1321. *Studies in the Indole Series. Part I. Indolylalkylamines*

By B. Heath-Brown and P. G. Philpott

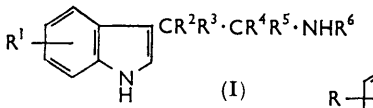
The preparation of a large series of indolylalkylamines is described, including α-alkyl-, αα-dialkyl-, and *N*-alkyltryptamines. New methods include a modification of the Abramovitch synthesis giving α*N*-dimethyltryptamines directly.

The synthesis of indole derivatives related to tryptamine has been studied intensively during recent years, this work having been inspired by interest in the pharmacological actions of 5-hydroxytryptamine (serotonin) and α-methyltryptamine. Some of the compounds which have been prepared are mono-amine oxidase inhibitors and have potential uses as antidepressant drugs.

We have prepared a large number of indole derivatives, and in the present Paper we describe a variety of substituted tryptamines (I) for some of which new methods have been developed. The pharmacology and biochemistry of these compounds have been examined, and the central stimulant properties of α-methyl-, αα-dimethyl-, and α*N*-dimethyl-tryptamines in mice, together with their actions on the uptake of 5-hydroxytryptamine by blood platelets, have been reported.[1] The results of further pharmacological and biochemical work will be reported elsewhere.

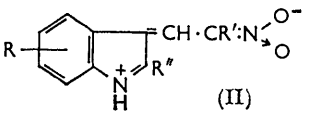
The primary α-alkyltryptamines (I; R^4 = alkyl, $R^5 = R^6 = H$) (Table 3) were prepared either by reduction of the nitronium salts (II) (Table 1) with lithium aluminium hydride in tetrahydrofuran [2] or by hydrogenation of the nitro-compounds (III) (Table 2).

[1] A. W. Lessin, R. F. Long, and M. W. Parkes, *Brit. J. Pharmacol.*, 1965, **24**, 49, 68.
[2] (*a*) E. H. P. Young, *J.*, 1958, 3493; (*b*) B. A. Whittle and E. H. P. Young, *J. Medicin. Chem.*, 1963, **6**, 378.

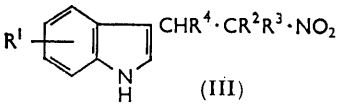


(I)

R^1 = H, Me, MeO, Cl, etc.
R^2, R^3 = H or Me
R^4 – R^6, see text

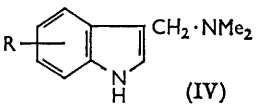


(II)



(III)

The primary αα-dialkyltryptamines (I; R^4,R^5 = alkyl; R^6 = H) (Table 4) were prepared by the latter method only. A few of the nitro-compounds have been described previously;[3,4] we have prepared these and others on a large scale and in high yield by the reaction of gramines (IV; R = H, Me, MeO, Cl) with nitroalkanes in the presence of sodium ethoxide and two equivalents of methyl sulphate.[5] This avoids the large excesses of nitroalkanes employed in published procedures. These routes were not used for the synthesis of the α-unsubstituted compounds (1), (7), and (12) (Table 3)* which were prepared instead by the reduction of the corresponding nitriles.



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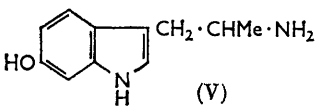

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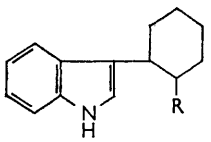


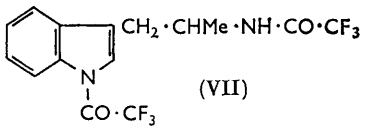
(VI)

Hydrogenolysis of the benzyl ether (12) gave 5-hydroxy-7-methyltryptamine (13). A similar debenzylation of compound (11) gave a chromatographically homogeneous product, but satisfactory analytical data were not obtained. Nevertheless, the product was almost certainly the phenol (V), and it is of interest that biochemical and chromatographic studies have shown it to be indistinguishable from the metabolite of 3-2′-aminopropylindole.[6,7]

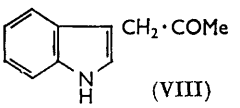
The cyclic tryptamine derivatives (16), (VI; R = NH_2),[8] and (47), (VI; R = NHMe) (not accommodated in the Tables), were prepared by a new method from indolylmagnesium bromide and cyclohexene oxide, to give the alcohol (VI; R = OH). This was converted into the amines through the bromo-compound (VI; R = Br).

The *N*-alkyltryptamines (I; R^4 = Me, R^5 = H or Me, R^6 = alkyl) (Table 5) were prepared by reduction of the *N*-acylated primary amines with lithium aluminium hydride. Acylation of 3-2′-aminopropylindole with trifluoroacetic anhydride, gave the 1,*N*-diacyl derivative (VII), which on reduction with lithium aluminium hydride gave the secondary amine (35) with elimination of the 1-trifluoroacetyl group (cf. ref. 9).

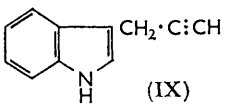
Because of the central stimulant properties observed in 3-2′-methylaminopropylindole (27),[1] alternative syntheses were examined, with a view to large-scale preparation. Two



(VII)



(VIII)



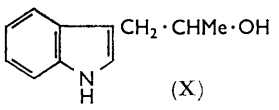
(IX)

routes were successfully developed, the first being the reductive alkylation of methylamine with indol-3-ylacetone (VIII).[10,11] Although the latter was obtained in 45% yield by the

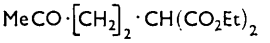
* For ease of identification, Arabic numbers have been given to compounds appearing in Tables 3—5 and Roman numbers to other formulæ.

[3] H. R. Snyder and L. Katz, *J. Amer. Chem. Soc.*, 1947, **69**, 3140.
[4] F. Troxler, F. Seeman, and A. Hoffman, *Helv. Chim. Acta*, 1959, **42**, 2097.
[5] N. F. Albertson, S. Archer, and C. M. Suter, *J. Amer. Chem. Soc.*, 1945, **67**, 36.
[6] S. Szara, *Experientia*, 1961, **17**, 76; A. Kalir and S. Szara, *Fed. Proc.*, 1962, **21**, 337.
[7] R. F. Long, personal communication.
[8] S. Pietra and G. Taconi, *Farmaco Ed. Sci.*, 1961, **16**, 5013.
[9] K. Banholzer, T. W. Campbell, and H. Schmid, *Helv. Chim. Acta*, 1952, **35**, 1577.
[10] J. B. Brown, H. B. Henbest, and E. R. H. Jones, *J.*, 1952, 3172.
[11] W. R. N. Williamson, *J.*, 1962, 2834.

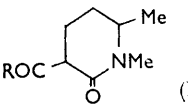
hydration of 3-prop-2-ynylindole (IX), a more convenient large-scale method was by the reduction of the nitronate (II; R = R″ = H, R′ = Me) with iron and acid.[12,13] A by-product of the reductive alkylation reaction was the alcohol (X), presumably identical with that of Novak *et al.*[14] A similar synthesis from 5-methoxyindol-3-ylacetone gave 5-methoxy-3-2′-methylaminopropylindole (40). The second successful route to the base (27) was a modified Abramovitch tryptamine synthesis.[15] This started from ethyl 3-oxobutylmalonate (XI) which has recently been used for the synthesis of 3-2′-aminopropylindole.[16,17] The alkylation of ethyl malonate with methyl vinyl ketone in the presence of



(X)

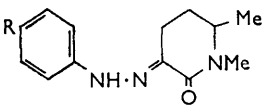


(XI)



(XII)

Triton B or sodium hydroxide gave the oxo-ester (XI) more conveniently than the published methods.[18,19] Catalytic hydrogenation of the diester in the presence of one equivalent of methylamine gave the *N*-methylpiperidone (XII; R = OEt). With an excess of methylamine, the methyl amide (XII; R = NHMe) was also formed. The acid (XII; R = OH), formed by mild alkaline hydrolysis of the ester, underwent a normal Japp–Klingemann reaction with benzenediazonium chloride, to give the hydrazone (XIII; R = H) only part of which was crystalline. Since, however, only one product, (XIV; R = H), was obtained on cyclisation with ethanolic hydrogen chloride, it is probable that the hydrazone occurred in two isomeric forms (see below; cf. ref. 17). The lactam (XIV; R = H) was submitted to vigorous alkaline hydrolysis, to give a solution of the amino-acid (XV; R = H) which was decarboxylated to the base (27) by prolonged heating with 6N-sulphuric acid.



