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.* ($C_{12}H_{15}N_3O_4$) 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 165–165.5°, 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-nitroindolyl-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 temperature 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 (singlet, C-2 H), 6.79 (doublet, *J* = 8 cps, C-7 H), and 7.68 (indole NH). *Anal.* ($C_{13}H_{14}N_2O$) 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-

(1) M. B. Chenoweth and L. P. McCarty, *Pharmacol. Rev.*, **15**, 673 (1963).
(2) N. P. Buu-Hoi, *Progr. Drug Res.*, **3**, 9 (1961).
(3) J. Lazar and W. A. Shepherd, *J. Med. Chem.*, **11**, 138 (1968).
(4) M. Sletzinger and W. A. Gaines (to Merck and Co., Inc.), U. S. Patent 3,046,300 (1962).

trifluoropropanes, fluorine analogs of methoxyamphetamines in which the α-CH_3 has been replaced by CF_3.

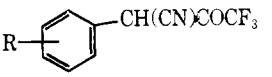
The title compounds were synthesized by the route used by Pinder and Burger[5] for 2-amino-3-phenyl-1,1,1-trifluoropropane itself. Several of the intermediates have been described in the patent literature,[4] but in our hands the method reported for hydrolysis of the α-trifluoroacetylphenylacetonitriles to the benzyl trifluoromethyl ketones gave only intractable tars. Furthermore, no physical data are given in the patent and we are reporting these for the first time.

The results of the pharmacological tests indicate that no amphetamine-like activity could be detected in a variety of tests designed to elicit behavioral responses. None of the title compounds displayed the typical central-stimulating effects of amphetamine in whole animals. However, the 3,4,5-trimethoxyphenyl derivative (**6**), in the head twitch test, showed activity of a type associated with hallucinogenic drugs; its activity in this respect was about one-tenth that of mescaline.

The results of this study and those of similar investigations[5] indicate that replacement of CH_3 by CF_3 in phenethylamine-type molecules has a deleterious effect on biological activity. Patent claims[4] indicating the beneficial effects of such substitutions have not been substantiated.[6] The difference in size between CH_3 and CF_3 is not such that it would be responsible for completely abolishing biological activity, particularly since both 1-ethyl- and 1-ethynylphenethylamine, with α groups of larger dimensions[7] than those of CF_3, are active as inhibitors of monoamine oxidase and as promoters of locomotor activity.[5] Furthermore, 1-cyanophenethylamine, where the α substituent is identical in size with the ethynyl group but with very different electronic characteristics, is without amphetamine-like activity.[9] It therefore seems that electronic considerations must play the major part in determining the biological activity of α-substituted phenethylamines. Certainly, the electron-withdrawing effect of CF_3 is sufficient to reduce the basicities of the amphetamines by almost 5pK_a units, as, for example, in amphetamine (pK_a = 9.93)[10] and **1** (pK_a = 4.97) and 3,4-dimethoxyamphetamine (pK_a = 9.60)[11] and **4** (pK_a = 5.00). α substitution by the nitrile group has an even greater effect, 1-cyanophenethylamine having a pK_a of 4.70. This sequence compares well with that in the aliphatic analogs, where basicity increases in the order aminoacetonitrile (pK_a = 5.3),[12] 2,2,2-trifluoroethylamine (pK_a = 5.7),[13] and ethylamine (pK_a = 10.75). Conversely, α substitution by CH_3 scarcely affects basicity, amphetamine being only slightly more basic than phenethylamine (pK_a = 9.86).[10] We must conclude that α substitution of phenethylamines by strong electron-withdrawing groups such as CF_3 or CN severely reduces the availability of the lone pair of electrons of the amino nitrogen, and this factor is responsible for the lack of biological activity in such compounds. However, it also seems possible that lack of activity in the CNS is due to the decreased ability of such compounds to pass the blood–brain barrier.

