on its back. Trials were terminated arbitrarily 3–4 hr after the loss of righting reflex if the animals continued to sleep.

Reserpine Inhibition.—Three groups of male albino mice (four animals each) were administered **1** (25 mg/kg), **2** (50 mg/kg), and **3** (50 mg/kg) intraperitoneally followed by 2.5 mg/kg sc of reserpine 45 min later. The animals were then checked for ptosis and other behavioral effects 45 min after reserpine. A fourth group received reserpine only (2.5 mg/kg). Similar tests were performed using imipramine (50 mg/kg), amphetamine (10 mg/kg), and α-ethyltryptamine (25 mg/kg) as the control compounds.

Three additional groups of mice (four animals each) were treated with reserpine (2.5 mg/kg sc), followed by the intraperitoneal administration of either **1**, **2**, or **3** (same doses as above) 4 hr later. Albino mice were used on the same test design using imipramine (25 and 50 mg/kg ip), amphetamine (5 and 10 mg/kg ip), and α-ethyltryptamine (25 mg/kg).

Studies on the Cholinergic Receptor. III.[1,2] Parasympatholytic Properties of *cis*- and *trans*-4-Dimethylaminomethyl-2-phenyl-1,3-dioxolane Methiodide

M. MAY, H. F. RIDLEY, AND D. J. TRIGGLE

Department of Biochemical Pharmacology, School of Pharmacy, and the Center for Theoretical Biology, State University of New York at Buffalo, Buffalo, New York 14214

Received September 23, 1968

2-Phenyl-4-dimethylaminomethyl-1,3-dioxolane methiodide (III) is a parasympatholytic agent[3] of undefined geometry.[4] Because the *cis* arrangement of the 2 and 4 substituents is known to be of importance[1,5] in the potent parasympathomimetic agent, 2-methyl-4-dimethylaminomethyl-1,3-dioxolane methiodide (V), it appeared to be of interest to prepare the *cis* and *trans* isomers of III and determine their parasympatholytic properties.

We now report that III, as prepared by the method of Fourneau and Chantaloux,[6] is a 1:1 mixture of the *cis* and *trans* isomers, thus further substantiating our previous observations[1,5] that molecular complex formation appears to be common among quaternary and other derivatives of 1,3-dioxolane. Samples of the *cis* and *trans* isomers of III, each enriched to the extent of about 80%, have been prepared by partial separation of the isomers at the intermediate 2-phenyl-4-chloromethyl-1,3-dioxolane stage. The assignment of structure was by nmr spectroscopy[1,7] and has been discussed in detail in the previous paper of this series. The parasympatholytic properties of IIIa and IIIb were determined using the rat jejunum preparation previously described.[8] IIIa and IIIb were found to be equipotent as antagonists of *cis*-2-methyl-4-dimethylaminomethyl-1,3-dioxolane methiodide (Figure 1).

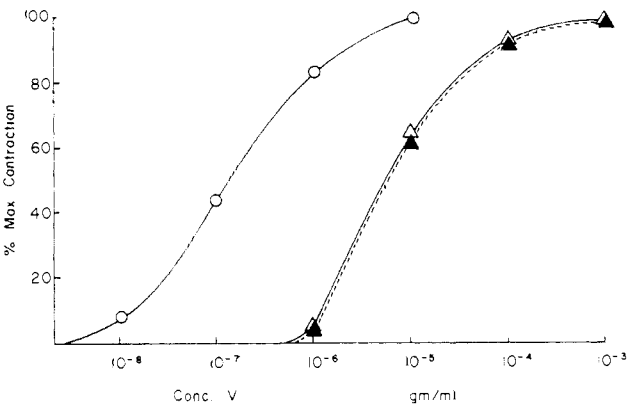
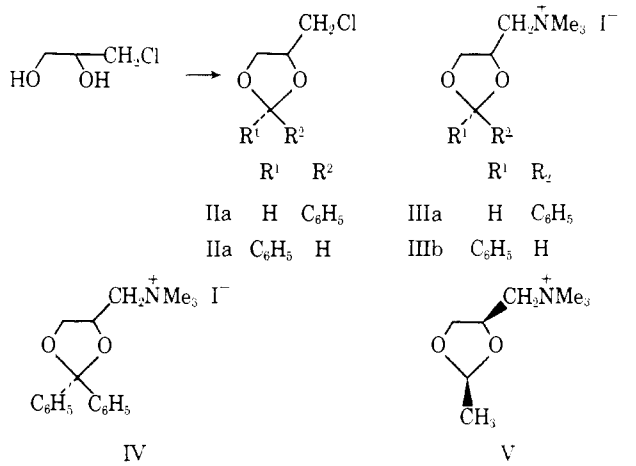


Figure 1.—Dose-response curves for *cis*-2-methyl-4-dimethylaminomethyl-1,3-dioxolane methiodide (V) in the absence (○) and in the presence of IIIa (△) and IIIb (▲), both 5×10^{-4} g/ml.