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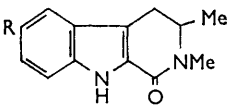

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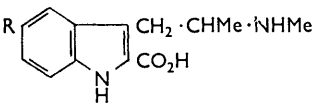
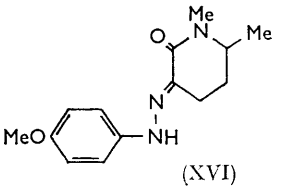


(XV)

A similar synthesis from *p*-methoxybenzenediazonium chloride gave two isomeric crystalline hydrazones (XIII; R = OMe), m. p. 187° and 68—70° (cf. ref. 17). Their structures are considered to be (XVI) and (XVII), respectively, on the grounds that the



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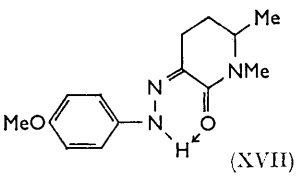
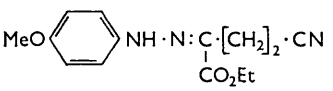


(XVII)



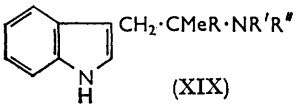
(XVIII)

low-melting form has its main ultraviolet maximum at a higher wavelength than that of the high-melting form. This agrees with the findings of Henecka *et al.*[20] who examined the

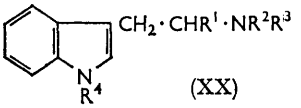
[12] H. B. Haas, A. G. Susie, and R. L. Heider, *J. Org. Chem.*, 1950, **15**, 8.
[13] Parke, Davis & Co., B.P. 974,895/1964.
[14] J. Novák, J. Ratusky, V. Šneberk, and F. Šorm, *Coll. Czech. Chem. Comms.*, 1957, **22**, 1848.
[15] R. A. Abramovitch and D. Shapiro, *J.*, 1956, 4589.
[16] A. G. Terzyan, R. R. Safrazbekyan, R. S. Sukasyan, and G. T. Tatevosyan, *Izvest. Akad. Nauk Armyan. S.S.R. Khim. Nauki*, 1961, **14**, 261 (*Chem. Abs.*, 1962, **57**, 8531).
[17] N. N. Suvorov, M. N. Preobrazhenskya, N. V. Uvarova, and Y. N. Sheinker, *Izvest. Akad Nauk S.S.S.R., Otdel. Khim. Nauk.* 1962, 729 and *Zhur. obshchei Khim.*, 1962, **32** 1567 (*Chem. Abs.*, 1962, **57**, 15,058; 1963, **58**, 4499).
[18] F. Korte and H. Machleidt, *Chem. Ber.*, 1958, **90**, 2143.
[19] N. C. Ross and R. Levine, *J. Org. Chem.*, 1964, **29**, 2350; T. A. Spencer, M. D. Newton, and S. W. Baldwin, *ibid.*, p. 789.
[20] H. Henecka, H. Timmler, R. Lorenz, and W. Geiger, *Chem. Ber.*, 1957, **90**, 1065.

corresponding forms of the hydrazone (XVIII). Infrared spectra confirm these structures, the high-melting (*trans*) form having the CO band at 1630 cm.$^{-1}$ whereas chelation in the low-melting (*cis*) isomer causes a shift to 1610 cm.$^{-1}$. The crystalline hydrazone (XIII; R = H) has the CO band at 1632 cm.$^{-1}$ and is presumably the *trans*-form. Both stereoisomers, (XVI) and (XVII), gave the same lactam (XIV; R = OMe) on cyclisation with ethanolic hydrogen chloride, and vigorous hydrolysis of this lactam gave a solution of the amino-acid (XV; R = OMe). Conditions for the decarboxylation were somewhat critical, and it was found that, whilst with 4·5—5N-sulphuric acid the 5-methoxy-amine (40) was obtained, more concentrated acid caused demethylation to the corresponding phenol (42). The latter was isolated as the creatinine sulphate double salt.

The remaining *N*-alkyltryptamines were prepared by various methods. The isopropyl derivative (30), (XIX; R = R′ = H, R″ = $CHMe_2$), was obtained by the reductive alkylation of isopropylamine with indol-3-ylacetone, and the benzyl derivatives (32), (XIX; R = R′ = H, R″ = $PhCH_2$), and (37), (XIX; R = Me, R′ = H, R″ = $PhCH_2$), were obtained by the hydrogenation of the Schiff bases formed from the appropriate primary amines and benzaldehyde. Treatment of the former of these benzyl derivatives with ethylene oxide gave the amino-alcohol (XIX; R = H, R′ = $[CH_2]_2$·OH, R″ = $PhCH_2$) which



(XIX)



(XX)

was catalytically debenzylated to the ethanolamine (33), (XIX; R = R″ = H, R′ = $[CH_2]_2$·OH). This method was considered preferable to the simple treatment of the primary base with ethylene oxide as it avoided possible disubstitution.

The *NN*-dimethyltryptamine (48), (XX; $R^1 = R^2 = R^3$ = Me, R^4 = H)* and the *N*-methyltryptamine (49), (XX; $R^1 = R^2 = R^4$ = H, R^3 = Me),[21] were made from the respective primary amines by formylation and reduction with lithium aluminium hydride. The 1-methyltryptamine (50), (XX; $R^1 = R^4$ = Me, $R^2 = R^3$ = H), prepared by the aklylation of the sodium derivative of 3-2′-aminopropylindole in liquid ammonia, had a higher melting point than that reported for the same product prepared by another method.[22]

Experimental

Light petroleum had b. p. 60—80°. Ether solutions were dried with activated calcium sulphate (Hydrite). Ultraviolet spectra were determined for ethanol solutions using a Perkin-Elmer 137 or Unicam S.P. 700 spectrophotometer. Infrared measurements were made using a Perkin-Elmer 21 (sodium chloride prism) or 237 (grating) spectrophotometer. Products were colourless, and salts were recrystallised from ethanol–ether, unless otherwise stated.

Indole-3-aldehydes.—The following substituted indole-3-aldehydes were made by reaction of the indoles with dimethylformamide and phosphorus oxychloride.[23] They were recrystallised from ethanol.

4-*Methyl*, m. p. 198—202° (82%) (lit.,[24] 192—194°) (Found: C, 75·6; H, 5·7. $C_{10}H_9NO$ requires C, 75·4; H, 5·70%). 6-*Methyl*, m. p. 190—192° (77%) (Found: C, 75·7; H, 5·3%). 7-*Methyl*, m. p. 212—214° (lit.,[24] 206—208°) (Found: C, 75·4; H, 5·85%). 5,7-*Dichloro*, m. p. 227—230° (96%) (Found: C, 50·5; H, 2·5. $C_9H_5Cl_2NO$ requires C, 50·5; H, 2·35%).

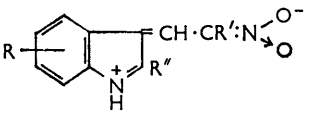
The Nitronates (II).—The *nitronates* (Table 1) were made by condensation of the indole-3-aldehydes with nitroalkanes, and crystallised from ethanol as orange-yellow solids.[2a]

Nitroalkylindoles.—The nitroalkylindoles (Table 2) were made by one or other of the methods given below. They were obtained as pale yellow syrups or white solids.

* Compounds 48—50 are not in the Tables.

[21] T. Hoshino and K. Shimodaira, *Annalen*, 1935, **520**, 26.
[22] R. V. Heinzelman, W. C. Anthony, D. A. Lyttle, and J. Szmuszkovicz, *J. Org. Chem.*, 1960, **25**, 1557.
[23] G. F. Smith, *J.*, 1954, 3842.
[24] Sandoz, Belg. P. 613,296/1962.

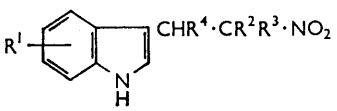
TABLE 1



R	R′	R″	M. p.	Yield (%)	Found (%) N	Formula	Required (%) N
H	Me	Me	159—160°	63	12·7	$C_{12}H_{12}N_2O_2$	13·0
4-Me	Me	H	187—188 *	75	13·0	$C_{12}H_{12}N_2O_2$	13·0
6-Me	Me	H	172—173	66	13·1	$C_{12}H_{12}N_2O_2$	13·0
7-Me	Me	H	175 †	65	12·7	$C_{12}H_{12}N_2O_2$	13·0
5,7-Cl_2	Me	H	227—230	89	10·3	$C_{11}H_8Cl_2N_2O_2$	10·3
5-MeO	Et	H	113—114	60	10·9	$C_{13}H_{14}N_2O_3$	11·4
6-MeO	Et	H	152—153	65	11·1	$C_{13}H_{14}N_2O_3$	11·4

* Lit.,[24] 184—185°. † Lit.,[24] 170—171°.

