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]

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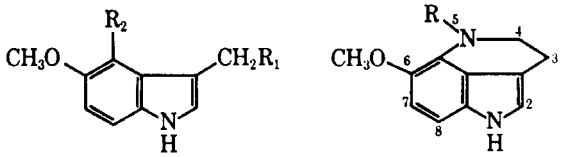
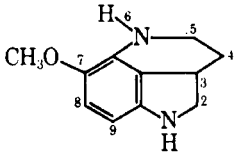
A variety of indoleethylamines including N,N-dimethyltryptamine,[2] N,N-dimethyl-4-hydroxytryptamine (psilocin),[3] and N,N-dimethyl-6-hydroxytryptamine[4] have been reported to have hallucinogenic activity. Of these psychoactive indoleethylamines, N,N-dimethyl-5-methoxytryptamine exhibits the highest 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.

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disks of different sizes was 33.8 μmoles/kg.[12] In this test, the O-methylnordehydrobufotenine (IIc) is approximately twice as active as mescaline (ED_{50} = 71.0 μmoles/kg),[11] but is much less active than its open-chain analog, N,N-dimethyl-5-methoxytryptamine, which from published data[5,8] can be estimated to be much more than 30 times as active a hallucinogen as mescaline. When injected subcutaneously into NIH general purpose white mice, IIc at 20 mg/kg causes only slight overt changes (reduction in spontaneous activity) while N,N-dimethyl-5-methoxytryptamine at 10 mg/kg causes profound effects. At this dosage the mice lose the ability to move normally and engage in locomotor activity with legs extended laterally.

Experimental Section[13]

5-Methoxy-4-nitrogramine (Ia).—A stirred mixture of 35 g (0.1713 mole) of 5-methoxygramine and 100 ml of AcOH was cooled to 10° and treated dropwise with a solution of 30 ml of concentrated HNO_3 (*d* 1.42) and 50 ml of AcOH over 30 min. The mixture was allowed to warm to room temperature, stirred overnight, and then diluted with 1 l. of ice–water. The resulting precipitate was filtered off, washed (H_2O), and dried. Recrystallization of the crude Ia from MeOH yielded 4.5 g (54%) of yellow-brown needles, mp 158–195.5°. The nmr spectrum was consistent with the structure. *Anal.* ($C_{12}H_{15}N_3O_3$) C, H, N.

5-Methoxy-4-nitroindolyl-3-acetonitrile (Ib).—A solution of 4.0 g (0.016 mole) of Ia and 0.5 ml of AcOH in 100 ml of dry THF was added dropwise to an ice-cold, stirred solution of 13 ml of Me_2SO_4 and 0.5 ml of AcOH in 50 ml of dry THF during 30 min. The resulting mixture was allowed to warm slowly to room temperature and to stand for 15 hr. The product was collected by filtration, washed (dry Et_2O), and then dried *in vacuo* over $CaCl_2$ to yield 4.5 g of methosulfate, mp 120–168°.

A mixture of 4.5 g of crude methosulfate, 120 ml of a NaOAc–HOAc buffer (3.0 g of AcOH and 4.1 g of NaOAc in 500 ml of H_2O), a few milliliters of Et_2O, and 4.0 g of NaCN was stirred at room temperature for 20 hr. The mixture was extracted (CH_2Cl_2), and the extract was washed (H_2O, dilute AcOH, saturated NaCl) and then dried (Na_2SO_4). After removal of the solvent, the crude product was recrystallized (MeOH) to yield 2.5 g (68%, based on Ib) of nitrile, mp 198.5–199.5°. *Anal.* ($C_{11}H_9N_3O_3$) C, H, N.

5-Methoxy-1,3,4,5-tetrahydropyrrolo[4,3,2-*d*,*e*]quinoline (IIa). Reductive Cyclization of 5-Methoxy-4-nitroindolyl-3-acetonitrile. (A) A mixture of 2 g (0.0086 mole) of Ib, 1 g of 10% Pd–C, and 250 ml of EtOAc was shaken with H_2 at 3.87 kg/cm² for 6 hr at 65° and for 15 hr at room temperature, and then filtered through Celite. After removal of the solvent, the crude product was recrystallized from Et_2O–petroleum ether (bp 30–60°) to yield 80 mg of fine white needles of 5-methoxy-4-aminoindolyl-3-acetonitrile (Ic), mp 142–143°. The white crystalline compound turned dark blue when exposed to air overnight. *Anal.* ($C_{11}H_{11}N_3O$) C, H, N.

