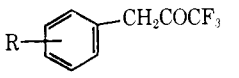
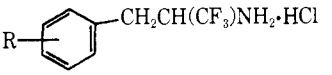
TABLE II
BENZYL TRIFLUOROMETHYL KETONES



R	Yield, %	Bp (bath) 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]	$C_{12}H_{14}F_3O_4 \cdot 2H_2O$	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.[a]	R	Yield, %	Mp, °C	Recrystd 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]	$C_{11}H_{14}F_3NO_2 \cdot HCl$	5.00
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]	$C_{12}H_{16}F_3NO_3 \cdot HCl$	5.00

[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.

Acknowledgments.—We thank B. H. Butcher for help in the preparation of some key intermediates, D. B. Coult for pK_a determinations, and A. C. Thomas and his staff for microanalytical determinations.

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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.
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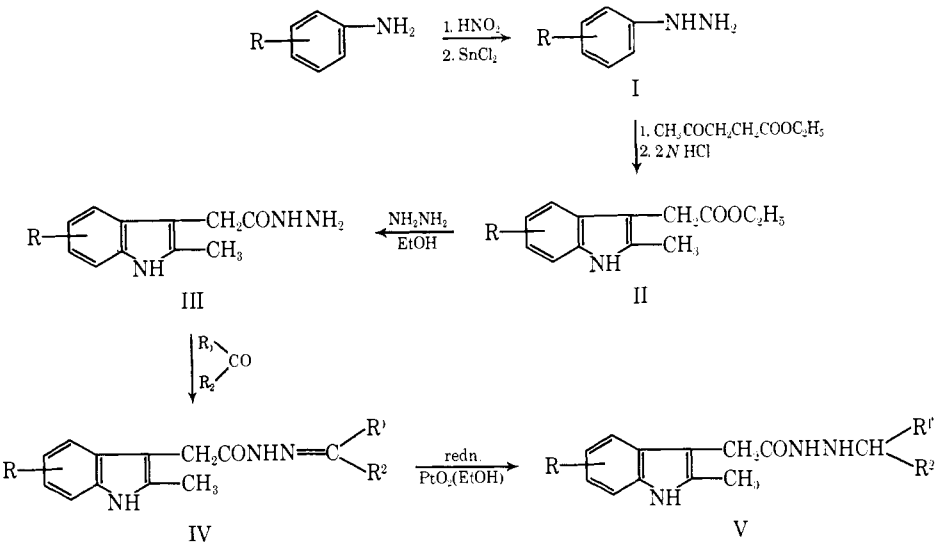
SCHEME I



R = *o*-CH_3, *p*-CH_3, *p*-OCH_3; R_1 = CH_3; R_2 = CH_3, C_2H_5

TABLE I

ETHYL 2,5-DISUBSTITUTED INDOLEACETATES

Deriv of ethyl indole-3-acetate	Bp, °C (mm)	Yield, %	Formula
2,5-Me_2	170 (5)	58	$C_{14}H_{17}NO_2$
2,7-Me_2	180 (5)	45	$C_{14}H_{17}NO_2$
2-Me	135–138 (5)	55	$C_{13}H_{15}NO_2$
2-Me-5-OMe	180 (6)	50	$C_{14}H_{17}NO_2$

In the present study attempts have been made to investigate the structure–activity relationship of these compounds with respect to their ability to inhibit rat liver MAO. The various substituted indole derivatives were synthesized by the route outlined in Scheme I.

Experimental Section

Substituted Alkoxy- and Alkylphenylhydrazines (I).—The hydrazines synthesized according to the methods reported earlier[6] were *o*-methyl-, *p*-methyl-, and *p*-methoxyphenylhydrazine.

Ethyl 2,5-Disubstituted Indoleacetates (II).—Cyclization of substituted phenylhydrazines and ethyl levulinate in 2 *N* EtOH–HCl was used. The crude products[7–10] isolated with Et_2O were washed ($NaHCO_3$, H_2O) and distilled under reduced pressure (Table I).

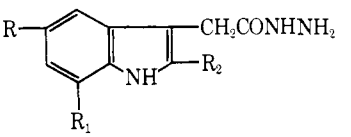
Substituted Indoleacyl Hydrazides (III).—The various substituted ethyl indoleacetates (0.1 mole) were refluxed with hydrazine hydrate (0.15 mole; 80%) in 25 ml of absolute EtOH for 8 hr. On distilling excess EtOH the hydrazides which separated out were filtered and recrystallized from appropriate solvents. The hydrazies (Table II) were characterized by their sharp melting points and elemental analyses.