TABLE 2



	R¹	R²	R³	R⁴	M. p. or b. p./mm.	Solvent	Method	Yield (%)
A.	H	$-[CH_2]_5-$		H	163—164°	EtOH	A(2)	69
B.	H	Me	CH_2OH	H	150/10^{-5} *	—	A(2)	
C.	H	Me	Me	Me	120—130/10^{-4}	—	B	71
D.	4-Me	Me	Me	H	130—131	C_6H_6–pet.	B	76
E.	6-Me	H	Me	H	125/10^{-4}	—	A(1)	81
F.	6-Me	Me	Me	H	84—86	C_6H_6–pet.	A(2)	73
G.	7-Me	Me	Me	H	104—107	,,	B	93
H.	5-MeO	H	Me	H	93—94	C_6H_6	A(1)	88
I.	5-MeO	Me	Me	H	84—85	,,	A(2)	83
J.	6-MeO	H	Me	H	80—82	C_6H_6–pet.	A(1)	70 †
K.	6-$PhCH_2$·O	H	Me	H	108	C_6H_6	A(1)	75
L.	5-Cl	H	Me	H	60	C_6H_6–pet.	A(1)	82
M.	5-Cl	Me	Me	H	92—93	,,	A(2)	81
N.	6-Cl	Me	Me	H	93—95	,,	B	76

	Found (%) C	H	N	Formula	Required (%) C	H	N
A.	69·8	7·0	10·9	$C_{15}H_{18}N_2O_2$	69·7	7·0	10·9
B.	—	—	12·7	$C_{12}H_{14}N_2O_3$	—	—	12·0
C.	—	—	11·7	$C_{13}H_{16}N_2O_2$	—	—	12·1
D.	67·5	6·85	11·6	$C_{13}H_{16}N_2O_2$	67·2	6·95	12·1
E.	—	—	13·5	$C_{12}H_{14}N_2O_2$	—	—	12·85
F.	67·4	7·0	11·9	$C_{13}H_{16}N_2O_2$	67·2	6·95	12·1
G.	67·3	6·9	12·0	$C_{13}H_{16}N_2O_2$	67·2	6·95	12·1
H.	—	—	11·7	$C_{12}H_{14}N_2O_3$	—	—	12·0
I.	—	—	11·2	$C_{13}H_{16}N_2O_3$	—	—	11·3
J.	61·3	6·2	12·0	$C_{12}H_{14}N_2O_3$	61·5	6·0	12·0
K.	—	—	8·8	$C_{18}H_{18}N_2O_3$	—	—	9·0
L.	—	—	11·7	$C_{11}H_{11}ClN_2O_2$	—	—	11·7
M.	—	—	11·0	$C_{12}H_{13}ClN_2O_2$	—	—	11·1
N.	57·4	5·4	11·1	$C_{12}H_{13}ClN_2O_2$	57·0	5·1	11·1

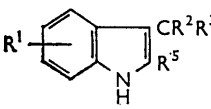
* Air-bath temperature. † The 6-methoxygramine used had m. p. 93—94·5°, in close agreement with N. N. Suvorov *et al.*, *Zhur. obshchei Khim.*, 1960, **30**, 3112 (*Chem. Abs.*, 1961, **55**, 17,621). E. D. Bergmann and E. Hoffmann (*J.*, 1962, 2828) report 85°.

3-2′-*Nitropropylindole.—General method A*(1). A stirred solution of sodium (75·9 g., 3·3 moles) in dry ethanol (2 l.) was treated with nitroethane (743 g., 9·9 moles) followed by gramine (522 g., 3 moles). The mixture was kept at 30—35° while a solution of methyl sulphate (564 ml., 6 moles) in dry ethanol (500 ml.) was added during ¾ hr., with slight cooling when necessary. After stirring for a further ½ hr., the virtually clear solution was almost neutral. It was poured

into excess water and extracted several times with ether. The extract was washed with 2N-acetic acid, water, ammonia, and water, dried, and evaporated. Distillation of the residue yielded 3-2′-nitropropylindole (460 g., 75%) as a yellow syrup, b. p. 142—144°/10^{-3} mm., n_D^{21} 1·5865. The picrate crystallised from benzene–light petroleum, m. p. 87—89° (lit.,[3] 171—172°) (Found: C, 47·4; H, 3·9; N, 16·2. Calc. for $C_{17}H_{15}N_5O_9$: C, 47·1; H, 3·5; N, 16·2%). This compound was also made (78%), on a smaller scale, by the method of Troxler, Seeman, and Hoffman.[4]

3-(2-*Methyl*-2-*nitropropyl*)*indole*.—*General method A*(2). Sodium (31·6 g., 1·1 × 1·25 moles) in dry ethanol (1870 ml.) was treated with 2-nitropropane (122·4 g., 1·1 × 1·25 moles), followed

TABLE 3



(R^2,R^3,R^5 = H, except where otherwise indicated)

No.	R^1	R^4		M. p. or b. p./mm.	Solvent	Method	Yield (%)
(1) *	H	H	R^2 = Me	193—195°	EtOH–EtAc	X	47
(2)	H	Me	R^5 = Me	120—125/10^{-5}	—	C	38
(3)	H	Me	R^2 = Me	103—106 (*a*)	C_6H_6–pet.	X	84
(4)	4-Me	Me		140—142 (*b*)	,,	C	63·5
(5)	6-Me	Me		92—93	C_6H_6	C	61
(6) (*c*)	7-Me	Me		108—109	,,	C	58
(7) *	6-Et	H		249·5—251·5	EtOH–EtAc	X	67
(8) (*d*)	5-MeO	Et		106—107	C_6H_6–pet.	C	47
(9) *	6-MeO	Me		139—141	— (*e*)	D	65
(10) *	6-MeO	Et		132—134	—	C	50
(11) * (*f*)	6-$PhCH_2$·O	Me		*ca.* 270	H_2O	D	47
(12) *	5-$PhCH_2$·O-7-Me	H		233—234	,,	X	42
(13) *	5-OH-7-Me	H		*ca.* 245 (decomp.)	,,	X	69
(14)	6-Cl	Me		122—123	C_6H_6	C	66
(15) (*h*)	5,7-Cl_2	Me		162—165	EtOH	C	61

	Found (%)				Required (%)		
No.	C	H	N	Formula	C	H	N
(1) *	62·5	7·2	13·3	$C_{11}H_{15}ClN_2$	62·7	7·1	13·3
(2)	76·25	8·6	—	$C_{12}H_{16}N_2$	76·5	8·6	—
(3)	76·5	8·6	15·1	$C_{12}H_{16}N_2$	76·5	8·6	14·9
(4)	76·5	8·5	—	$C_{12}H_{16}N_2$	76·5	8·6	—
(5)	76·65	8·6	—	$C_{12}H_{16}N_2$	76·5	8·6	—
(6) (*c*)	—	—	14·7	$C_{12}H_{16}N_2$	—	—	14·9
(7) *	62·6	7·75	12·7	$C_{12}H_{17}ClN_2$,0·25H_2O	62·9	7·6	12·2
(8) (*d*)	—	—	13·2	$C_{13}H_{18}N_2O$	—	—	12·8
(9) *	60·1	6·4	—	$C_{16}H_{20}N_2O_5$	60·0	6·3	—
(10) *	61·3	6·6	—	$C_{17}H_{22}N_2O_5$	61·1	6·6	—
(11) * (*f*)	64·0	6·7	—	$C_{36}H_{44}N_4O_7S$	63·9	6·6	—
(12) *	61·1	6·3	8·1	$C_{36}H_{48}N_4O_9S$	60·7	6·8	7·9
(13) *	41·9	6·0	16·1	$C_{15}H_{23}N_5O_6S$,1·5H_2O	42·0	6·1	16·3
(14)	—	—	13·4	$C_{11}H_{13}ClN_2$ (*g*)	—	—	13·4
(15) (*h*)	54·3	5·1	—	$C_{11}H_{12}Cl_2N_2$	54·3	5·0	—

* (1) and (7) obtained as the *hydrochlorides*, (9) and (10) as the *maleates*, (11) as the *sulphate monohydrate*, (12) as the *sulphate trihydrate*, and (13) as the *creatinine sulphate complex* + 1·5H_2O. (*a*) A. V. Mkhitaryan *et al.* (*Chem. Abs.*, 1963, **59**, 2753) give m. p. 94—96°. (*b*) Lit.,[24] m. p. 137—138°, without analysis. (*c*) *Hydrochloride*, m. p. 215—218° (Found: C, 63·8; H, 7·6. $C_{12}H_{16}N_2$,HCl requires C, 64·1; H, 7·6%). C. S. Franklin and A. C. White (*J.*, 1963, 1337) give m. p. 106—107° without analysis. Sandoz [24] have described only the maleate. (*d*) *Hydrochloride*, m. p. 226—227° (from EtOH) (Found: C, 61·4; H, 7·6. $C_{13}H_{18}N_2O$,HCl requires C, 61·3; H, 7·5%). The acetates of this compound and compound (10) have been described by J. Hester (*J. Medicin. Chem.*, 1964, **7**, 276). (*e*) The base, b. p. 132°/10^{-5} mm., did not crystallise. The picrate had m. p. 225° (decomp.). Laboratories Francois de Chimiotherapie (B.P. 887,914), give m. p. 227°. (*f*) Debenzylation yielded a product isolated as the creatinine sulphate complex, m. p. 130—132° (from aqueous ethanol). Despite repeated recrystallisation this did not give a satisfactory analysis for the expected 3-2′-aminopropyl-6-hydroxyindole salt. (*g*) Found: Cl, 16·9. Reqd., 17·0%. The hydrochloride had m. p. 218—220° (lit.,[25] 220—222°) (Found: C, 54·1; H, 6·0. Calc. for $C_{11}H_{13}ClN_2$,HCl: C, 53·9; H, 5·75%). (*h*) *Hydrochloride* (from 0·01N-HCl), m. p. 292—295° (decomp.) (Found: Cl, 38·0; N, 10·2. $C_{11}H_{12}Cl_2N_2$,HCl requires Cl, 38·0; N, 10·0%).

by gramine (217·5 g., 1·25 moles). Methyl sulphate (236 ml., 2 × 1·25 moles) in ethanol (236 ml.) was added as previously described, and the mixture stirred for ½—1 hr. It was then evaporated *in vacuo* and treated with water and ether. The ether layer was washed, dried, and evaporated as in method A(1), and the residue recrystallised from benzene–light petroleum. The 3-(2-methyl-2-nitropropyl)indole (225 g., 83%) had m. p. 74—75° (lit.,[3] 66·5—68°) (Found: N, 13·0. Calc. for $C_{12}H_{14}N_2O$: N, 12·85%).