TABLE I

α-TRIFLUOROACETYLPHENYLACETONITRILES



R	Yield, %	Mp, °C[a]	Formula[b]
3-OCH_3	69	79–80.5	$C_{11}H_8F_3NO_2 \cdot H_2O$
4-OCH_3	61	73–74	$C_{11}H_8F_3NO_2 \cdot H_2O$
3,4-$(OCH_3)_2$	63	151–152	$C_{12}H_{10}F_3NO_3$
3,5-$(OCH_3)_2$	83	86–87	$C_{12}H_{10}F_3NO_3$
3,4,5-$(OCH_3)_3$	80	136–137	$C_{13}H_{12}F_3NO_4 \cdot H_2O$

[a] Recrystallized from C_6H_6. [b] All compounds were analyzed for C, H, N. Their ir and nmr spectra were as expected.

Experimental Section

Melting points were determined in a Gallenkamp capillary melting point apparatus and are corrected. Where analyses are indicated only by symbols of the elements, analytical results obtained for those elements were within ±0.4% of the theoretical values. pK_a values were determined potentiometrically using a Radiometer Titrograph SBR 2c, and are accurate to ±0.05 unit.

α-Trifluoroacetylphenylacetonitriles (Table I).—In a typical preparation, a mixture of 3,4,5-trimethoxyphenylacetonitrile (20.7 g, 0.1 mole) and CF_3CO_2Et (14.2 g, 0.1 mole) in EtOH (100 ml) was added over 30 min to a gently refluxing solution of Na (2.3 g, 0.1 g-atom) in EtOH (30 ml). The whole was heated under reflux for 14 hr. The cold dark red solution was poured into a mixture of concentrated HCl (20 ml) and H_2O (500 ml), extracted with Et_2O (two 250-ml portions), washed (H_2O), and dried ($MgSO_4$). Distillation gave a red oil which was crystallized from C_6H_6, yield 26 g.

Benzyl Trifluoromethyl Ketones (Table II).—Typically, α-trifluoroacetyl(3,4,5-trimethoxy)phenylacetonitrile hydrate (16.1 g, 0.05 mole) was added to a mixture of 98% H_2SO_4 (85 g) and H_2O (50 ml) in a flask equipped with a 30-cm unpacked insulated column. The mixture was heated to 180–200° and steam distillation from the top of the column began at 95–98°. H_2O was added slowly from the dropping funnel at such a rate that the temperature was maintained at 100°. After 6 hr, the distillate was extracted with Et_2O, dried ($MgSO_4$), and distilled under reduced pressure, yield 5.3 g.

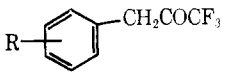
The **oximes** were prepared by refluxing the ketones and $NH_2OH \cdot HCl$ in pyridine–EtOH (1:1, v/v) for 2 hr, decomposing the cooled reaction mixture with 3 *N* HCl, and extracting into Et_2O.

2-Amino-3-phenyl-1,1,1-trifluoropropane Hydrochlorides (Table III).—For example, a solution of 4-methoxybenzyl trifluoromethyl ketoxime (6.6 g, 0.028 mole) in dry Et_2O (100 ml) was added dropwise under N_2 to a stirred suspension of $LiAlH_4$ (1.2 g, 0.03 mole) in dry Et_2O (50 ml). The mixture was heated under reflux for 5 hr, and excess $LiAlH_4$ was destroyed (H_2O). Then 10% NaOH (100 ml) was added, the solid material was filtered off, and the Et_2O layer separated and was dried ($MgSO_4$). Removal of ether gave a yellow oil, from which the hydrochloride was prepared in ether–petroleum ether (bp 30–60°). Sublimation at 150–160° (1.0 mm) gave a colorless powder, yield 4.5 g.