Substituted Indole Isopropylidenehydrazides (IV).—Substituted indole hydrazides (0.2 mole) and 50 ml of Me_2CO or EtCOMe were refluxed for 13 hr. The reaction mixture was filtered hot and concentrated *in vacuo*. On cooling, the solid mass which separated out was filtered and recrystallized from the appropriate solvent (see Table III).

Substituted Indole N-Isopropylhydrazides (V).—A solution of 2 g of a substituted indole isopropylidenehydrazide (0.01 mole) in 150 ml of absolute EtOH was hydrogenated with 0.1 g of PtO_2 at an initial pressure of 2.8 kg/cm². The required amount of H_2 was absorbed in 15 hr. The mixture was filtered and the

TABLE II

SUBSTITUTED INDOLEACYL HYDRAZIDES

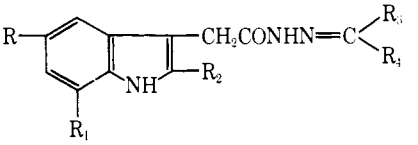


R	R_1	R_2	Mp, °C[a]	Yield, %	Formula[b]
H	H	CH_3	156	70	$C_{11}H_{13}N_3O$
CH_3	H	H	135	60	$C_{11}H_{13}N_3O$
CH_3	H	CH_3	156	70	$C_{12}H_{15}N_3O$
H	CH_3	CH_3	140	70	$C_{12}H_{15}N_3O$
CH_3O	H	CH_3	158	70	$C_{12}H_{15}N_3O$

[a] Melting points were taken in open capillary tubes and are graphically corrected. [b] All compounds were analyzed for C, H, N and analyses were found within limits.

TABLE III

SUBSTITUTED INDOLE ISOPROPYLIDENEHYDRAZIDES



R	R_1	R_2	R_3	R_4	Mp, °C[a]	Yield, %	Formula[b]
H	H	CH_3	CH_3	CH_3	142	50	$C_{14}H_{15}N_3O$
H	H	CH_3	CH_3	C_2H_5	140	60	$C_{15}H_{19}N_3O$
CH_3	H	CH_3	CH_3	CH_3	165	60	$C_{15}H_{19}N_3O$
CH_3	H	CH_3	CH_3	C_2H_5	170	55	$C_{16}H_{21}N_3O$
H	CH_3	CH_3	CH_3	CH_3	138	60	$C_{15}H_{19}N_3O$
H	CH_3	CH_3	CH_3	C_2H_5	168	50	$C_{16}H_{21}N_3O$
CH_3O	H	CH_3	CH_3	CH_3	180	60	$C_{15}H_{19}N_3O_2$
CH_3O	H	CH_3	CH_3	C_2H_5	135	50	$C_{16}H_{21}N_3O_2$

[a] Melting points were taken in open capillary tubes and are graphically corrected. [b] All compounds were analyzed for C, H, N and analyses were found within limits.

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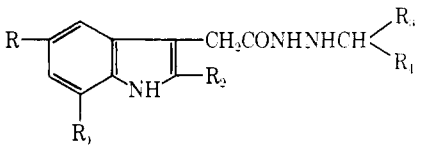
TABLE IV
SUBSTITUTED INDOLE N-ISOPROPYLHYDRAZIDES



R	R_1	R_2	R_3	R_4	Mp, °C[a]	Yield, %	Formula[b]	MAO inhib,[c] %
H	H	CH_3	CH_3	CH_3	85	50	$C_{14}H_{19}N_3O$[d]	50.0, 49.0 (49.5)
H	H	CH_3	CH_3	C_2H_5	70	50	$C_{15}H_{21}N_3O$	42.3, 41.5 (41.9)
CH_3	H	CH_3	CH_3	CH_3	148	65	$C_{15}H_{21}N_3O$	50.0, 50.0 (50.0)
CH_3	H	CH_3	CH_3	C_2H_5	105	70	$C_{16}H_{23}N_3O$	42.0, 40.0 (41.0)
H	CH_3	CH_3	CH_3	CH_3	145	60	$C_{15}H_{21}N_3O$	50.0, 48.4 (49.2)
H	CH_3	CH_3	CH_3	C_2H_5	100	65	$C_{16}H_{23}N_3O$	48.0, 47.0 (47.5)
CH_3O	H	CH_3	CH_3	CH_3	110	60	$C_{15}H_{21}N_3O_2$	50.0, 48.0 (49.0)
CH_3O	H	CH_3	CH_3	C_2H_5	80	65	$C_{16}H_{23}N_3O_2$[e]	48.0, 50.0 (49.0)