(B) The reaction conditions employed for reductive cyclization of 5-methoxy-4-nitroindolyl-3-acetonitrile were identical with method A except that EtOH was used as the solvent. The product was purified in the same manner and eluted from a silica gel column with PhH–Et_2O (4:1) to yield 350 mg of solid which was recrystallized from Et_2O–petroleum ether to give 140 mg of colorless crystalline needles, mp 105–105.5°, of IIa. The nmr spectrum was consistent with the structure. *Anal.* ($C_{11}H_{12}N_2O$) C, H, N.

The second fraction, eluted from the silica gel with ether, was recrystallized from Et_2O–petroleum ether to give 50 mg of colorless crystalline needles, mp 170–171°. The structure of this compound was assigned as 7-methoxy-1,2,3,4,5,6-hexahydropyrrolo[4,3,2-*d*,*e*]quinoline (III). The molecular weight determined by mass spectrometry was 190. The nmr spectrum was consistent with the structure. *Anal.* ($C_{11}H_{14}N_2O$) C, H, N.

(C) A mixture of 4.0 g of 5-methoxy-4-nitrolindolyl-3-acetonitrile, 4.0 g of 10% Pd–C, and 300 ml of EtOH was hydrogenated for 4 hr at 65° at H_2 pressure of 3.87 kg/cm². The mixture was filtered and washed with 20 ml of EtOH. After the EtOH was removed, the blue-pink residue was chromatographed over silica gel to give the only identifiable product, IIa (0.8 g).

6-Methoxy-5-formyl-1,3,4,5-tetrahydropyrrolo[4,3,2-*d*,*e*]quinoline (IIb).—To 2 ml of formic–acetic anhydride, cooled in an ice bath, was added slowly 300 mg (0.0016 mole) of IIa. The solution was stirred at room temperature for 2 hr. After Et_2O (4 ml) was added and the solution was stirred for an additional 16 hr, it was diluted (H_2O), and then extracted (CH_2Cl_2). The extract was washed (H_2O, dilute NH_4OH, NaCl solution), dried (Na_2SO_4), and concentrated *in vacuo*. The yield of crude formyl derivative was 220 mg. The crude product was recrystallized from EtOH–Et_2O to give a white crystalline solid, mp 145–146°. *Anal.* ($C_{12}H_{12}N_2O_2$) C, H, N.

O-Methylnordehydrobufotenine (IIc).—To 5 ml of 1.0 *M* borane in THF (0.005 mole of BH_3) at room temperatue was added dropwise, with stirring, a solution of 180 mg (0.0083 mole) of IIb in 10 ml of THF. The solution was stirred at room temperature for 24 hr. MeOH (10 ml) was added cautiously to the reaction mixture, followed by 10 ml of 5% aqueous NaOH. The solution was extracted ($CHCl_3$) and dried (Na_2SO_4). After the solvent was removed *in vacuo*, the residue was recrystallized from hexane to give 100 mg of white crystalline solid: mp 84.5–85.5°; mass spectrum mol wt, 202; nmr, 3.00 (triplet, 3-CH_2), 3.40 (triplet, 4-CH_2), 3.25 (singlet, NCH_3), 3.90 (OCH_3), 6.61 (doublet, J = 8 cps, C-8 H), 6.60 (singelt, C-2 H), 6.79 (doublet, J = 8 cps, C-7 H), and 7.68 (indole NH). *Anal.* ($C_{12}H_{14}N_2O$) C, H, N.

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(13) Melting points are corrected. Where analyses are indicated by symbols of the elements, analytical results were obtained within ±0.4% of the theoretical values. Spectral data were in agreement with assigned structures. Nmr data are reported in ppm from a TMS internal standard in $CDCl_3$ unless otherwise noted. Mass spectra were obtained with an AEI MS-9 mass spectrometer. Petroleum ether used had bp 30–60°.

2-Amino-3-phenyl-1,1,1-trifluoropropanes. Fluorine Analogs of Amphetamines

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The trifluoromethyl group is well suited because of its unique chemical and physiological stability[1,2] to replace the methyl group in known pharmacologically active compounds. Since a CF_3 group appears to be approximately the same size as CH_3,[3] amphetamines with CH_3 replaced by CF_3 should have the same steric requirements. However, the strong electron-withdrawing properties of CF_3 will alter the basicity of the adjacent amino moiety. Similar analogs of α-methylphenylalanines, such as α-trifluoromethyldopa, have been claimed to be as active as the parent α-methyl compounds but with more specific effects.[4] We are therefore reporting the synthesis and some pharmacology of a series of 2-amino-3-methoxylated-phenyl-1,1,1-

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