250. *Synthesis of Some 5-Substituted-2-methyltryptamines and their N-Mono- and -Di-alkyl Derivatives.*

By N. B. Chapman, K. Clarke, and H. Hughes.

A series of 5′-substituted 2-(2-methylindol-3-yl)ethylamines and their *N*-mono- and -di-alkyl derivatives has been prepared for pharmacological evaluation. The compounds were obtained by treating 5-substituted 2-methylindoles (prepared by the Fischer reaction) with oxalyl chloride, and condensing the resulting glyoxyloyl chloride with ammonia, or with a primary or secondary amine. The resulting amides, on reduction with lithium aluminium hydride, gave the corresponding substituted tryptamines which were isolated as their maleates.

The indole nucleus occurs in many naturally occurring pharmacologically active compounds, and recently a number of Papers [1] and patents [2] have described the synthesis of substituted indolylethylamines as potential serotonin antagonists. The main methods available for the preparation of indoles unsubstituted in the heterocyclic ring involve as the final stage either (*a*) decarboxylation, or (*b*) the reduction of a 2,ω-dinitrostyrene. Neither of these steps gives satisfactory yields on a large scale and the synthesis of substituted tryptamines without prior preparation of the corresponding indole, described by Abramovitch and his co-workers,[3] was a great step forward. However, such a synthesis is not applicable to the preparation of the 5-substituted 2-methyltryptamines now described.

Although 5-methoxy- and 5,6-methylenedioxy-2-methylindole can be prepared by the reduction of the appropriate 2,ω-dinitrostyrene,[4] this method is unsatisfactory for the large-scale preparation of the 5-halogeno-2-methylindoles. 4-Chloro-2,ω-dinitrostyrene on

[1] Shaw and Woolley, *J. Biol. Chem.*, 1953, **203**, 69, 979.
[2] Anthony and Speeter, U.S.P. 2,825,734; B.P. 778,823, 797,258.
[3] Abramovitch and Shapiro, (*a*) *J.*, 1956, 4589; (*b*) *J. Amer. Chem. Soc.*, 1955, **77**, 6690.
[4] (*a*) Woodward, Bader, Bickel, Frey, and Kierstead, *Tetrahedron*, 1958, **2**, 1; (*b*) Burton and Driffield, *J.*, 1949, 78.

reduction with hydrogen and palladium-on-charcoal gave 2-methylindole as the only product.

The Fischer reaction was therefore chosen for the large-scale preparation of the required 5-substituted 2-methylindoles. The necessary 4-halogenophenylhydrazines were usually prepared by reduction of the corresponding diazonium salts with sodium sulphite,[5] but 4-methyl- and 4-methoxy-phenylhydrazine were best obtained by using stannous chloride.[6] Reaction with acetone under an inert atmosphere gave the corresponding substituted acetone phenylhydrazones in theoretical yield.

The Fischer indole synthesis of 5-substituted 2-methylindoles has been described by a number of workers [7] and the yields are usually rather poor. A survey of the various cyclising agents which have been employed was therefore undertaken, using acetone 4-chlorophenylhydrazone as the starting material. In a standard reaction, hydrochloric acid, hydrogen chloride, boron trifluoride, polyphosphoric acid, cuprous chloride, and various proportions of zinc chloride were examined as catalysts. Polyphosphoric acid gave a low yield of a white crystalline solid, thought to be 2,2′-dimethyl-5,5′-bi-indolyl. Anhydrous zinc chloride was shown to be the most effective catalyst, and the best results were obtained by using equal weights of the acetone phenylhydrazone and anhydrous zinc chloride in cumene, as high-boiling solvent. Oxalyl chloride reacted readily with these indole derivatives in ethereal solution at 0° to yield the corresponding 3-indolylglyoxyloyl chlorides,[8] which were then condensed with ammonia, methylamine, dimethylamine, or pyrrolidine. The resulting amides were reduced with lithium aluminium hydride in anhydrous tetrahydrofuran to the substituted tryptamines,[9] which were isolated as maleates.