[a] Melting points were taken in open capillary tubes and are graphically corrected. [b] The compounds were analyzed for C, H, N. [c] Vessel contents and the assay procedures are as indicated in the text. Each experiment was done in duplicate. Figures in the parentheses indicate mean values. [d] *Anal.* C: calcd, 68.46; found, 69.15. [e] *Anal.* C: calcd, 66.43; found, 65.92.

solvent was removed under reduced pressure. The hydrazines were crystallized by dissolving in a minimum amount of EtOH and adding petroleum ether (bp 40–60°) to incipient turbidity. The crude product was recrystallized from the appropriate solvent (see Table IV).

Determination of Monoamine Oxidase Activity.—The spectrophotofluorometric method of Kramer[11] was used for the determination of the MAO activity of rat liver homogenate using kynuramine as the substrate. The 4-hydroxyquinoline, formed during oxidative deamination of kynuramine, was measured fluorometrically in an Aminco Bowman spectrophotofluorometer using activating light of 315 mμ and measuring fluorescence at the maximum of 380 mμ.

Male adult rats weighing approximately 150–200 g were killed by decapitation. Livers were quickly removed and homogenized in ice-cold 0.25 *M* sucrose with the help of Potter-Elvehjem homogenizer. The reaction mixture consisted of phosphate buffer, 0.5 ml (pH 7.5, 0.5 *M*), 0.5 ml of kynuramine (100 μg), and 0.5 ml of liver homogenate (corresponding to 5 mg of wet weight of the tissue). The MAO activity of the liver homogenate was determined by incubation for 30 min at 37° in air. The various inhibitors, used at the final concentration of 1×10^{-3} *M*, were added to the liver homogenate and incubated for 10 min before the addition of kynuramine. The mixture was further incubated for 30 min. The reaction was stopped by the addition of 2 ml of 10% TCA and the precipitated proteins were removed by centrifugation. Suitable aliquots of the supernatant were taken in 1 *N* NaOH solution and were assayed for 4-hydroxyquinoline. Increase in the optical density provided a direct measurement of the 4-hydroxyquinoline which was taken as an index of the enzyme activity. The per cent inhibition was calculated from the decrease observed in the optical density.

Results and Discussion

The MAO inhibitory activities of substituted indole N-isopropylhydrazides using rat liver homogenate during oxidative deamination of kynuramine are shown in Table IV. The various indole hydrazides shown in Table III were found to be devoid of enzyme inhibitory properties. Reduction of some of these hydrazides (Table III) led to the corresponding hydrazines (Table IV) which, however, exhibited MAO inhibitory properties. Similar results have been reported earlier by Zeller[12] where no inhibition of the enzyme MAO could be observed with isoniazid, as compared to iproniazid. All the substituted indolecacylhydrazines were equally effective in inhibiting the enzyme activity since the degree of inhibition produced by these compounds was fairly constant. Substitution in the indole nucleus or in the hydrazine side chain was found to have no specific effect on their ability to inhibit rat liver MAO. At present it is difficult to evaluate a structure–activity relationship of these substituted hydrazines. It is presumed that investigations dealing with the determination of the substrate specificity and the inhibitory effects of these compounds during oxidation of tryptamines could provide better knowledge regarding their structure–activity relationship as MAO inhibitors.

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The Synthesis and Pharmacological Properties of a Series of 2-Substituted Aminomethyl-1,4-benzodioxanes

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Since Fourneau and Bovet[2] first described benzodioxanes as epinephrine antagonists a large number of related compounds possessing similar properties have been reported. Bovet and Simon[3] investigated the adrenolytic and sympatholytic properties of a series of aminomethylbenzodioxanes and noted the effect of these compounds on the CNS. The preparation of N,N′-ethylenedianine and piperazine derivatives structurally related to 2-diethylaminomethyl-1,4-benzodioxane (prosympal) and 2-(1-piperidylmethyl)-1,4-benzodioxane (piperoxan) have been described[4] and the pharmacological properties of some of these compounds

(1) To whom enquiries should be addressed.

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