TABLE IX (*Continued*)

Compd. no. or ref.	2,2-Substituents	Benzene substituents	Concentration, γ/ml.[a]	% Growth inhibition in *L. casei*[b]
			5	−86
			1	−55
			0.4	0
Ref. 5, 7	$(CH_3)_2$	3-Cl	100	−93
			5	−90
Ref. 3, 5, 7	$(CH_3)_2$	3,4-Cl_2	100	−99
			5	−90
			1	−51
			0.1	0
XVII	$(CH_3)_2$	3,5-$(CH_3)_2$	100	−95
			5	−94
			1	−66
			0.1	0

[a] As hydrochloride salt. [b] In OFA medium which contains 0.046 mμg. of folic acid per ml.[27] A negative sign indicates growth inhibition, whereas a + sign indicates that the substance promotes growth.

and are only useful in showing a trend, when considered over the range of a large number of compounds.

Testing results are shown in Tables V–VIII.

The *L. casei* Screen.—Details of this screening procedure, which was designed for the preliminary screening of substances for activity as antagonists of nucleic acid synthesis, are described by Hitchings and co-workers.[27] Results are shown in Table IX.

TABLE X

ACUTE TOXICITY OF SELECTED ARYLDIHYDROTRIAZINES

Compound no.	2,2-Substituents	Benzene substituents	LD_{50}, mg./kg.[a] I.P.	P.O.
XXXVI	$-CH_2CH_2CHCH_2CH_2-$ (CH$_3$ at 4)	4-Cl	129	>20,000
XXXIII	$-CH_2CH_2CHCH_2CH_2-$ (CH$_3$ at 4)	2-Br	70	5,000
XXXVII	$-CH_2CH_2CHCH_2CH_2-$ (CH$_3$ at 4)	4-Br	*ca.* 95	>1,000
XXX	$-CH_2CH_2CHCH_2CH_2-$ (CH$_3$ at 4)	—	66	*ca.* 1,000
XXV	$-(CH_2)_5-$ (CH$_3$ at 1)	2-C_2H_5	47	1,500
XVIII	$(CH_3)_2$	2,4,5-$(CH_3)_3$	90	1,370
XXXVIII	$-CH_2CH_2CHCH_2CH_2-$ (CH$_3$ at 4)	2,6-$(CH_3)_2$	56	1,180
XXIX	$-CH_2CHCH_2CH_2CH_2-$ (CH$_3$ at 2)	4-Cl	48	1,100
Ref. 7	$-(CH_2)_5-$	4-Cl	56	1,058
XXXII	$-CH_2CH_2CHCH_2CH_2-$ (CH$_3$ at 3)	2-C_2H_5	—	*ca.* 1,000
Ref. 5, 7	$-(CH_2)_4-$	4-Cl	—	870
IV	$(CH_3)_2$	2-C_4H_9-*n*	72	809
XXI	CH_3, C_3H_7-*n*	2-C_2H_5	78	707
XXVII	$-(CH_2)_5-$	2,6-$(CH_3)_2$	35	612
XXIV	$-(CH_2)_4-$	2-C_2H_5	43	436

[a] As hydrochloride salt.

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(27) G. H. Hitchings, G. B. Elion, E. A. Falco, P. B. Russell, M. B. Sherwood, and H. Vanderwerff, *J. Biol. Chem.*, **183**, 1 (1950).

The Synthesis and Pharmacological Activity of Some Chloro-α-alkyltryptamines[1]

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The synthesis of eight new monochloro analogs of α-methyl- and α-ethyltryptamines are described. These compounds were prepared by condensations of 4-, 5-, 6-, and 7-chloroindole-3-aldehydes with either nitroethane or nitropropane and subsequent reduction of the condensation products with lithium aluminum hydride. The tryptamines have been found to possess stimulant and anticonvulsant properties in rodents and to produce behavioral changes in cats.