General method B (based on that of Snyder and Katz). Gramine (81 g., 0·465 mole), 2-nitropropane (405 ml.), and sodium hydroxide (20·4 g., 1·1 × 0·465 mole) were stirred and boiled under nitrogen for 20 hr. The mixture was cooled, and treated with excess 2N-acetic acid and ether, and the solvent layer was washed with 2N-acetic acid and water, dried, and evaporated. The excess nitropropane was evaporated *in vacuo*, and the residue recrystallised from benzene–light petroleum. The product, m. p. 73° (92 g., 91%), was identical with that made by method A(2). In a few cases the products were purified by chromatography on alumina.

α-Monosubstituted Tryptamines.—The *α-monosubstituted tryptamines* (Table 3) were made either by reducing the nitronates (II) with lithium aluminium hydride in tetrahydrofuran [2] (*Method C*), or by hydrogenating the appropriate nitroalkylindoles (*Method D*). In the latter case the starting materials were either reduced in ethanol in presence of platinum oxide at 20°/1 atm., or preferably in ethanol or ethanolic ammonia in presence of Raney nickel. When W7 nickel was used the reductions were carried out at 20°/1 atm., but with W2 nickel it was preferred to work at elevated temperature and pressure, *e.g.*, 50—100°/50 atm. The bases were obtained after acid extraction, and were either recrystallised or converted directly into salts.

Compounds marked " X " were made by special methods given below. Compound (16) could not be accommodated in the Table; its preparation and properties are given separately.

3-(2-*Amino*-1-*methylethyl*)*indole* (1).—(*a*) A solution of 3-(1-isopropylaminoethyl)indole [25] (4·04 g., 0·02 mole) in ethanol (25 ml.) was added to a solution of potassium cyanide (1·42 g., 0·022 mole) in water (10 ml.), and the resulting solution was heated under reflux for 12 hr. during which time isopropylamine was evolved. The solution was evaporated and the residue was dissolved in ethyl acetate, washed with 2N-hydrochloric acid, water, and sodium hydrogen carbonate solution, and dried. The residue from the dried extract (3·15 g.) was adsorbed on to alumina and eluted with ethyl acetate, to give a mobile gum (1·39 g.), whose infrared spectrum showed it to be the nitrile. On further elution with ethyl acetate containing 5—10% of ethanol, the related amide was obtained as a glass (1·21 g.). The two crude products were combined in solution in dry ether (270 ml.) and reduced with lithium aluminium hydride (2·0 g.) under reflux for 2½ hr. The excess of lithium aluminium hydride was decomposed with ethyl acetate (2 ml.), and sodium hydroxide solution (2N; 10 ml.) added cautiously. The solution was filtered and the basic product isolated as a colourless oil. The picrate crystallised from ethanol as orange polyhedra, m. p. 222·5—223·5° (lit.,[26] 224°). The *hydrochloride* crystallised from ethanol–ethyl acetate as rhombohedra.

(*b*) A mixture of 3-(1-isopropylaminoethyl)indole (4·04 g., 0·02 mole) and sodium cyanide (1·1 g., 0·022 mole) in ethylene glycol (20 ml.) was heated at 150° under nitrogen until isopropylamine was no longer detectable. The ethylene glycol was evaporated at 140°(bath)/10 mm., and the residue treated with water and extracted with ether. The extracts were washed with 2N-hydrochloric acid, water, and 2N-sodium carbonate. The residue from the dried extracts was purified by chromatography as in (*a*), to give the nitrile (2·88 g., 85·2%). No amide was formed under these conditions. The nitrile was reduced in refluxing ethanol (150 ml.) with sodium (7·0 g.) added during 30 min. The cooled solution was treated with water (33 ml.) and concentrated hydrochloric acid (33 ml.) and evaporated to small bulk. The residue was partitioned between ether and water and the aqueous phase basified and extracted with ether. The residue from the dried extracts gave a hydrochloride (1·03 g., 29%) identical with that obtained in (*a*). In another reaction (0·05 mole), the crude nitrile (76%) was reduced by hydrogenation in ethanolic ammonia (125 ml.) in the presence of Raney nickel W7, to give the amine hydrochloride (47%).

3-(2-*Amino*-1-*methylpropyl*)*indole* (3).—The crude 3-(1-methyl-2-nitropropyl)indole, prepared by method B from 3-(1-isopropylaminoethyl)indole (10·1 g., 0·05 mole) and nitroethane, was hydrogenated in the presence of Raney nickel W7 in ethanolic ammonia, to give the *base* (5·35 g.).

[25] H. R. Snyder and D. S. Matteson, *J. Amer. Chem. Soc.*, 1957, **79**, 2219.
[26] K. Eiter and O. Svierak, *Monatsh.*, 1952, **83**, 1453.

5-Ethyl-2-methylformanilide.—5-Ethyl-2-methylaniline (34·1 g.), prepared from *o*-toluidine in three stages [27] (cf. ref. 28), was heated at 100° with formic acid (13·6 ml.) for 16 hr. The hot solution was treated with ethyl acetate (100 ml.) and chilled. The solid was collected, washed with ethyl acetate, and dried. The mother-liquors were washed with 2N-hydrochloric acid and water, dried, and concentrated, to give a second crop. The *anilide* (33·9 g., 82·4%) had m. p. 109·5—110·5° (Found: C, 73·1; H, 7·7; N, 8·6. $C_{10}H_{13}NO$ requires C, 73·5; H, 8·0; N, 8·6%).

6-Ethylindole.—5-Ethyl-2-methylformanilide (68·8 g., 0·42 mole) was added to a solution of potassium t-butoxide in t-butyl alcohol [from potassium (24·6 g., 0·63 mole) and t-butyl alcohol (500 ml.)] in a nitrogen atmosphere in the apparatus described by Tyson.[29] The alcohol was distilled off and the residue heated in a metal-bath. At *ca.* 290° the reaction became exothermic with vigorous gas evolution, and at 310° some 5-ethyl-2-methylaniline distilled. The bath was held at 340° for 25 min. by which time a dark brown solid remained in the reaction flask. This residue was cooled under nitrogen, treated with water (250 ml.), and steam-distilled (8 l.). The distillate was saturated with sodium chloride and extracted with ether. The extracts were washed with 2N-hydrochloric acid, water, sodium carbonate solution, and water, dried, and evaporated. The residue was distilled *in vacuo*, to give *6-ethylindole* (27·8 g., 45·8%), b. p. 78—82°/0·07 mm., which crystallised on standing (m. p. 45—46°) (Found: C, 82·1; H, 7·5; N, 9·6. $C_{10}H_{11}N$ requires C, 82·6; H, 7·5; N, 9·65%). Gas chromatography showed the product to be homogeneous. $\lambda_{max.}$ 220·9, 271·9, 281·7, and 292·4, with inflexions at 274—276 and 285·0 mμ, and $\lambda_{min.}$ 243·8, 278·8, and 289·9 mμ (log ε 4·62, 3·83, 3·81, 3·73, 3·82, 3·78, 3·33, 3·79 and 3·66). 5-Ethyl-2-methylaniline (30·4 g.) was recovered.

6-Ethyltryptamine (7).—6-Ethylgramine was prepared from 6-ethylindole in 75% yield (cf. ref. 30) and was converted, without purification, into the nitrile (60%) by the sodium cyanide–ethylene glycol method given above, b. p. 138—140°/5·2 × 10^{-5} mm., m. p. 66·5—68·5°. The nitrile was reduced in ethanolic ammonia at 100°/65 atm. in the presence of Raney nickel W7. Treatment of the ethyl acetate extracts of the base with hydrogen chloride gave the *hydrochloride* as square plates.

3-2′-Aminoethyl-5-benzyloxy-7-methylindole (12).—(a) *5-Benzyloxy-3-dimethylaminomethyl-7-methylindole.* A mixture of 5N-aqueous dimethylamine solution (15 ml., 1·1 × 0·0683 mole) and glacial acetic acid (27 ml.) prepared at 0—10° was treated with 40% aqueous formaldehyde solution (5·6 ml., 1·1 × 0·0683 mole). 5-Benzyloxy-7-methylindole [31] (16·2 g., 0·0683 mole) was added portionwise with stirring, keeping the temperature at about 20°. The mixture was stirred for 18 hr., diluted with water, and filtered from some insoluble matter. The solution was made alkaline with 10N-ammonia, giving the *base* (16·5 g., 81·8%), m. p. 129—131° (from ethyl acetate) (Found: N, 9·2. $C_{19}H_{22}N_2O$ requires N, 9·5%).