This lack of stereospecificity is of some interest and suggests that a large nonpolar binding surface exists at the receptor surface capable of binding equally well the phenyl groups of IIIa and IIIb. In accordance with this, introduction of a second phenyl group (IV) produces a marked increase in parasympatholytic activity.[3] However, the relationship between this binding site and that occupied by the methyl group of the agonist compound remains undetermined. Conceivably, the methyl group occupies a unique portion of the large nonpolar area as suggested in the model of the cholinergic receptor advanced by Belleau.[9,10] Alternatively, the two binding sites may be completely distinct as would be the case if the agonist and antagonist molecules bind to different areas of the receptor surface.

Experimental Section

Melting points were determined on a Thomas–Koffler hot stage and are corrected. The nmr spectra, in CD_3CN solution, methiodides, or neat material (TMS), were recorded on a Varian A-60 spectrometer. Glpc analyses, on 10% Carbowax columns, were carried out using an F & M Scientific instrument (Model

(1) Part II: D. R. Garrison, M. May, H. F. Ridley, and D. J. Triggle, *J. Med. Chem.*, **12**, 130 (1969).

(2) This work was supported by grants from the National Institutes of Health (GM 11603) and NASA (NGR-33-015-016).

(3) J. M. van Rossum and E. J. Ariëns, *Arch. Int. Pharmacodyn. Ther.*, **118**, 418 (1959).

(4) D. J. Triggle, "Chemical Aspects of the Autonomic Nervous System," Academic Press, London, 1965, p 112.

(5) D. J. Triggle and B. Belleau, *Can. J. Chem.*, **40**, 1201 (1962).

(6) E. Fourneau and S. Chantaloux, *Bull. Soc. Chim. France*, **12**, 845 (1945).

(7) N. Baggett, K. W. Buck, A. B. Foster, R. Jeffries, B. H. Rees, and J. M. Webber, *J. Chem. Soc.*, 3382 (1965).

(8) M. May and D. J. Triggle, *J. Pharm. Sci.*, **57**, 511 (1968).

(9) B. Belleau, *Advan. Drug Res.*, **2**, 89 (1965).

(10) B. Belleau, *Ann. N. Y. Acad. Sci.*, **144**, 705 (1967).

5750). Analyses were performed by Dr. A. E. Bernhardt, Mülheim, West Germany; where indicated only by symbols of the elements the analytical results obtained for those elements are within ±0.4% of the theoretical values.

Mixtures of *cis*- and *trans*-4-Chloromethyl-2-phenyl-1,3-dioxolane (IIa and IIb).—A 1:1 mixture of these isomers, bp 98–100° (3 mm), was obtained from 1,2-dihydroxy-3-chloropropane and benzaldehyde, according to the method of Fourneau and Chantaloux.[6] Repeated fractional distillation of this mixture through a Teflon spinning-band column (Nester Faust) afforded two enriched fractions (indicated by glpc and nmr) containing 3:1 of IIa and IIb, respectively, bp 96–98° (3 mm), and 2:1 of IIb and IIa, respectively, bp 100–102° (3 mm). Numerous intermediate fractions were also obtained. Glpc (200° isothermal; He 30 ml/min) retention times were 10 and 12 min for IIa and IIb, respectively. Nmr[7] absorption was observed at τ 2.7 (aromatic multiplet), 4.16 [singlet C_2-H (IIb)], 4.36 [singlet, C_2-H (IIa)], 5.7–6.4 (multiplet C_4-H and C_5-H), 6.67 (doublet, CH_2Cl).

Mixtures of *cis*- and *trans*-4-Dimethylaminomethyl-2-phenyl-1,3-dioxolane Methiodide (IIIa and IIIb).—A 1:1 mixture was obtained from a 1:1 mixture of the chloromethyl-1,3-dioxolanes (IIa and IIb), according to the method of Fourneau and Chantaloux,[6] and had mp 152–154° (lit.[6] mp 155°). A 4:1 mixture of IIIa and IIIb, respectively, was obtained by fractional crystallization of the methiodides derived from the fraction of 4-chloromethyl-2-phenyl-1,3-dioxolane enriched in IIa and had mp 162–164° from acetone. *Anal.* ($C_{13}H_{20}INO_2$) C, H, I, N.

A 4:1 mixture of IIIb and IIIa, respectively, was obtained by fractional crystallization of the methiodides derived from the 4-chloromethyl-2-phenyl-1,3-dioxolane enriched in IIb and had mp 168–170° from acetone. *Anal.* ($C_{13}H_{20}INO_2$) C, H, I, N.

Nmr peaks of the above mixtures were at τ 2.52 (aromatic multiplet), 3.91 [singlet, C_2-H (IIIb)], 4.12 [singlet, C_2-H (IIIa)], 5.80–6.56 (multiplet, C_4-H, C_5-H, $-CH_2N$), and 6.66 (singlet, NCH_3).

