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Studies on the Cholinergic Receptor. 6.[1] Synthesis and Muscarinic Activity of 2-Methyl-4-(2-dimethylaminoethyl)-1,3-dioxolane Methiodide[2]

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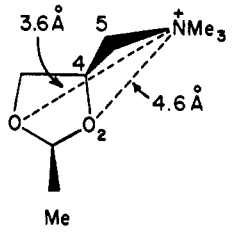
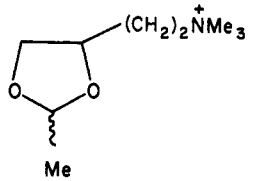
Previous studies[3a-c] utilizing conformationally restricted 1,3-dioxolane analogs of the highly potent muscarinic agent I have suggested that the "active" conformation of I is that in which the N^+Me_3 group is maximally extended from O_1 and O_3. Some further confirmation of this is offered by the finding that II (approximately 80% cis, 20% trans) in which the N^+Me_3 group can sweep an area significantly greater than in I but cannot attain conformation I is very significantly less active than I (ED_{50}, I, 3×10^{-8} *M*; II, 1.9×10^{-5} *M*; *inter alia*, I and II = 1).



I



II

It is of interest that the conformation I deduced by us on the basis of conformationally restricted analogs is in reasonable agreement with that obtained for *cis*-2(*S*)-methyl-4(*R*)-dimethylaminomethyl-1,3-dioxolane methiodide by Pauling and Petcher through X-ray analysis[4] (torsion angle, $O_2C_4C_5N^+$, +94°, $N^+ \rightarrow O_1$, 3.2 Å, $N^+ \rightarrow O_2$ 4.79 Å). However, a number of arguments can be advanced[1,5,6] to suggest quite strongly that there is not a single unique binding conformation for muscarinic agonists: hence, the conformation shown in I may be quite irrelevant to the binding conformations of other agents, particularly if they are structurally unrelated.

(1) Part V of this series: J. F. Moran and D. J. Triggle in "Cholinergic Ligand Interactions," D. J. Triggle, J. F. Moran, and E. A. Barnard, Ed., Academic Press, London and New York 1971.

(2) Supported by grants from National Institutes of Health (NS 09573) and National Aeronautics and Space Administration (NGR-33-015-016).

(3) (a) M. May and D. J. Triggle, *J. Pharm. Sci.*, **57**, 511 (1968); (b) D. R. Garrison, M. May, H. F. Ridley, and D. J. Triggle, *J. Med. Chem.*, **12**, 130 (1969); (c) H. F. Ridley, S. S. Chatterjee, J. F. Moran, and D. J. Triggle, *ibid.*, **12**, 931 (1969).

(4) P. Pauling and T. J. Petcher, *ibid.*, **14**, 3 (1971).

(5) J. F. Moran and D. J. Triggle, in "Fundamental Concepts in Drug-Receptor Interactions," J. F. Danielli, J. F. Moran, and D. J. Triggle, Ed., Academic Press, London and New York, 1970.

(6) D. J. Triggle in "Neurotransmitter-Receptor Interactions," Academic Press, London and New York, 1971, pp 257–276.

Experimental Section

Chemistry.—Melting points were determined on a Thomas-Kofler hot stage and are corrected. Nmr spectra were recorded with a Varian A-60; glpc analyses were carried out with a 10% Carbowax column using an F and M Research Chromatograph (Model 5750). Elemental analyses were by Dr. A. E. Bernhardt and, where indicated only by symbols of the elements, are within ±0.4% of the theoretical values.

2,2-Dimethyl-4-(2-hydroxyethyl)-1,3-dioxolane was prepd in 46% yield from acetone (6.4 g, 0.11 mole), 1,2,4-trihydroxybutane (10.6 g, 0.1 mole), and *p*-TsOH (0.05 g) in refluxing PhH (50 ml) with azeotropic removal of H_2O and had bp 52–55° (0.2 mm); nmr (neat, Me_4Si), 2-CH_3, τ 8.66, 8.74 (singlets, cis and trans, respectively, to the 4 substituent), CH_2CH_2OH, 8.21 (asymmetric quartet), multiplets at 6.36, and 5.91. *Anal.* ($C_7H_{14}O_3$) C, H.

2-Methyl-4-(2-dimethylaminoethyl)-1,3-dioxolane Methiodide (II).—2,2-Dimethyl-4-(2-hydroxyethyl)-1,3-dioxolane (0.1 mole) was converted to the chloro compound by treatment in $CHCl_3$ (50 ml) with an equimolar amt of $SOCl_2$ at 0°. The mixt was stirred at 35° for 120 min, and then refluxed with an equal vol of MeOH for 15 min and stripped *in vacuo*. The residue was taken up in $CHCl_3$, washed (aq K_2CO_3), dried, and stripped to give crude 4-chloro-1,2-dihydroxybutane which was converted to 2-methyl-4-(2-chloroethyl)-1,3-dioxolane by reaction with paraldehyde in refluxing PhH with azeotropic removal of H_2O; this had bp 56° (15 mm); nmr (neat, Me_4Si), 2-CH_3, τ 8.71 (major doublet, cis), 8.75 (minor doublet, trans), 2-H, 5.0 (unsymmetrical quartet). *Anal.* ($C_6H_{11}ClO_2$) C, H, Cl. 2-Methyl-4-(2-chloroethyl)-1,3-dioxolane was treated with Me_2NH in PhH at 100° for 24 hr and subsequently quaternized with MeI in Et_2O to give II (65%) as colorless prisms with mp 148–151°; nmr (CD_3CN, Me_4Si), 2-CH_3, τ, 8.65 (major doublet, cis), 8.70 (minor doublet, trans). 2-H, 5.0 (overlapping quartets), $N^+(CH_3)_3$, 6.80. *Anal.* ($C_9H_{20}INO_2$), C, H, I, N.

Biology.—Muscarinic activities were determined using the rat jejunum as previously described.[3a-c]

Potential Folic Acid Antagonists. 5. Synthesis and Dihydrofolate Reductase Inhibitory Activities of 2-Amino-4,6-substituted-5-arylazopyrimidines

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Our previous studies of the structural requirements of 5-arylazopyrimidines[1] for inhibitory activity toward dihydrofolate reductase have been largely concerned with 2,4,6-triamino-5-arylazopyrimidines. Optimum activity was found with 2,4,6-triamino-5-(2 ethylphenyl)azopyrimidine.[2] We now report the effect of additional substitution in the pyrimidine ring.

The data in Table I show, in accord with much previous work,[3,4] that significant activity is associated with the 2,4-diaminopyrimidine nucleus. However, optimum activity is found with the 2,4-diamino-6-hydroxypyrimidine nucleus (**4** and **5**) an observation contrasting

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