(b) *5-Benzyloxy-7-methylindolylacetonitrile.* The above gramine derivative (7·9 g., 0·0268 mole) was added in small portions to a stirred solution of dimethyl sulphate (12·7 ml., 5 equiv.) in dry benzene (65 ml.), after which the mixture was heated for 1 hr. at 50°. The semi-solid quaternary salt was extracted with water (65 ml.) at 50°, and the solution was at once treated with potassium cyanide (5·2 g., 3 × 0·0268 mole) after which it was stirred and heated at 80—85° until evolution of trimethylamine had ceased (2½—3 hr.). The cooled mixture was extracted with ether, and the extract was washed with 2N-acetic acid, sodium hydrogen carbonate solution, and water. The dried extract yielded the *nitrile* (5·64 g., 76%), needles, m. p. 117—118° (from benzene–light petroleum) (Found: N, 9·9. $C_{18}H_{16}N_2O$ requires N, 10·1%).

(c) *3-2′-Aminoethyl-5-benzyloxy-7-methylindole.* The above nitrile (5·32 g., 0·0192 mole) in methanolic ammonia (25%; 53 ml.) was hydrogenated at 60°/80 atm. for 6 hr. in the presence of Raney nickel W2 (1—1·5 ml. of settled catalyst). The solution was filtered and diluted to 125 ml. A portion (25 ml.) was evaporated *in vacuo*, treated with 2N-sulphuric acid (1·92 ml.) and water (50 ml.), and heated to boiling. The solution was treated with charcoal, filtered hot, and allowed to cool, giving the *sulphate* (0·74 g., 42%), m. p. 233—234°.

3-2′-Aminoethyl-5-hydroxy-7-methylindole (13).—The remaining 100 ml. of solution from the above reduction were similarly evaporated and treated with 2N-sulphuric acid (7·7 ml.) and water

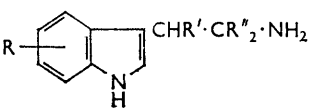
[27] N. P. Buu-Hoi, B. Eckert, and R. Royer, *Compt. rend.*, 1951, **233**, 627.
[28] Huang-Minlon, *J. Amer. Chem. Soc.*, 1946, **68**, 2487.
[29] F. T. Tyson, *J. Amer. Chem. Soc.*, 1941, **63**, 2024.
[30] H. N. Rydon, *J.*, 1948, 705.
[31] Part III, B. Heath-Brown and P. G. Philpott, *J.*, 1965, 7185.

(200 ml.). The solution was then treated with charcoal and hydrogenated at 70—75°/1 atm. in the presence of 20% palladium–charcoal (0·25 g.). Two equivalents of hydrogen were absorbed in 2—3 hr. The filtered solution was evaporated *in vacuo* to 5—10 ml. and treated with a solution of creatinine sulphate (2·5 g.) in water (5 ml.). After keeping at 0° for 18 hr. the product was filtered off and washed with ice–water, giving the *creatinine sulphate complex* (4·22 g.); it formed needles.

2-3′-*Indolylcyclohexylamine* (16).—(*a*) 2-3′-*Indolylcyclohexanol.* Methylmagnesium iodide (from 0·37 mole of magnesium) in dry ether (370 ml.) was stirred at 0° while indole (43·3 g., 0·37 mole) in dry ether (200 ml.) was added. The mixture was heated under reflux for ½ hr. and cooled, after which a solution of cyclohexene oxide (36·1 g., 0·37 mole) in dry benzene (72 ml.) was added dropwise with stirring. After 18 hr. at 20° the solvent was evaporated and the residue heated at 100° for 4 hr. The dark complex was decomposed with warm benzene and ammonium chloride solution, and the benzene layer washed with 2N-acetic acid, sodium hydrogen carbonate solution, and water, and evaporated to 100 ml. The product which separated on standing was filtered off and washed with ethyl acetate. By evaporation of the liquors followed by distillation at 150°(air-bath)/10^{-5} mm. and crystallisation of the distillate, a further crop was obtained (total 19·0 g., 24%). The *alcohol* crystallised from ethyl acetate–light petroleum, m. p. 157° (Found: C, 78·5; H, 7·85; N, 6·3. $C_{14}H_{17}NO$ requires C, 78·1; H, 8·0; N, 6·5%), $\nu_{max.}$ (Nujol) 3535, 1100 (OH), 3270 cm.$^{-1}$ (NH).

(*b*) 2-3′-Indolylcyclohexanol (19·0 g., 0·088 mole) was suspended in dry benzene (500 ml.) and treated with phosphorus tribromide (2·8 ml., ⅓ × 0·088 mole) in benzene (50 ml.). The addition was made with cooling and the mixture was stirred for 4 hr. at 15—20°. Ice–water

TABLE 4



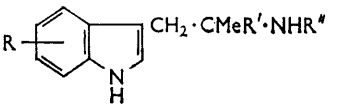
No.	R	R′	R″	M. p.	Solvent	Yield (%)
(17) *	H	H	Me_2	203—205°	EtOH–EtAc	100 (*a*)
(18)	H	Me	Me_2	137—139	EtAc–pet.	20
(19)	H	H	$-[CH_2]_5-$	167—168	C_6H_6	54·7 (*b*)
(20) *	4-Me	H	Me_2	258—260	EtOH–EtAc	65
(21) *	6-Me	H	Me_2	258—259	,,	67
(22) *	7-Me	H	Me_2	296—297	,,	68
(23)	5-MeO	H	Me_2	117—118	C_6H_6	77 (*c*)
(24) *	6-MeO	H	Me_2	268—270	EtOH–EtAc	88
(25)	5-Cl	H	Me_2	150—152	C_6H_6	50 (*d*)
(26) *	6-Cl	H	Me_2	275—277	EtOH–EtAc	91 (*e*)

	Found (%)				Required (%)		
No.	C	H	N	Formula	C	H	N
(17) *	63·7	7·55	12·15	$C_{12}H_{17}ClN_2$	64·1	7·6	12·5
(18)	77·05	9·0	13·7	$C_{13}H_{18}N_2$	77·2	8·9	13·9
(19)	—	—	12·3	$C_{15}H_{20}N_2$	—	—	12·3
(20) *	65·0	7·8	11·8	$C_{13}H_{19}ClN_2$	65·4	8·0	11·7
(21) *	65·2	8·0	11·45	$C_{13}H_{19}ClN_2$	65·4	8·0	11·7
(22) *	65·5	8·0	11·7	$C_{13}H_{19}ClN_2$	65·4	8·0	11·7
(23)	—	—	12·35	$C_{13}H_{18}N_2O$	—	—	12·8
(24) *	61·4	7·4	11·0	$C_{13}H_{19}ClN_2O$	61·3	7·5	11·0
(25)	—	—	12·35	$C_{12}H_{15}ClN_2$	—	—	12·6
(26) *	55·35	6·1	10·6	$C_{12}H_{16}Cl_2N_2$	55·6	6·2	10·8

* Compound isolated as the *hydrochloride.* (*a*) The free base had m. p. 130—131° (lit.,[3] 130—131°). (*b*) *Hydrochloride* (from water), m. p. 281—282° (Found: C, 68·1; H, 8·0. $C_{15}H_{20}N_2$,HCl requires C, 68·0; H, 8·0%).. The mother-liquors from the base contained a by-product, m. p. 140° (from ethanol), possibly the N-*ethyl derivative* (Found: C, 79·9; H, 8·7; N, 10·9. $C_{17}H_{24}N_2$ requires C, 79·6; H, 9·4; N, 10·9%); its *hydrochloride* (from water) had m. p. *ca.* 318° (Found: C, 70·0; H, 7·9; Cl, 12·3; N, 9·8. $C_{17}H_{24}N_2$,HCl requires C, 69·7; H, 8·6; Cl, 12·1; N, 9·6%). (*c*) *Hydrochloride,* m. p. 237—239° (Found: C, 61·0; H, 7·3; N, 10·9. $C_{13}H_{18}N_2O$,HCl requires C, 61·3; H, 7·5; N, 11·0%). (*d*) *Hydrochloride,* m. p. 266° (Found: C, 55·3; H, 6·5; Cl, 27·7; N, 11·1. $C_{12}H_{15}ClN_2$,HCl requires C, 55·6; H, 6·2; Cl, 27·4; N, 10·8%). (*e*) Obtained by hydrogenation of the nitro-compound in 10% EtOH–NH_3 at 20°/1 atm. in the presence of Raney Nickel W7; no dehalogenation occurred.

was added and the benzene layer was washed with sodium hydrogen carbonate solution, dried and evaporated. The crude bromide was then heated for 8 hr. at 120° in an autoclave with ethanolic ammonia (250 ml.; 10%). After evaporation the residue was shaken vigorously with benzene and 2N-hydrochloric acid (100 ml.), giving a sticky solid. The latter was dissolved by heating with a further acid extract, and the solution was treated with charcoal and cooled