Experimental

Substituted Phenylhydrazines.—The 4-halogenophenylhydrazines, prepared by the reduction of the corresponding diazonium chlorides with sodium sulphite as described by Chattaway and Humphrey,[5] were isolated as their hydrochlorides. Addition of the finely powdered hydrochloride to a stirred, ice-cold solution of potassium hydroxide gave the free base. 4-Methyl- and 4-methoxy-phenylhydrazine [6] were prepared by using stannous chloride as the reducing agent. Yields and m. p.s are given in Table 1.

Table 1.

Substituted phenylhydrazines and the derived acetone phenylhydrazones.

	4-X·C_6H_4·NH·NH_2			4-X·C_6H_4·NH·N:CMe_2	5-X-2-Methylindole	
X	M. p. Hydrochloride	M. p. Base	Yield (%)	M. p.	Yield (%)	M. p.
H	—	—	—	—	85	59—60°
F	199°	39°	75	56—60°	55	102—103
Cl	228—230	90	84	83—84	50	117—119
Br	219—220	106	90	94—95	45	104—105
Me	195 *	—	56	50—52	70	114—115
OMe	—	60—61	—	59—60	1	89—90
NO_2	—	—	—	148—149	0	—

* M. p. of stannichloride.

Substituted Acetone Phenylhydrazones.—The 4-substituted phenylhydrazine (0·2 mole), acetone (13·2 g., 0·2 mole), sodium acetate (25 ml. of a saturated aqueous solution), and water (500 ml.) were shaken for 10 min. in a large separating funnel which had been thoroughly flushed out with nitrogen. The hydrazone was extracted with ether, the ethereal solution was dried ($MgSO_4$), and the solvent was removed. Crystallisation from aqueous ethanol gave the hydrazones (Table 1) in almost theoretical yield.

[5] Chattaway and Humphrey, *J.*, 1927, 1323.
[6] Hunsberger, Shaw, Fugger, Ketcham, and Lednicer, *J. Org. Chem.*, 1956, **21**, 394.
[7] (*a*) Fischer, *Ber.*, 1886, **19**, 1563; (*b*) Snyder and Smith, *J. Amer. Chem. Soc.*, 1943, **65**, 2452.
[8] (*a*) Kharasch, Kane, and Brown, *J. Amer. Chem. Soc.*, 1940, **62**, 2242; (*b*) Speeter and Anthony, *ibid.*, 1954, **76**, 6208.
[9] B.P. 778,823, 797,258.

TABLE 2.

5-Substituted 2-methylindol-3-ylglyoxyloylamides, 5-X·C_9H_7N·CO·CO·NRR′.

					Required (%)				Found (%)		
X	R	R′	M. p.	Yield (%)	C	H	N	Formula	C	H	N
H	H	H	242°	94	65·3	5·0	13·9	$C_{11}H_{10}N_2O_2$	65·1	4·9	14·2
H	Me	H	207—208	88	66·6	5·6	13·0	$C_{12}H_{12}N_2O_2$	66·1	5·6	12·9
H	Me	Me	168—169	83	67·8	6·1	12·2	$C_{13}H_{14}N_2O_2$	67·6	6·2	12·0
H	Pyrrolidyl		160—161	78	70·3	6·3	10·9	$C_{15}H_{16}N_2O_2$	70·1	6·2	10·7
F	H	H	240—241	92	60·0	4·1	12·7	$C_{11}H_9FN_2O_2$	59·7	4·4	12·5
F	Me	H	193—194	91	61·5	4·7	12·0	$C_{12}H_{11}FN_2O_2$	61·3	4·9	12·2
F	Me	Me	174—175	86	62·9	5·3	11·3	$C_{13}H_{13}FN_2O_2$	63·1	5·3	11·2
F	Pyrrolidyl		166—167	85	65·7	5·5	10·2	$C_{15}H_{15}FN_2O_2$	65·8	5·2	10·5
Cl	H	H	248—250	94	55·8	3·8	11·8	$C_{11}H_9ClN_2O_2$	55·6	4·0	11·7
Cl	Me	H	212—213	87	57·5	4·4	11·2	$C_{12}H_{11}ClN_2O_2$	57·3	4·9	11·3
Cl	Me	Me	218—219	89	59·0	5·0	10·6	$C_{13}H_{13}ClN_2O_2$	59·0	4·5	10·3
Cl	Pyrrolidyl		220—221	81	62·0	5·2	9·6	$C_{15}H_{15}ClN_2O_2$	61·6	5·2	9·5
Br	H	H	243—244	90	47·0	3·2	10·0	$C_{11}H_9BrN_2O_2$	46·7	3·2	9·5
Br	Me	H	223—224	83	48·8	3·8	9·5	$C_{12}H_{11}BrN_2O_2$	49·1	3·5	9·8
Br	Me	Me	222—223	86	50·5	4·2	9·1	$C_{13}H_{13}BrN_2O_2$	50·2	4·3	9·0
Br	Pyrrolidyl		228—229	77	53·8	4·5	8·4	$C_{15}H_{15}BrN_2O_2$	54·0	4·7	8·2
Me	H	H	255	94	66·6	5·6	13·0	$C_{12}H_{12}N_2O_2$	66·5	5·1	12·8
Me	Me	H	237—238	81	67·8	6·1	12·2	$C_{13}H_{14}N_2O_2$	67·7	6·0	11·9
Me	Me	Me	224—225	89	68·8	6·6	11·5	$C_{14}H_{16}N_2O_2$	68·5	6·5	11·7
Me	Pyrrolidyl		195—196	83	71·1	6·7	10·4	$C_{16}H_{18}N_2O_2$	71·0	6·8	10·5

