A-60A system.

4-Cyclohexyl-1-ethylpiperidine, b.p. 124-126°/7 mm., n_D^{21} 1.4820, was prepared in 93% yield by hydrogenation (4.3-4.7 atm.) of 10.0 g. of 4-phenyl-1-ethylpiperidine, as the hydrochloride in 130 ml. of ethanol, over 0.70 g. of Adams' catalyst. (Anal. Calcd. for $C_{13}H_{25}N$: C, 79.93; H, 12.90; N, 7.17. Found: C, 79.70; H, 12.66; N, 7.22.) Quaternization of 4-cyclohexyl-1-ethylpiperidine, as a 0.2 $\underline{\underline{M}}$ solution in dry acetonitrile, with methyl iodide at 30° gave a 3.44:1[7] mixture of the corresponding piperidinium iodides. As the major product was the same as that obtained by reduction of the 4-phenyl-1-ethylpiperidine methiodides, the quaternizations of 4-cyclohexyl- and 4-phenyl-1-ethylpiperidine with methyl iodide in acetonitrile must be stereoselective in the same manner.

Quaternizations of 4-cyclohexyl- and 4-phenyl-1-ethylpiperidine with methyl benzenesulfonate in acetonitrile at 30° gave product ratios of 4.26:1 and 3.73:1, respectively.[7,9] That the principal piperidinium salts formed by reactions with methyl benzenesulfonate had the same stereochemistry as those formed by reactions with methyl iodide was concluded from examination of NMR spectra of mixtures of the benzenesulfonates and corresponding iodides. Thus, the quaternizations with methyl benzenesulfonate and methyl iodide are stereoselective in the same manner.

The rate constant at 30° for the reaction in dry acetonitrile of methyl benzenesulfonate and 4-cyclohexyl-1-ethylpiperidine (6.94×10^{-3} $\underline{\underline{M}}^{-1}\text{sec.}^{-1}$) is nearly twice that for 4-phenyl-1-ethylpiperidine (3.58×10^{-3} $\underline{\underline{M}}^{-1}\text{sec.}^{-1}$). It can be expected that the faster reaction would favor quaternization by the more stable conformer (cf. ref. 2 and 5). Further, when the solvent is changed from acetonitrile to benzene, thereby decreasing the rate of reaction, quaternizations of 4-cyclohexyl- and 4-phenyl-1-ethylpiperidine with methyl benzenesulfonate give smaller product

ratios [3.65:1 and 3.43:1, respectively[7]]; for both reactions, the major product is the same as that in acetonitrile.[10] When the rate of quaternization of a 1,2,3-trialkylaziridine with an alkyl benzenesulfonate is slowed by changing the solvent from methanol to benzene, a greater percentage of the product is formed from the less stable amine conformer.[5] We therefore conclude that the major products from these quaternizations of the 1-ethylpiperidines are formed from the equatorial-1-ethyl conformers.[11]

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References

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1711 (1965), reported that quaternization of 4-phenyl-1-ethylpiperidine with methyl iodide in acetone gave a product ratio between 5:1 and 20:1; they also determined the NMR spectrum of the diastereomeric products in deuterium oxide at 40-Mc. Very recently, D. R. Brown, B. G. Hutley, J. McKenna, and J. M. McKenna, Chem. Comm., 719 (1966), described the NMR spectrum of the 4-phenyl-1-ethylpiperidine methiodides taken in deuteriochloroform; their data are in good agreement with ours. They also provided data which indicates that the N-dideuteriobenzyl derivatives of 2-methylpiperidine and trans-decahydroquinoline undergo quaternization with benzyl iodide in acetone primarily via the equatorial N-dideuteriobenzyl conformers.

9. The chemical shifts and assignments of the bands used to determine these ratios are given in an accompanying communication [A. T. Bottini and M. K. O'Rell, Tetrahedron Letters, (1966)].

10. Product ratios from reactions of 4-cyclohexyl- and 4-phenyl-1-ethylpiperidine with methyl iodide are also decreased, but to a smaller degree [3.34:1 and 2.34:1, respectively[7]], when the solvent is changed from acetonitrile to benzene.

11. The effect of solvent on the stereochemistry of reactions of 4-t-butyl-1-methylpiperidine with benzyl chloride is even more dramatic. As the solvent is changed from methanol to acetonitrile to benzene, the product ratio changes from 1.35:1 to 0.95:1 to 0.63:1.[9,12] As this reaction occurs most rapidly in methanol and least rapidly in benzene, we conclude that the major product in benzene is formed from the less stable axial-1-methyl conformer.

12. If the 4-t-butyl group has no effect on the resonance frequencies of the exo-α-hydrogens, the time-averaged 1-benzyl and 1-methyl resonance frequencies in the spectrum of 1-benzyl-1-methylpiperidinium chloride in deuteriochloroform allow calculation of values of 2.27±0.10 and 1.9±0.3, respectively, for the conformational equilibrium constant for ax-1-benzyl-eq-1-methylpiperidinium chloride ⇄ eq-1-benzyl-ax-1-methylpiperidinium chloride. This seems to give added support to the stereochemical assignments.