Pharmacology. (a) Reversal of Reserpine Sedation in Mice.—All compounds (**1**–**6**) (Table III) were tested for amphetamine-like activity in reversing the reserpine-induced sedation in mice.[14] In this test, reserpine (25 mg/kg) was injected subcutaneously to male albino mice; 2.5 hr later when all the animals were prostrate and unresponsive to stimuli, intraperitoneal

(5) R. M. Pinder and A. Burger, *J. Pharm. Sci.*, **56**, 970 (1967).
(6) M. Sletzinger, personal communication.
(7) R. K. Ouelette, *J. Amer. Chem. Soc.*, **86**, 3089 (1964); M. E. Wolff and T. Jen, *J. Med. Chem.*, **6**, 726 (1963).
(8) A. Burger, S. E. Zimmerman, and E. J. Ariens, *ibid.*, **9**, 469 (1966).
(9) R. M. Pinder and A. Burger, unpublished work.
(10) G. P. Lewis, *Brit. J. Pharmacol.*, **9**, 488 (1954).
(11) E. B. Leffler, H. M. Spencer, and A. Burger, *J. Amer. Chem. Soc.*, **73**, 2611 (1951).
(12) S. Soloway and A. Lipschitz, *J. Org. Chem.*, **23**, 613 (1958).
(13) E. R. Bissell and M. Finger, *ibid.*, **24**, 1256 (1959).
(14) R. M. Burton, M. A. Sodd, and A. Goldin, *Arch. Int. Pharmacodyn. Ther.*, **112**, 188 (1957).

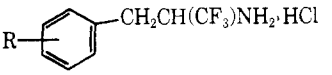
TABLE II
BENZYL TRIFLUOROMETHYL KETONES



R	Yield, %	Bp (mm) or mp, °C	Formula[a]	Mp of oxime,[b] °C	Formula[c]
3-OCH_3	60	73–77 (1.0)	$C_{10}H_9F_3O_2$	55–56	$C_{10}H_{10}F_3NO_2$
4-OCH_3	68	67–70 (0.5)	$C_{10}H_9F_3O_2$	51–52	$C_{10}H_{10}F_3NO_2$
3,4-$(OCH_3)_2$	58	102–104 (0.7)	$C_{11}H_{11}F_3O_3$	98–99	$C_{11}H_{12}F_3NO_3$
3,5-$(OCH_3)_2$	27	66–67[d]	$C_{11}H_{11}F_3O_3 \cdot 2H_2O$	91–92	$C_{11}H_{12}F_3NO_3$
3,4,5-$(OCH_3)_3$	38	88–89[d]	$C_{12}H_{13}F_3O_4 \cdot 2H_2O$	Not isolated	

[a] All ketones were analyzed for C, H. Their ir and nmr spectra were as expected. [b] Recrystallized from C_6H_6–petroleum ether (bp 30–60°). [c] See footnote *b*, Table I.

TABLE III
2-AMINO-3-PHENYL-1,1,1-TRIFLUOROPROPANE HYDROCHLORIDES



No.[e]	R	Yield, %	Mp, °C	Recrystn solvent	Formula[a]	pK_a
2	3-OCH_3	68	171–173	*i*-PrOH–petr ether[c]	$C_{10}H_{12}F_3NO \cdot HCl$[b]	4.98
3	4-OCH_3	71	188–190	Sublimed[d]	$C_{10}H_{12}F_3NO \cdot HCl$	5.06
4	3,4-$(OCH_3)_2$	73	176–177	Sublimed[d]	$C_{11}H_{14}F_3NO_2 \cdot HCl$	5.001
5	3,5-$(OCH_3)_2$	75	222–223	EtOH–petr ether[c]	$C_{11}H_{14}F_3NO_2 \cdot HCl$	4.98
6	3,4,5-$(OCH_3)_3$	60	217–218	*i*-PrOH–petr ether[c]	$C_{12}H_{16}F_3NO_3 \cdot HCl$	5.001

[a] See footnote *b*, Table I. [b] C: calcd, 46.97; found, 46.43. [c] Bp 60–80°. [d] Compounds were sublimed at 150–160° (1.0 mm). [e] Compound **1** is 2-amino-3-phenyl-1,1,1-trifluoropropane hydrochloride, pK_a = 4.97.

injections of the drugs under study were given. Doses of *dl*-amphetamine of 5 mg/kg and above regularly reversed the effects of reserpine; the mice became alert and showed spontaneous activity. Doses of 40 mg/kg of **1**–**6** were completely without effect.