TABLE 3.

Maleates, 5-X·C_9H_7N·CH_2·CH_2·NRR′,HO_2C·CH:CH·CO_2H, of 5-substituted 2-methyltryptamines and their *N*-alkyl derivatives.

X	R	R′	M. p.	Yield (%)	Required (%) C	Required (%) H	Required (%) N	Formula	Found (%) C	Found (%) H	Found (%) N	Anti-serotonin activity E.D.$_{50}$ (mg./kg.)	Toxicity L.D.$_{50}$ (mg./kg.)
H	Me	H *	—	—	—	—	—	—	—	—	—	—	—
H	Me	Me	127—128°	52	64·1	7·0	8·8	$C_{17}H_{22}N_2O_4$	64·3	7·1	8·9	32—64	256
F	H	H	178—179	62	58·4	5·5	9·1	$C_{15}H_{17}FN_2O_4$	58·6	5·6	8·9	64	350
F	Me	H	146—147	58	59·6	5·9	8·7	$C_{16}H_{19}FN_2O_4$	59·5	5·8	8·4	64	300
F	Me	Me	165—166	59	60·7	6·3	8·3	$C_{17}H_{21}FN_2O_4$	60·5	6·8	8·5	>64	200
F	Pyrrolidyl		145—146	55	62·9	6·4	7·7	$C_{19}H_{23}FN_2O_4$	62·8	6·3	7·4	32	200
Cl	H	H	186—187	40	55·5	5·3	8·6	$C_{15}H_{17}ClN_2O_4$	55·8	5·2	8·4	<32	200
Cl	Me	H	157—158	51	56·7	5·6	8·3	$C_{16}H_{19}ClN_2O_4$	57·0	5·4	8·3	64	200
Cl	Me	Me	174—175	57	57·8	6·0	7·9	$C_{17}H_{21}ClN_2O_4$	58·1	6·0	7·6	64	400
Cl	Pyrrolidyl †		105—106	35	58·6	7·5	6·0	$C_{19}H_{23}ClN_2O_4$	58·4	7·4	6·2	64—128	200
Br	H	H	185—186	65	48·8	4·6	7·6	$C_{15}H_{17}BrN_2O_4$	48·9	4·3	7·3	>64	128
Br	Me	H	153—154	20	50·1	5·0	7·3	$C_{16}H_{19}BrN_2O_4$	50·4	5·1	7·1	128	256
Br	Me	Me	169—170	48	51·4	5·3	7·1	$C_{17}H_{21}BrN_2O_4$	51·6	5·4	7·0	32	400
Br	Pyrrolidyl ‡		95—96	15	53·7	6·2	6·0	$C_{19}H_{23}BrN_2O_4$	53·4	5·9	6·1	128	200
Me	H	H	184—185	70	63·1	6·6	9·2	$C_{16}H_{20}N_2O_4$	63·4	6·6	9·4	64	256
Me	Me	H	152—153	55	64·1	7·0	8·8	$C_{17}H_{22}N_2O_4$	64·0	7·0	8·6	32	—
Me	Me	Me	165—166	59	65·1	7·3	8·4	$C_{18}H_{24}N_2O_4$	65·2	7·0	8·2	32—64	256
Me	Pyrrolidyl		150—151	59	67·0	7·3	7·8	$C_{20}H_{26}N_2O_4$	67·4	7·5	7·9	64	128
BAS §			—	—	—	—	—	—	—	—	—	8	225
Cyproheptadine			—	—	—	—	—	—	—	—	—	1	75