The Synthesis of O-Methylnordehydrobufotenine, a New Psychoactive Indole[1]

FRED G. H. LEE,

Regis Chemical Company, Chicago, Illinois 60610

JOHN W. DALY,

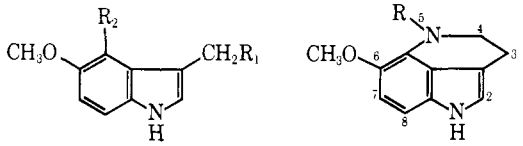
Laboratory of Chemistry, National Institute of Arthritis and Metabolic Diseases, National Institutes of Health, Bethesda, Maryland 20014

AND ALBERT A. MANIAN

Psychopharmacology Research Branch, National Institute of Mental Health, Chevy Chase, Maryland 20203

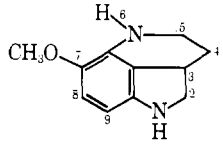
Received July 31, 1968

A variety of indoleethylamines including N,N-dimethyltryptamine,[2] N,N-dimethyl-4-hydroxytryptamine (psilocin),[3] and N,N-dimethyl-6-hydroxytryptamine[4] have been reported to have hallucinogenic activity. Of these psychoactive indoleethylamines, N,N-dimethyl-5-methoxytryptamine exhibits the highest activity in disrupting conditioned responses in rats.[5] Attempts have been made to develop theoretical structure–activity relationships for these and other psychotomimetic compounds.[6,7] Because of the high CNS activity shown by N,N-dimethyl-5-methoxytryptamine, the synthesis of the structurally related tricyclic indole, O-methylnordehydrobufotenine (6-methoxy-5-methyl-1,3,4,5-tetrahydropyrrolo[4,3,2-*d*,*e*]-quinoline, IIc), was undertaken. The synthetic route is parallel to the method for synthesis of 1,3,4,5-tetrahydropyrrolo[4,3,2-*d*,*e*]quinoline[8] and dehydrobufotenine.[9] Recently, an alternate synthesis of the tetrahydropyrroloquinoline ring system has been reported from N-methyl-5-bromotryptamine and an alkyllithium to form 5-methyl-1,3,4,5-tetrahydropyrrolo-[4,3,2-*d*,*e*]quinoline *via* an intramolecular aryne addition reaction.[10] Treatment of 5-methoxygramine with concentrated HNO_3 afforded 5-methoxy-4-nitrogramine (Ia) which was quaternized with Me_2SO_4 and then converted to 5-methoxy-4-nitroindolyl-3-acetonitrile (Ib) with NaCN. Catalytic hydrogenation of Ib with Pd–C in EtOAc at approximately 65° yielded 5-methoxy-4-aminoindolyl-3-acetonitrile (Ic) instead of the expected product, 6-methoxy-1,3,4,5-tetrahydropyrrolo[4,3,2-*d*,*e*]quinoline (IIa). In ethanol the same hydrogenation of Ib yielded two products: the desired 6-methoxy-1,3,4,5-tetrahydropyrrolo[4,3,2-*d*,*e*]-quinoline (IIa) and 7-methoxy-1,2,3,4,5,6-hexahydropyrrolo[4,3,2-*d*,*e*]quinoline (III). Reaction of IIa with formic–acetic anhydride formed the N-formyl derivative (IIb). Reduction with diborane resulted in the formation of O-methylnordehydrobufotenine (IIc).



Ia, $R_1 = N(CH_3)_2$; $R_2 = NO_2$
b, $R_1 = CN$; $R_2 = NO_2$
c, $R_1 = CN$; $R_2 = NO_2$

IIa, R = H
b, R = CHO
c, R = CH_3



III

Pharmacology.—Pharmacologic activity was determined in squirrel monkeys trained in the Wisconsin General Test Apparatus by Dr. E. T. Uyeno and his associates in the Biobehavioral Science Laboratory of Stanford Research Institute using published techniques.[11] The median effective dose (ED_{50}) of IIc that disrupted the ability to discriminate between

(1) This investigation was supported by the Psychopharmacology Research Branch, National Institute of Mental Health, Contract SA-43-ph-3021.

(2) S. Szara in "Psychotropic Drugs," S. Garattini and V. Ghetti, Ed., Elsevier Publishing Co., Amsterdam, 1957, pp 460–467.

(3) A. Hofmann, A. Frey, H. Ott, T. Petrizilka, and F. Troxler, *Experientia*, **14**, 397 (1958).

(4) S. Szara and E. Hearst, *Ann. N. Y. Acad. Sci.*, **96**, 134 (1962).

(5) P. K. Gessner, D. D. Godse, A. H. Krull, and J. M. McMullan, *Life Sci.*, **7**, 267 (1968).

(6) S. H. Snyder and C. R. Merril, *Proc. Natl. Acad. Sci. U. S.*, **54**, 258 (1965).

(7) S. H. Snyder and E. Richelson, *ibid.*, in press.

(8) J. B. Hester, Jr., *J. Org. Chem.*, **29**, 1158 (1964).

(9) W. F. Gannon, J. D. Benigni, J. Suzuki, and J. W. Daly, *Tetrahedron Letters*, 1531 (1967).

(10) M. Julia, Y. Huang, and J. Igolen, *Compt. Rend.*, **265**, 110 (1967).

(11) E. T. Uyeno, L. S. Otis, and C. Mitoma, *Comm. Beh. Biol.*, A 1, 83 (1968).