Included in a program of work,[2] which involved the synthesis of a series of tryptamine derivatives related to the physiologically active substance 5-hydroxytryptamine and their examination for biological activity on the cardiovascular and central nervous systems, were the two compounds, α-methyl- and α-ethyltryptamine. Earlier, Govier, *et al.*,[3] had shown that α-ethyltryptamine was an inhibitor of tyramine oxidation and its activity as an inhibitor of the enzyme monoamine-oxidase was confirmed in our Laboratories. α-Methyltryptamine was also found to be a more potent monoamine oxidase inhibitor than the α-ethyl homolog. Both compounds caused reversal of reserpine ptosis in mice but α-methyltryptamine evoked a striking change in the behavior of the animals.[4] An account of the pharmacology of these tryptamines has been given by Greig, *et al.*,[5] and the efficacy of α-ethyltryptamine as an antidepressant drug in man has been

(1) U. K. Patent Application, 20171/61.

(2) E. H. P. Young, *J. Chem. Soc.*, 3493 (1958).

(3) W. M. Govier, B. G. Howes, and A. J. Gibbons, *Science*, **118**, 596 (1953).

(4) Personal communication from Dr. A. Spinks of these Laboratories who is thanked for permission to quote unpublished results.

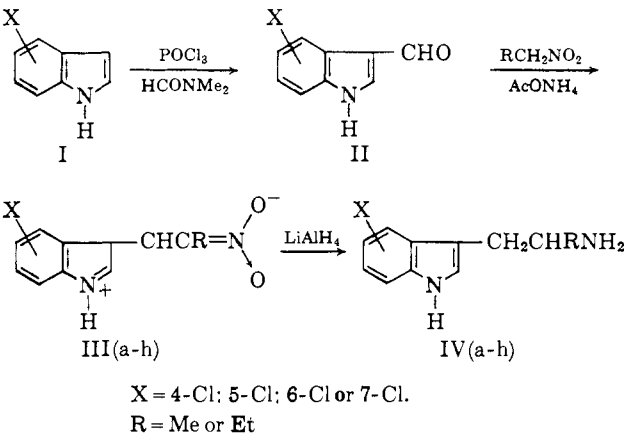
(5) M. E. Greig, R. A. Walk, and A. J. Gibbons, *J. Pharmacol. Exptl. Therap.*, **127**, 110 (1959).

well documented.[6] It is perhaps of interest that α-methyltryptamine which was observed to effect a behavioral change in mice has been found to cause hallucinations in man.[7]

A study of a series of halogenated derivatives of these two tryptamines was undertaken for two reasons. First, the substitution of the aromatic ring, particularly in the 5 and 6 positions, by a halogen atom might be expected to prevent hydroxylation and conjugation, one of the normal metabolic pathways for tryptamines. Such a metabolic block should result in sustained drug action. The addition of a halogen atom would also tend to increase drug persistence by increasing the solubility of the compound in lipoid material and fat deposits in the body. Furthermore, Szara[8,9] has shown that many indole derivatives are not psychomimetic *per se* but are psychomimetic because they are converted *in vivo* into their hydroxy derivatives. Metabolic blockade of α-methyltryptamine by halogenation might, it was argued, abolish the psychomimetic effects of the drug.

Second, the introduction of halogen atoms instead of diminishing or abolishing the psychomimetic action sometimes leads to enhanced action as was shown by Benington, *et al.*,[10] in their studies on a series of ring substituted phenethylamines. Psychomimetic agents have been used in men and animals to promote "model psychoses" in attempts to discover the nature and causes of schizophrenia,[11-14] and although the validity of the results obtained is the subject of some controversy, further new compounds able to influence behavior may be of some assistance in the furthering of these studies.

Chemistry.—4-, 6-, and 7-chloroindoles were converted into the corresponding aldehydes by reaction with phosphorus oxychloride in dimethylformamide under conditions previously described for 5-chloroindole.[2] The aldehydes were condensed with either nitroethane or nitropropane by heating the reactants together in an open flask to allow water vapor to escape and in the presence of ammonium acetate as a catalyst. Ammonium acetate has been found to be superior in all these reactions with indole aldehydes to the more usual amine catalysts, and in all cases the use of an excess of the nitroparaffin as solvent has been found to be preferable to the use of other solvents such as ethanol or acetic acid. The condensation products, which have the nitronium salt structure[15] (III), were reduced to the tryptamines (IV) with lithium aluminum hydride in ether; a Soxhlet extraction technique being used because of the low solubility of the nitronium salts in ether.