* Characterised as the picrate , m. p. 189—190° (Found: C, 51·9; H, 5·1; N, 16·6. $C_{19}H_{20}N_5O_7$ requires C, 51·7; H, 4·6; N, 16·8%). † Contained 2 molecules of ethanol of crystallisation. ‡ One molecule of ethanol of crystallisation. § 1-Benzyl-2-methyl-5-methoxytryptamine.

5-*Substituted 2-Methylindoles.*—Powdered anhydrous zinc chloride (20 g.) was added to a solution of acetone phenylhydrazone (20 g.) in pure dry cumene (60 g.) and the resulting mixture was boiled for 1 hr. under a nitrogen atmosphere. Two alternative procedures were then adopted.

(*a*) The cumene was decanted from the solid residue and, on evaporation under reduced pressure, yielded the crude 2-methylindole which was recrystallised from light petroleum (b. p. 40—60°). The solid residue was boiled with 0·2N-hydrochloric acid to dissolve inorganic material. The cooled solution was shaken with ether and the ethereal solution was dried (Na_2SO_4), concentrated, and passed down an alumina column. Elution with light petroleum (b. p. 40—60°), followed by evaporation, gave more 2-methylindole which was recrystallised as before and had m. p. 59—60°. Yield, 13·4 g. (85%).

(*b*) The cumene was distilled from the mixture under reduced pressure and the residue was boiled with 0·2N-hydrochloric acid and worked up as before. This gave lower yields of 2-methylindole itself, but was quite satisfactory for the 5-halogeno-2-methylindoles.

5-*Substituted 2-Methylindol-3-ylglyoxyloylamides.*—Oxalyl chloride (7·5 ml., 0·088 mole) in anhydrous ether was added to a stirred, ice-cold solution of the substituted 2-methylindole (0·05 mole) in anhydrous ether (250 ml.). After 30 min., the pale yellow indolylglyoxyloyl chloride was filtered off, washed with anhydrous ether, and used in the next stage without further purification. The glyoxyloyl chloride was added to a stirred, aqueous solution of the appropriate base (3—4 mol.) at room temperature. After several hours, the precipitated *amide* (Table 2) was collected and crystallised from ethanol. The reaction with pyrrolidine was best carried out in anhydrous benzene.

5-*Substituted 2-Methyltryptamines and their* N-*Alkyl Derivatives.*—The glyoxyloylamide (4·0 g.) was added to a suspension of lithium aluminium hydride (4·0 g.) in pure, dry tetrahydrofuran (150 ml.) and the mixture was refluxed for 24 hr. under an atmosphere of nitrogen. (The primary amides were added by Soxhlet extraction, and required a reaction time of 48 hr.) The excess of lithium aluminium hydride was destroyed by adding water, any inorganic material was filtered off and washed with hot tetrahydrofuran, and the combined filtrates were dried ($MgSO_4$). Addition of a solution of maleic acid in pure dry tetrahydrofuran gave the required tryptamine as its *maleate* (Table 3), which was recrystallised from ethanol.

The pharmacological results included in Table 3 show that the compounds listed have a somewhat weak anti-serotonin activity, by comparison with established antagonists. Occasionally they have relatively low toxicity. Their antagonism to serotonin is by no means specific, but antagonism to histamine and acetylcholine is only weak.

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