TABLE 5



No.	R	R′	R″	M. p. or b. p./mm.	Yield (%)	B. p./mm. of base
(27)	H	H	Me	92—93°	X 52	—
(28)	H	H	Et	$150/10^{-3}$	— (*a*)	—
(29)	H	H	Pr^n	$150/10^{-4}$	66·5 (*b*)	—
(30) *	H	H	Pr^i	221—222	X —	*ca.* $110/10^{-5}$
(31) *	H	H	Bu^n	178—180	29	*ca.* $150/10^{-5}$
(32) *	H	H	$PhCH_2$	177—179	X 78	$170/10^{-5}$
(33)	H	H	$CH_2{\cdot}CH_2{\cdot}OH$	*ca.* $150/10^{-5}$	X 59	—
(34)	H	H	CO_2Et	$145—148/10^{-5}$	X 65	—
(35)	H	H	$CH_2{\cdot}CF_3$	120—130/10^{-5} (air-bath)	— (*c*)	—
(36) *	H	Me	Me	193—195	— (*d*)	—
(37) *	H	Me	$PhCH_2$	250—252	X 70	—
(38)	4-Me	H	Me	135—136	26	—
(39) *	6-Me	H	Me	145	44·5	140/0·2
(40) *	5-MeO	H	Me	125—127	X 57	$140/10^{-5}$
(41) *	6-MeO	H	Me	140—142	43	$126/10^{-5}$
(42) *	5-OH	H	Me	175—177	X —	*ca.* 220/10^{-5} (air-bath)
(43) *	5-Cl	H	Me	133—135	38	—
(44)	6-Cl	H	Me	100—102	63 (*e*)	—
(45) *	6-Cl	Me	Me	196—199	72 (*f*)	—
(46)	5,7-Cl_2	H	Me	149—150	45·5	—

	Found (%)				Required (%)		
No.	C	H	N	Formula	C	H	N
(27)	76·4	8·5	14·9	$C_{12}H_{16}N_2$	76·5	8·6	14·9
(28)	—	—	13·2	$C_{13}H_{18}N_2$	—	—	13·85
(29)	—	—	12·4	$C_{14}H_{20}N_2$	—	—	12·95
(30) *	66·15	8·3	—	$C_{14}H_{21}ClN_2$	66·5	8·4	—
(31) *	67·4	8·7	10·5	$C_{15}H_{23}ClN_2$	67·5	8·7	10·5
(32) *	62·95	6·8	—	$C_{19}H_{24}N_2O_3S$	63·3	6·7	—
(33)	71·9	8·4	—	$C_{13}H_{18}N_2O$	71·5	8·3	—
(34)	68·45	7·5	11·1	$C_{14}H_{18}N_2O_2$	68·3	7·4	11·4
(35)	60·7	5·9	—	$C_{13}H_{15}F_3N_2$	60·9	5·9	—
(36) *	65·1	7·8	11·5	$C_{13}H_{18}ClN_2$	65·4	8·0	11·7
(37) *	72·3	7·5	9·1	$C_{19}H_{23}ClN_2$	72·5	7·3	8·9
(38)	77·1	9·0	13·6	$C_{13}H_{18}N_2$	77·2	9·0	13·85
(39) *	64·2	7·0	8·95	$C_{17}H_{22}N_2O_4$	64·1	7·0	8·8
(40) *	60·7	6·7	8·4	$C_{17}H_{22}N_2O_5$	61·1	6·6	8·4
(41) *	61·6	6·8	—	$C_{17}H_{22}N_2O_5$	61·1	6·6	—
(42) *	44·2	6·2	—	$C_{16}H_{27}N_5O_7S$	44·3	6·3	—
(43) *	56·5	5·7	—	$C_{16}H_{19}ClN_2O_4$	56·7	5·7	—
(44)	—	—	12·4	$C_{12}H_{15}ClN_2$	—	—	12·6
(45) *	57·3	6·8	10·3	$C_{13}H_{18}Cl_2N_2$	57·1	6·6	10·8
(46)	56·1	5·55	—	$C_{12}H_{14}Cl_2N_2$	56·1	5·5	—

* The m. p., formulæ, and analyses refer to the following derivatives: *hydrochlorides* of (30), (31), (36), (37), and (45); *methanesulphonate* of (32); *maleates* of (39)—(41) and (43); *creatinine sulphate monohydrate complex* of (42), crystals (from ethanol–water) (Found: O, 26·0. Reqd. 25·85%). (*a*) *Hydrochloride* (from ethanol–ethyl acetate), m. p. 187—189° (Found: C, 65·1; H, 8·2. $C_{13}H_{18}N_2$,HCl requires C, 65·4; H, 8·0%). (*b*) *Hydrochloride*, m. p. 185° (Found: C, 66·3; H, 8·3. $C_{14}H_{20}N_2$,HCl requires C, 66·5; H, 8·4%). (*c*) The intermediate *di(trifluoracetyl) derivative*, m. p. 139—141° (from benzene), was presumably substituted on both nitrogen atoms. The ind-*N*-substituent was lost on reduction (Found: N, 7·8. $C_{15}H_{12}F_6N_2O_2$ requires N, 7·65%). (*d*) The intermediate *formyl derivative* had m. p. 111—113° (from ether–ethanol) (Found: C, 72·5; H, 6·9; N, 12·9. $C_{13}H_{16}N_2O$ requires C, 72·1; H, 7·5; N, 12·95%. (*e*) *Maleate*, m. p. 172—173° (Found: C, 57·1; H, 5·9. $C_{16}H_{19}ClN_2O_4$ requires C, 56·7; H, 5·7%). (*f*) The intermediate formyl derivative had m. p. 153·5—155·5°.

to 0°, giving the *hydrochloride* (5·6 g., 25·4%) which crystallised from water or from ethanol–ether, m. p. *ca.* 317° (decomp.) (Found: C, 66·8; H, 7·5. $C_{14}H_{18}N_2$,HCl requires C, 67·0; H, 7·6%). The free base had m. p. 183—184° (Found: C, 78·4; H, 8·5. Calc. for $C_{14}H_{18}N_2$: C, 78·5; H, 8·5%) (lit.,[8] m. p. 176—177°.)

αα-*Disubstituted Tryptamines*.—These *tryptamines* (Table 4) were made by general method D, with the exception of compound (25) whose preparation is described separately.

3-(2-*Amino*-2-*methylpropyl*)-5-*chloroindole* (25).—A solution of 5-chloro-3-(2-methyl-2-nitropropyl)indole (19·7 g., 0·078 mole) in ether (100 ml.) was added to lithium aluminium hydride (8·9 g., 3 × 0·078 mole) in ether (100 ml.). The mixture was stirred for 1½ hr., and then heated under reflux for 4 hr. After decomposition, the base was obtained by acid extraction and recrystallisation from benzene; distillation of the mother-liquors (b. p. 135°/10^{-4} mm.) yielded a further crop (total 8·7 g.).

N-*Alkyltryptamines*.—The majority of the N-*alkyltryptamines* (Table 5) were made from the primary amines by acylating with excess ethyl formate in an autoclave for 5—6 hr. at 100°, or by treating with the appropriate acid anhydride, or with the acyl chloride in pyridine. The acyl derivatives obtained as neutral products after appropriate extraction were reduced with lithium aluminium hydride in tetrahydrofuran. The bases were obtained by acid extraction. Yields are calculated from primary to secondary amine. Compounds marked " X " were made by special methods described below. Bases were recrystallised from benzene–light petroleum, or distilled. Compound (47) could not be accommodated in the Table and is described separately.

3-2′-*Methylaminopropylindole* (27).—(a) *From indol*-3-*ylacetone*. The starting material (m. p. 117—118°) was made by reducing α-methyl-β-indolenideniumethyl nitronate [2a] with iron dust and hydrochloric acid; the yield on a 1·5 mole scale was 58%; for the method see 5-methoxy-indol-3-ylactone (below). It could also be made by hydrating 3-prop-2′-ynylindole according to Williamson.[11] This acetylenic indole had b. p. 112—116°/0·25 mm., n_D^{20} 1·613, m. p. 32—33°; the *picrate* formed red-orange needles, m. p. 132—134° (Found: C, 53·0; H, 3·2. $C_{17}H_{12}N_4O_7$ requires C, 53·1; H, 3·15%).

Indol-3-ylacetone (173·2 g., 1 mole) and 33% ethanolic methylamine (470 ml., 5 moles) were hydrogenated at 100°/50 atm. in the presence of Raney nickel W2 (25 ml. of settled catalyst) until the pressure drop ceased. The solution was filtered and evaporated, and the residue was treated with excess aqueous acetic acid and extracted with ether. The ether yielded a small amount of 3-2′-hydroxypropylindole, b. p. 90—100°/10^{-5} mm., m. p. 44—45° (lit.,[14] 37·5°). The acid layer was treated with excess alkali and ether, and the ether extract was washed with water. The dried extract yielded a product which was distilled, b. p. 125—128°/10^{-4} mm. (165 g.). Recrystallisation from benzene–light petroleum yielded the *base* (150 g., 80%). The *hydrochloride* crystallised from 4N-hydrochloric acid, m. p. 112—116° (Found: C, 64·4; H, 7·8. $C_{12}H_{16}N_2$,HCl requires C, 64·1; H, 7·6%). The *maleate* had m. p. 152—153° (Found: C, 63·3; H, 6·6. $C_{16}H_{20}N_2O_4$ requires C, 63·15; H, 6·6%).

(b) *By the Abramovitch route*. (i) *Ethyl* γ-*oxobutylmalonate*. A solution of ethyl malonate (800 g., 5 moles) in dioxan (500 ml.) containing Triton B (50 ml.) was treated with methyl vinyl ketone (175 g., 2·5 moles) at such a rate that an exothermic reaction was maintained. The temperature was kept at about 14° by occasional cooling. After stirring for 2 hr. the solution was poured into water and extracted several times with ether. The extract was washed with water. The dried ether was evaporated and yielded the keto-ester, b. p. 110—120°/0·4 mm., n_D^{20} 1·438 (479 g., 83%).