X = 4-Cl; 5-Cl; 6-Cl or 7-Cl.
R = Me or Et

Experimental

4-Chloroindole-3-aldehyde.—Phosphorus oxychloride (25 ml.) was added dropwise, with stirring, at 10–20° to dimethylformamide (75 ml.). A solution of 4-chloroindole (14.1 g.) in dimethylformamide (25 ml.) was added gradually at 20–30°. The solution was then kept at 35–37° for 45 min. and finally poured into stirred ice (200 g.) and water (150 ml.). Sodium hydroxide (48 g.) in water (250 ml.) was added during 0.5 hr. at 20–30°, the rate of addition being such that when *ca.* 0.75 of the sodium hydroxide solution had been added the mixture was at pH 8. The remainder was then added at once. The mixture was boiled for 5 min. and then cooled rapidly to 50°. The aldehyde was collected, washed with cold water, and dried at 100° (15.1 g., m.p. 164°). Crystallization from water gave white needles, m.p. 177–178°.

Anal. Calcd. for C_9H_6ClNO: C, 60.2; H, 3.3; N, 7.8. Found: C, 60.1; H, 3.3; N, 7.6.

Similarly the following indole-3-aldehydes were obtained: **6-chloro-,** yield 73%; m.p. 206°, needles from aqueous ethanol.

Anal. Calcd. for C_9H_6ClNO: C, 60.2; H, 3.3; N, 7.8. Found: C, 60.0; H, 3.9; N, 7.9.

7-chloro-, yield 91%; m.p. 181°, needles from aqueous ethanol.

Anal. Calcd. for C_9H_6ClNO: C, 60.2; H, 3.3; N, 7.8. Found: 60.0, 60.6; H, 3.2, 3.2; N, 7.6.

Chloro α-alkyl-β-indolenideniumethyl Nitronates. 4-Chloro-α-methyl-β-indolenideniumethyl Nitronate.—4-Chloroindole-3-aldehyde (10 g.), nitroethane (40 ml.), and ammonium acetate (2 g.) were heated in an open flask on the steam bath with occasional shaking for 0.5 hr. On cooling, the crystals (11.2 g., m.p. 203–204°) were collected, washed with hot water (2 × 50 ml.), and crystallized from methanol; the product (m.p. 205–206°) was then obtained as orange prisms. The remaining nitronates shown in Table I were obtained by a similar procedure.

Chlorotryptamines. 4-Chloro-α-methyltryptamine Hydrochloride.—Lithium aluminum hydride (15 g.) was added to ether (500 ml.) in the flask of a Soxhlet extractor. Finely ground 4-chloro-α-methyl-β-indolenideniumethyl nitronate (10 g.) was then extracted from the thimble with ether for 8 hr. The product was cooled and water (100 ml.) was added dropwise to decompose the excess of lithium aluminum hydride and the addition complex. The solid was filtered off and washed with ether (2 × 100 ml.), and the ethereal solution was dried (KOH) and then saturated with hydrogen chloride. The hydrochloride was collected and washed with ether; it (9.4 g.) had m.p. 264–265° dec. The product was purified by crystallization from a methanol–ethyl acetate mixture from which it separated as silvery plates, 7.3 g., m.p. 269–270° dec. The 3-(2-aminoalkyl)indoles described in Table II were similarly prepared.

Pharmacology. Methods. Amine Oxidase and Decarboxylase Inhibition.—The compounds IVa–h together with α-methyltryptamine (αMT) and α-ethyltryptamine were examined as inhibitors of guinea pig and rat kidney monoamine oxidase (MAO) and tryptophan decarboxylase (TD). 5-Hydroxytryptophan (5 HTP) is decarboxylated by TD to give 5-hydroxytryptamine (5HT). 5HT is oxidized in the presence of MAO to give among other products a pigment which can be extracted with 1-butanol and estimated colorimetrically at 400 mμ. With 5HT as the substrate only MAO is involved in the production of pigment; 5HTP must first be decarboxylated to 5HT and then oxidized. Compounds which only inhibit MAO will be active

(6) Various authors in "Symposium: Depression: Its Diagnosis and Treatment," *J. Neuropsychiatry*, **2**, Supplement No. 1 (1961).