(b) **Production of Head Twitches in Mice.**—The method[15] has been claimed to detect activity of drugs producing hallucinogenic effects in man. In this laboratory, subcutaneous doses of *dl*-amphetamine produce no characteristic head twitches in male albino mice while doses of mescaline of 5 mg/kg and above regularly produce an appreciable number of such twitches. Compounds **1**–**6** were used initially at 40 mg/kg but only **6** produced any head twitches. Assayed against mescaline in a six-point assay using ten mice per group, **6** showed a potency relative to mescaline of 0.11.

(c) **Neuropharmacological Action in Conscious Cats.**—Cats with chronically implanted stainless steel electrodes sited over association and auditory areas of the cortex were prepared according to the method of Bradley and Elkes.[16] The animals were placed in a sound-proof chamber and their behavior was observed with the aid of closed circuit television. Electrocortical activity was recorded on an eight-channel Elema-Mingograph electroencephalograph. In the chamber the cats soon became drowsy and showed a characteristic pattern of electrocortical activity consisting of synchronized large-amplitude (1–3 cps) waves with bursts of spindle activity at 8–12 cps. A dose of *dl*-amphetamine (2 mg/kg ip) produced marked behavioral alerting and increased attentiveness. The alerting effect persisted for over 3 hr and during this period the EEG showed continuous, alert, desynchronized activity consisting of 15–30-cps low-amplitude waves. In this test, doses of up to 25 mg/kg of **1** or **6** caused no detectable change either in the behavior or in the electrocortical activity of the cats.

(d) **Actions in Cat Encephalé Isolé Preparations.**—The experiments were carried out according to the method of Bradley and Key,[17] and enabled the effects of drugs on electrocortical and behavioral responses produced by electrical stimulation of the brain stem to be studied. A dose of *dl*-amphetamine (0.5 mg/kg iv) decreased both behavioral and electrocortical arousal thresholds by 50%. After a total dose of 1.0 mg/kg the preparation remained behaviorally alert and there was typical desynchronized activity in the EEG. Total doses of 20 mg/kg of **1** or **6** had no effect in this test.

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(15) S. J. Cuyne and R. W. Pickering, *Psychopharmacologia*, **11**, 65 (1967).
(16) P. B. Bradley and J. Elkes, *Brain*, **80**, 77 (1957).
(17) P. B. Bradley and B. J. Key, *EEG Clin. Neurophysiol.*, **10**, 97 (1958).

Synthesis of Indole Hydrazines as Monoamine Oxidase Inhibitors[1a]

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Monoamine oxidase inhibitors have been reported to possess antidepressant[2] and pronounced anticonvulsant properties.[3] In addition, clinical efficacy of 3-(2-aminobutyl)indole for the treatment of some types of depression[4] and its ability to inhibit reversibly rat brain and rat liver monoamine oxidase[5] led us to synthesize substituted indoleacyl hydrazides as compounds affecting the activity of the central nervous system.

(1) (a) The investigation was supported in part by the Council of Scientific and Industrial Research, New Delhi, and the State Council of Scientific and Industrial Research, Lucknow (Junior Research Fellowship to V. K. A.). (b) Postdoctoral Research Fellow of the Council of Scientific and Industrial Research. (c) Enquiries should be addressed to Professor S. S. Parmar.

(2) E. A. Zeller, S. Sarkar, R. Banerjee, and M. S. Ise, *Helv. Chim. Acta*, **43**, 430 (1960).
(3) D. J. Prockop, P. A. Shore, and B. B. Brodie, *Ann. N. Y. Acad. Sci.*, **80**, 643 (1959).
(4) L. J. Meduna, *J. Neuropsychiat., Suppl.*, **2**, 150 (1961).
(5) M. E. Grieg, P. H. Seay, and W. A. Freyburger, *ibid.*, **2**, 131 (1961).