The above reaction was also carried out in the presence of sodium hydroxide (10 g., 0·25 mole) instead of Triton B. The reaction mixture was neutralised with glacial acetic acid, filtered, and distilled, giving the keto-ester (421 g., 73%). The semicarbazone had m. p. 118° (lit.,[32] 118°).

(ii) 3-*Ethoxycarbonyl*-1,6-*dimethyl*-2-*piperidone*. The above keto-ester (115·1 g., 0·5 mole) and 33% ethanolic methylamine (94 ml., 1 mole) in ethanol (350 ml.) were hydrogenated at 100°/50 atm. in the presence of Raney nickel W2 (25 ml. of settled catalyst) after heating in an autoclave for 1 hr. without shaking. After 6 hr. the mixture was cooled and filtered, the alcohol was evaporated through a Vigreux column, and the *piperidone* was distilled, b. p. 112—120°/0·4 mm., n_D^{21} 1·472 (71·5 g., 71·6%). It was water-soluble (Found: N, 7·0. $C_{10}H_{17}NO_3$ requires

[32] C. Mannich and J. P. Fourneau, *Ber.*, 1938, **71**, 2091.

N, 7·0%), $\nu_{max.}$ (film) 1735 (CO), 1640 cm.$^{-1}$ (CO). When the amount of methylamine was increased to 10 equiv. the corresponding *carboxymethylamide* was obtained, crystals, m. p. 162° (from water) (Found: N, 15·1. $C_9H_{16}N_2O_2$ requires N, 15·2%).

(iii) *1,6-Dimethylpiperidine-2,3-dione 3-phenylhydrazone.* The piperidone described above (99·6 g., 0·5 mole) was allowed to stand for 20 hr. with 2N-sodium hydroxide (250 ml., 0·5 mole) and then neutralised at 0° with 2N-hydrochloric acid (250 ml., 0·5 mole). It was next stirred and treated with benzenediazonium chloride solution made from aniline (46·5 g., 0·5 mole), concentrated hydrochloric acid (133 ml., 3 × 0·5 mole), sodium nitrite (38 g., 1·1 × 0·5 mole), and water (250 ml.). The pH was adjusted to 4·5 by addition of crystalline sodium acetate (140 g.). Benzene (300 ml.) and ether (50 ml.) were added, and the mixture was stirred at 0° for 8 hr. After filtration the product was washed with benzene and water and dried. The *hydrazone* (67 g., 58%) formed pale yellow crystals, m. p. 175—176° (from dioxan) (Found: C, 66·8; H, 7·3. $C_{13}H_{17}N_3O$ requires C, 67·5; H, 7·4%), $\lambda_{max.}$ 230, 295, 328, $\lambda_{min.}$ 215, 262, 299 mμ (log ε 4·01, 4·01, 4·33, 3·92, 3·53, and 4·00). The benzene liquors yielded a non-crystallisable *oil* (48 g.) (see below).

(iv) *The lactam* (XIV; R = H). The above hydrazone (67 g., 0·29 mole) in boiling ethanol (670 ml.) was saturated with dry hydrogen chloride. After a total of 2 hr. it was allowed to cool. The product was filtered off, washed with ice-cold ethanol and water, and dried, giving the *lactam* (52 g.). A second crop (6 g.) (total 93%) was obtained from the liquors. After recrystallisation from ethanol the m. p. was 195—197° (Found: C, 72·8; H, 6·5; N, 13·4. $C_{13}H_{14}N_2O$ requires C, 72·85; H, 6·6; N, 13·1%), $\lambda_{max.}$ 228, 304, $\lambda_{min.}$ 213, 264 mμ (log ε 4·36, 4·20, 4·25, and 3·33). Similar cyclisation of the non-crystallisable oil from the hydrazone preparation (48 g.) yielded the same lactam, m. p. 194—195°(11 g.).

(v) *3-2′-Methylaminopropylindole.* The lactam (68·8 g. 0·32 mole) was heated with a solution of potassium hydroxide (106 g., 5 equiv.; 85% KOH) in water (212 ml.) and ethanol (848 ml.) in an autoclave at 150° for 15 hr. The solution was evaporated *in vacuo* and neutralised with 6N-sulphuric acid followed by enough concentrated sulphuric acid to bring the concentration back to 6N. It was then heated under reflux for 10 hr., and decarboxylation was then complete. The solution was cooled strongly, made alkaline with excess 2N-sodium hydroxide, extracted several times with ether, and the extract washed, dried, and evaporated. The residue distilled at about 120°/10^{-4} mm., and after recrystallisation yielded the amine (46·1 g., 76·6%), m. p. 92—93°, identical to that made from indol-3-ylacetone.

This base was also made from 3-2′-aminopropylindole by formylation, followed by reduction with lithium aluminium hydride (yield 52% on a 0·25 mole scale).

3-2′-Isopropylaminopropylindole (30).—A solution of indol-3-ylacetone (1·4 g., 0·008 mole), isopropylamine (5 ml.), and ethanol (45 ml.) was hydrogenated at 100°/50 atm. for 5 hr. in the presence of Raney nickel W2 (0·5 g.). The product was worked up in the same manner as was used for 3-2′-methylaminopropylindole, method (*a*), and yielded the base as a gum, b. p. *ca.* 110°/10^{-5} mm.

3-2′-Benzylaminopropylindole (32).—3-2′-Aminopropylindole (3·48 g., 0·02 mole) and benzaldehyde (2·34 g., 1·1 × 0·02 mole) were heated for 1 hr. at 100° and evacuated at 14 mm./100° for a short time. The product was hydrogenated in ethanol (50 ml.) in the presence of 10% palladium–charcoal catalyst (1 g.) until 2 equiv. of hydrogen had been absorbed. The viscous *base*, obtained after evaporation, had b. p. 170°/2·3 × 10^{-5} mm. (4·1 g., 78%) (Found: N, 10·8. $C_{18}H_{20}N_2$ requires N, 10·6%).

3-(2-2′-Hydroxyethylaminopropyl)indole (33).—The crude 3-2′-benzylaminopropylindole (above) (2·25 g., 0·0085 mole) was heated with ethylene oxide (5 ml.) in ethanol (15 ml.) for 4 hr. at 100°. The mixture was evaporated, redissolved in ethanol (20 ml.), and hydrogenated in the presence of 10% palladium–charcoal (0·5 g.) until 2 equiv. had been absorbed. The product obtained on evaporation yielded the *base* as a viscous syrup (1·4 g., 75%).

3-[2-(N-Ethoxycarbonylamino)propyl]indole (34).—3-2′-Aminopropylindole (3·48 g., 0·02 mole), in dry pyridine (15 ml.) at 0°, was treated with ethyl chloroformate (1·91 ml., 0·02 mole). It was left to stand for 18 hr., evaporated *in vacuo*, and treated with water and ether. The ether was washed with 2N-hydrochloric acid and water, and yielded the *urethane* as a very viscous syrup (3·2 g.).

3-(2-Benzylideneamino-2-methylpropyl)indole.—A mixture of 3-(2-amino-2-methylpropyl)-indole (18·8 g.) with benzaldehyde (12·7 g., 1·2 equiv.) was heated at 100° until homogeneous (10 min.), and then at 100°/150 mm. until no more water was removed. The residue was dissolved

in benzene and chromatographed on alumina, to give a yellow gum which crystallised from light petroleum to give polyhedra of the *Schiff base*, m. p. 90—92° (19·3 g., 70·0%) (Found: C, 82·6; H, 7·5; N, 10·2. $C_{19}H_{20}N_2$ requires C, 82·6; H, 7·2; N, 10·1%).

3-(2-*Benzylamino*-2-*methylpropyl*)*indole* (37).—A solution of the above Schiff base (2·76 g., 0·01 mole) in ethanol (35 ml.) was hydrogenated in the presence of Adams catalyst (100 mg.). Hydrogen (250 ml.) was rapidly absorbed, and the solution was filtered and evaporated. The residue was converted into a *hydrochloride* which crystallised from methanol–ethanol–ethyl acetate in rhombohedra, m. p. 250—252° (decomp.) (3·1 g., 98%).

5-*Methoxy*-3-2′-*methylaminopropylindole* (40).—(a) *From* 5-*methoxyindol*-3-*ylacetone*. (i) 5-Methoxy-α-methyl-β-indolenidenium ethyl nitronate [2a] (116 g., 0·5 mole) was stirred at 55° with dioxan (150 ml.), water (350 ml.), ferric chloride (1 g.), and iron dust (140 g., 2·5 mole). Concentrated hydrochloric acid (42·5 ml., 0·5 mole) was added in portions of 10 ml. every 10 min., the exothermic reaction being controlled to keep the internal temperature at 60°. After a further ½ hr. at 60° the mixture was cooled, extracted with ether, and filtered. The residue was extracted several times with hot benzene. The combined ether–benzene extract was washed with 2N-hydrochloric acid, sodium hydrogen carbonate solution, and water, and evaporated. The crude product (71 g.) was chromatographed on an alumina column, giving the *ketone* (39 g., 38·4%), m. p. 109—110° (from benzene) (Found: N, 6·8. $C_{12}H_{13}NO_2$ requires N, 6·9%), $\nu_{max.}$ (Nujol) 1710 cm.$^{-1}$ (CO).