(7) H. B. Murphree, E. H. Jenny, and C. C. Pfeiffer, *The Pharmacologist*, **2**, 64 (1960).

(8) S. Szara, *Experientia*, **17**, 76 (1961).

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

(10) F. Benington, R. D. Morin, L. C. Clark, and R. P. Fox, *J. Org. Chem.*, **23**, 1979 (1958).

(11) L. E. Hollister, *Ann. N. Y. Acad. Sci.*, **96**, 80 (1962).

(12) W. Mayer-Gross, *Brit. Med. J.*, (2), 317 (1951).

(13) R. W. Russell, in "Drugs and Behavior," L. Uhr and J. G. Miller, Editors, J. Wiley and Sons, Inc., New York, N. Y., 1960, p. 19.

(14) M. Jarvick and following discussion in "Psychopharmacology," H. H. Pennes, Ed., P. B. Hoeber Inc., New York, N. Y., 1958, Chapter IX, pp. 203–247.

(15) R. V. Heinzelman, W. C. Anthony, D. A. Lyttle, and J. Szmuskovicz, *J. Org. Chem.*, **25**, 1548 (1960).

TABLE I

CHLORO-α-ALKYL-β-INDOLENIDENIUMETHYL NITRONATES (III)

Compound III	X	R	Yield, %	Reaction time[a] (min.)	M.p.,[b] °C.	Molecular formula	Analyses, % Calcd. C	Calcd. H	Calcd. N	Found C	Found H	Found N
a	4-Cl	Me	85	30	205–206	$C_{11}H_9ClN_2O_2$	55.8	3.8	11.8	55.6	3.8	11.8
b	4-Cl	Et	86	60	200–201	$C_{12}H_{11}ClN_2O_2$	57.5	4.4	11.2	57.7	4.2	11.3
c	5-Cl	Me	74	45	205–206	$C_{11}H_9ClN_2O_2$	55.8	3.8	11.8	55.7	3.9	11.8
d	5-Cl	Et	40	90	168–169	$C_{12}H_{11}ClN_2O_2$	57.5	4.4	11.2	57.3	4.3	11.3
e	6-Cl	Me	82	60	226–228	$C_{11}H_9ClN_2O_2$	55.8	3.8	11.8	55.7	3.8	11.9
f	6-Cl	Et	48	90	183–184	$C_{12}H_{11}ClN_2O_2$	57.5	4.4	11.2	57.5	4.6	10.8
g	7-Cl	Me	79	90	181–183	$C_{11}H_9ClN_2O_2$	55.8	3.8	11.8	55.9	3.8	11.9
h	7-Cl	Et	40	120	158–159	$C_{12}H_{11}ClN_2O_2$	57.5	4.4	11.2	57.4	4.4	11.4

[a] The reaction temperature was 95–100°. [b] The nitronates were crystallized from methanol.

TABLE II

CHLORO-3-2′-AMINOALKYLINDOLES (IV)

Compound IV	X	R	Yield, %	M.p.,[a] °C	Molecular formula	Analyses, % Calcd. C	Calcd. H	Calcd. N	Found C	Found H	Found N
a	4-Cl	Me	74	269–270 dec.	$C_{11}H_{13}ClN_2 \cdot HCl$	53.9	5.7	11.4	54.3	5.7	11.4
b	4-Cl	Et	64	295–296 dec.	$C_{12}H_{15}ClN_2 \cdot HCl$	55.6	6.2	10.8	55.7	5.9	10.5
c	5-Cl	Me	68	240–241 dec.	$C_{11}H_{13}ClN_2 \cdot HCl$	53.9	5.7	11.4	54.0	5.7	11.2
d	5-Cl	Et	52	241–242	$C_{12}H_{15}ClN_2 \cdot HCl$	55.6	6.2	10.8	56.1	6.3	10.6
e	6-Cl	Me	29	220–222	$C_{11}H_{13}ClN_2 \cdot HCl$	53.9	5.7	11.4	54.3	5.7	11.5
f	6-Cl	Et	64	235–236	$C_{12}H_{15}ClN_2 \cdot HCl$	55.6	6.2	10.8	55.4	6.4	10.8
g	7-Cl	Me	67	255–257	$C_{11}H_{13}ClN_2 \cdot HCl$	53.9	5.7	11.4	54.2	5.9	11.5
h	7-Cl	Et	28	230–232	$C_{12}H_{15}ClN_2 \cdot HCl$	55.6	6.2	10.8	55.7	6.4	10.9

[a] The tryptamine hydrochlorides were crystallized from a methanol-ethyl acetate mixture.