(ii) A mixture of 5-methoxyindol-3-ylacetone (20·3 g., 0·1 mole) and 33% ethanolic methylamine solution (47 ml., 0·5 mole) was hydrogenated at 100°/50 atm. in the presence of Raney nickel W2 (2·5 ml. of settled catalyst). The product was worked up in the manner already described for 3-2′-methylaminopropylindole [method (*a*)], and yielded the base (14·8 g., 68%).

(b) *By the Abramovitch route.* (i) 1,6-*Dimethylpiperidine*-2,3-*dione* 3-p-*methoxyphenylhydrazone*. 3-Ethoxycarbonyl-1,6-dimethyl-2-piperidone (19·9 g., 0·1 mole) was mixed with 2N-sodium hydroxide (50 ml., 0·1 mole). After 20 hr. it was neutralised with 2N-hydrochloric acid (50 ml., 0·1 mole) and treated with a solution of *p*-methoxybenzenediazonium chloride made from *p*-anisidine (12·3 g., 0·1 mole), concentrated hydrochloric acid (25·5 ml., 0·3 mole), sodium nitrite (7·6 g., 1·1 × 0·1 mole), and water (45 ml.). Sodium acetate was added to bring the pH to 4, 5% ether–benzene (30 ml.) added, and the mixture stirred for 6 hr. at 0° and then for 11 hr. at 20°. Filtration yielded a *hydrazone* which was washed with benzene and water and dried (10·9 g., 41·7%); it formed straw-coloured crystals from benzene, m. p. 187° (Found: C, 64·4; H, 7·2. $C_{14}H_{19}N_3O_2$ requires C, 64·35; H, 7·3%), $\lambda_{max.}$ 201·8, 231br, 308·4, 339·7, $\lambda_{min.}$ 209·8, 267·7, 317·2 mμ (log ε 4·12, 4·06, 4·19, 4·31, 3·99, 3·46, 4·16), $\nu_{max.}$ (Nujol) 1630 cm.$^{-1}$ (CO). The benzene liquors were washed, dried, and evaporated. The residue (11·1 g.) was distilled, yielding a viscous red syrup, b. p. 142°/10^{-4} mm. with slight decomposition (6·8 g.). After further purification by alumina chromatography in benzene solution, the product gradually solidified and yielded an *isomeric hydrazone*, pale yellow crystals from ethanol or benzene–light petroleum, m. p. 68—70° (Found: C, 64·3; H, 7·15%), $\lambda_{max.}$ 202·4, 246·3, 318·7, 365·6, $\lambda_{min.}$ 216·8, 278·0, 325·7 mμ (log ε 4·08, 3·99, 3·96, 4·27, 3·83, 3·48, 3·95), $\nu_{max.}$ (Nujol) 1610 cm.$^{-1}$ (CO).

(ii) *The lactam* (XIV; R = OMe).—The hydrazone, m. p. 187° (130·6 g., 0·5 mole) was stirred with 3N-ethanolic hydrogen chloride (500 ml., 3 × 0·5 mole) while warming until a vigorous reaction took place, after which it was heated under reflux for 1 hr. and cooled to 0°. The product was filtered off, washed with ice-cold ethanolic hydrogen chloride and water, and dried, giving the *lactam* (94 g.). The liquors yielded a second crop (10 g.) (total 85·2%), m. p. 206—207° (from methanol) (Found: C, 68·5; H, 7·0; N, 11·3. $C_{14}H_{16}N_2O_2$ requires C, 68·8; H, 6·6; N, 11·5%), $\lambda_{max.}$ 310, $\lambda_{min.}$ 265 mμ (log ε 4·30 and 3·43).

Similar cyclisation of the isomeric hydrazone (44 g. of oil obtained after chromatography but before final crystallisation) yielded the identical lactam, m. p. 204—206° (21 g., 51%).

(iii) 5-*Methoxy*-3-2′-*methylaminopropylindole*. The above-described lactam (61·1 g., 0·25 mole) was heated at 150° for 15 hr. with a solution of 85% potassium hydroxide (82·5 g., 5 × 0·25 mole) in water (165 ml.) and ethanol (660 ml.). The ethanol was removed *in vacuo* and the residual solution neutralised with 6N-sulphuric acid and treated cautiously with concentrated sulphuric acid to about 4·5—5N. The resulting solution was heated under reflux for 24 hr., cooled, and made alkaline with sodium hydroxide solution. The crude base, obtained by ether extraction, was distilled, b. p. 140°/10^{-5} mm. (23·8 g., 43·7%). The maleate, m. p. 125—127°, was identical with that obtained from 5-methoxyindol-3-ylacetone. The base was

also obtained by formylating 5-methoxy-3-2′-aminopropylindole followed by reduction with lithium aluminium hydride (yield 57% on a 0·19 mole scale).

5-Hydroxy-3-2′-methylaminopropylindole (**42**).—The hydrolysis of the lactam and the decarboxylation were repeated as described above, except that the normality of the acid was kept at 6. The solution was made alkaline with sodium hydroxide solution and extracted with ether as before. The alkaline liquors were adjusted to pH 8, giving a tarry precipitate which was collected and dried. An ethanolic extract was filtered, evaporated, and distilled, giving a clear viscous gum, b. p. (air-bath) *ca.* 220—230°/10^{-5} mm. The product was soluble in dilute acids and in sodium hydroxide solution and formed a *creatinine sulphate complex*.

2-Indol-3-yl-1-methylaminocyclohexane (**47**).—The crude bromide, made as described above from 2-indol-3-ylcyclohexanol (2·48 g., 0·0115 mole), and 33% ethanolic methylamine (10 ml.) were heated at 100° in an autoclave. After 6 hr. the mixture was evaporated and treated with 2N-acetic acid and ether. The acid extract was made alkaline, and the solid product filtered off and dried. After crystallisation from benzene–light petroleum it gave the *base* as nodules, m. p. 135° (0·52 g., 20%) (Found: C, 79·2; H, 8·8; N, 11·9. $C_{15}H_{20}N_2$ requires C, 78·9; H, 8·8; N, 12·25%).

3-2′-Dimethylaminopropylindole (**48**).—3-2′-Methylaminopropylindole (6·6 g., 0·035 mole) and methyl formate (40 ml.) were heated in an autoclave for 6 hr. at 100°, after which the excess ester was evaporated. The neutral product (7·4 g.) in dry tetrahydrofuran (50 ml.) was added to lithium aluminium hydride (2·59 g.) in tetrahydrofuran (50 ml.) and heated under reflux for 3 hr. After isolation in the usual manner, the *base* was distilled, b. p. 100—110°/10^{-5} mm. (4·8 g., 68%). It crystallised from benzene–light petroleum, m. p. 113—114° (Found: C, 77·2; H, 9·1; N, 13·9. $C_{13}H_{18}N_2$ requires C, 77·2; H, 9·0; N, 13·85%).

3-2′-Methylaminoethylindole (**49**).—A solution of tryptamine (50 g.) in dry ethyl formate (250 ml.) was heated under reflux for 16 hr. The solution was evaporated and the residual *N*-formyltryptamine in dry tetrahydrofuran (100 ml.) was added dropwise to a suspension of lithium aluminium hydride (20 g., 1 mole equiv.) in dry tetrahydrofuran (200 ml.); the suspension was stirred and heated under reflux for 8 hr. It was decomposed with ethyl acetate (25 ml.) and N-sodium hydroxide (100 ml.), filtered, and the filtrate evaporated. The oily residue was dissolved in ethyl acetate and converted into a *hydrochloride* which was recrystallised from ethanol–ethyl acetate, to give elongated hexagonal plates, m. p. 180—181·5° (18·3 g., 28%) (lit.,[33] 176—177°; lit.,[34] 175—177°); no analyses are given by these authors (Found: C, 62·7; H, 7·3; N, 13·2. $C_{11}H_{15}ClN_2$ requires C, 62·7; H, 7·1; N, 13·3%). The mother-liquors were evaporated, and the free base isolated and distilled *in vacuo*, to give 22·1 g. (40·5%), b. p. 130—137°/0·05 mm. (total yield 68·5%).

3-2′-Aminopropyl-1-methylindole (**50**).—A solution of sodamide (from sodium, 2·4 g., 0·105 mole) in liquid ammonia (400 ml.) was prepared in the usual way and treated with finely powdered 3-2′-aminopropylindole (17·4 g., 0·1 mole),[3] in portions during 5 min. After stirring the solution for a further 10 min. methyl iodide (16 g., 0·11 mole) was added dropwise, and the ammonia allowed to evaporate. The residue was partitioned between water and chloroform, and the aqueous phase extracted with chloroform. The residue from the dried extracts was converted into 3-2′-aminopropyl-1-methylindole hydrochloride (20·7 g., 92%), m. p. 236—238°. Recrystallisation from ethanol–ethyl acetate gave needles, m. p. 240—242° (lit.,[22] 223—227°, in a synthesis from 3-formyl-1-methylindole) (Found: C, 64·1; H, 7·7; Cl, 15·9. $C_{12}H_{17}ClN_2$ requires C, 64·15; H, 7·6; Cl, 15·8%).

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