TABLE III

PHARMACOLOGICAL ACTIVITY OF CHLOROTRYPTAMINES[a]

Compound	Acute LD_{50} in mice	50% Inhibitory concentrations, μg./ml. Substrate 5HT	Substrate 5HTP	Reserpine reversal ED_{15}[b]	Spontaneous diurnal activity ED_{200}	Spontaneous nocturnal activity ED_{200}	Anticonvulsant activity: Mouse electroshock ED_{50}	Rat low current electroshock[c] ED_{50}
IVa	370	28	16	78		>100	NA[d]	
IVb	370	96	43	76		NA	150	25
IVc	700	26	26	78	98	70	>100	7
IVd		35	27	70		>100	150	17.5
IVe	370	>100	>100	100	<100	<100	>100	
IVf	560	>100	>100	>100	NA	66	70	16
IVg	370	18	8	58	<100	38	66	12
IVh		20	3.5	100	<100	30	100	20
α-Methyltryptamine	600	34	16	16	45	29	60	5
α-Ethyltryptamine	400	41	41	37	68	30	32	8

[a] All doses are in mg./kg. unless otherwise indicated. [b] Ref. 16. [c] J. Y. Bogue and H. C. Carrington, *Brit. J. Pharmacol.*, **8**, 230 (1953). [d] N.A. = Not active at the highest dose tested—150 mg./kg. for anticonvulsants; 100 mg./kg. in other tests.

at the same concentration whichever substrate is used. Inhibitors of TD and MAO will inhibit at lower concentrations when the substrate is 5HTP. The results in Table III give the 50% inhibitory concentrations of the compounds against MAO and indicate whether any inhibition of TD was exhibited.

In Vivo **Tests.** (a) **Reserpine Reversal.**—Mice treated with reserpine show typical ptosis and depression which can be reversed by MAO inhibitors. The intensiy of this hyperactivity can be quantitated reproducibly by means of a rating scale. The doses quoted in Table III produce marked hyperactivity.[16]

(b) **Spontaneous Diurnal Activity (SDA).**—Spontaneous activity was measured in photobeam cages using groups of 3 mice during the day. The results are expressed as the dose which produces a doubling of activity (number of times a light beam was interrupted) of the group of mice compared with controls.

(c) **Spontaneous Nocturnal Activity (SNA).**—SNA was measured in the same way as SDA except that the determination was carried out during the hours of darkness when mice are normally more active.

Mouse Electroshock Test.—Mice were dosed orally with the compounds and shocked after 2 hr. (20 ma. for 0.3 sec. from a constant current stimulator).

Results.—Compound IVh was the most active of the chlorotryptamines as an inhibitor of MAO and TD. All 8 compounds were less active than αMT as amine oxidase inhibitors and in their anti-reserpine activity.

In the rat electroshock anticonvulsant test compound IVc gave the greatest protection. There appeared to be little correlation between *in vitro* activity against either enzyme and anticonvulsant or stimulant activity. Compounds IVc and IVd both caused marked behavioral changes in conscious cats. The animals showed many features of sympathomimetic stimulation at doses of 5 mg./kg. The effects were defensive hostility associated with piloerection, exophthalmos, and arched back. These effects can be explained as the results of sympathetic stimulation but the extreme pupillary constriction seen with IVc (but not IVd) does not fit in with this picture.

The time course of the anticonvulsant activity of IVc was similar to that of α-methyltryptamine, and α-ethyltryptamine and in other tests the compounds had similar times of peak activity and duration.

(16) A. F. Crowther, A. Spinks, and E. H. P. Young, *Intern. J. Neuropharmacol.*, **1**, 141 (1962).