POTENTIAL RESERPINE ANALOGUES

PART I. DERIVATIVES OF TRYPTAMINE

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The six amides, *cis*-*N*-(3-indolylethyl)-3-methoxycyclohexanecarboxylic acid amide (II), *cis*-*N*-(3-indolylethyl)-*N*-3-methoxycyclohexylmethylacetamide (IV), *N*-(3-indolylethyl)-3,4,5-trimethoxybenzamide (V), *N*-(3-indolylethyl)-3,4-dimethoxyphenylacetamide (VII), 3-indolyl-*N*-(3,4-dimethoxyphenethyl)acetamide (VIII) and 4-methoxycyclohexylacetotryptamide (X), have been prepared. II has been reduced to *cis*-*N*-(3-methoxycyclohexylmethyl)tryptamine (III); VII and VIII have both been reduced to *N*-(3,4-dimethoxyphenethyl)tryptamine (IX), X has been reduced to *N*-(4-methoxycyclohexylethyl)tryptamine (XI) and V to *N*-(3,4,5-trimethoxybenzyl)tryptamine (VI). Nine of the compounds, II–VI, VIII–XI, were compared with reserpine for their power to potentiate barbiturate hypnosis in mice, and to deplete the 5-hydroxytryptamine content of rat brain. Only compound (IV) was active in both tests, having about one-thirteenth the activity of reserpine. Compound (V) was about one-eighth as active as reserpine in producing potentiation of barbiturate hypnosis.

SINCE the elucidation of the structure of reserpine (I) by Mueller, Schlittler and others[1], many analogues have been synthesised in attempts to reproduce the pharmacologically-active fragments of the molecule[2–29]. The most promising compounds differ from reserpine only in the nature of the acyl group on carbon atom 18[26–28]. These have been subjected to thorough pharmacological tests by Garattini and colleagues[30], and some appear to be more effective in certain tests than reserpine itself. The evaluation of such analogues is difficult, however, as the pharmacological actions of reserpine are complex.

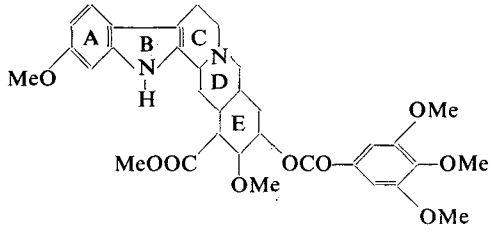
The present work describes the preparation of six amides, *cis*-*N*-(3-indolylethyl)-3-methoxycyclohexanecarboxyamide, (II); *cis*-*N*-(3-indolylethyl)-*N*-3-methoxycyclohexylmethylacetamide (IV); *N*-(3-indolylethyl)-3,4,5-trimethoxybenzamide, (V); *N*-(3-indolylethyl)-3,4-dimethoxyphenylacetamide (VII); 3-indolyl-*N*-(3,4-dimethoxyphenethyl)acetamide (VIII) and 4-methoxycyclohexylacetotryptamide (X).

The insolubility of the amides in dilute acid and the evidence available from the preparation of 3-β-(*o*-tolylacetamido)ethylindole by Clemo and Swan[31], 3,4-dimethoxyphenylacetotryptamide by Onda and colleagues[5] and 4-methoxycylohexylacetotryptamide by Protiva and colleages[22] prove that the acylation has taken place at the β-*N*, and not at the α-*N* of the tryptamine molecule.

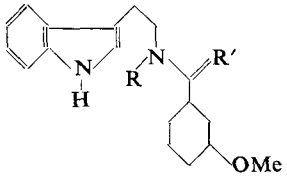
The amides were then converted to their corresponding amines by lithium aluminium hydride reduction; (III) was obtained from (II); (IX) from both (VII) and (VIII); (VI) from (V) and (XI) from (X).

The amine (III) was also obtained by the condensation of tryptamine with *cis*-3-methoxycyclohexylmethyl chloride.

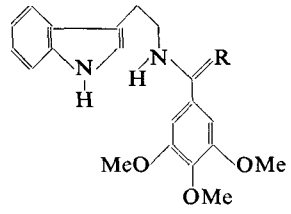
The structural relations between these compounds to reserpine may be seen in Fig. 1.



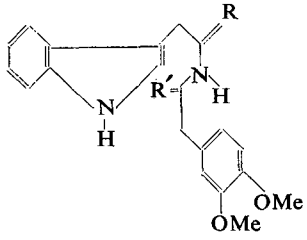
I Reserpine.



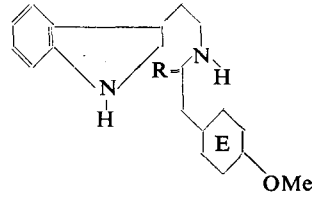
II, R = H; R′ = O
III, R = H; R′ = H_2
IV, R = COMe; R′ = H_2



V, R = O
VI, R = H_2



VII, R = H_2; R′ = O
VIII, R = O; R′ = H_2
IX, R = R′ = H_2



X, R = O
XI, R = H_2

FIG. 1.

Pharmacological Data

The compounds were compared with reserpine for their power (i) to potentiate the hypnosis in mice produced by intravenous doses of hexobarbitone (50 mg./kg.) and (ii) to deplete the 5-hydroxytryptamine (5-HT) content of rat brain. In the first test, the standard intraperitoneal dose of reserpine was 5 mg./kg.; in the second, reserpine was given intraperitoneally at a dose of 1 mg./kg. The doses of the new compounds used in the present experiments are shown in Table I, together with their pharmacological activities.

We should like to express our thanks to Miss S. A. P. Price and Dr. G. B. West of the Department of Pharmacology of this School for carrying out the pharmacological tests.

Discussion of Pharmacological Results

Of the nine compounds tested, only one (IV, Table I) produced a depletion of the 5-HT content of rat brain. This compound differed from the remainder in having its aliphatic secondary amine group acetylated (i.e. there is no free –NH– group in the carbon chain joining the ring systems). This compound also showed slight barbiturate potentiation at the dose level used.

TABLE I

COMPARISON OF THE PHARMACOLOGICAL ACTIVITIES OF VARIOUS TRYPTAMINE DERIVATIVES (RESERPINE ACTIVITY IS TAKEN AS 100 FOR EACH TEST)

	Potentiation of barbiturate hypnosis in mice		Depletion of 5-HT in rat brain	
Tryptamine derivative	Max. dose used (mg./kg.)	Relative activity	Max. dose used (mg./kg.)	Relative activity
II	400*	0	100	0
III	200*	0	50	0
IV	40	2·5	20	5
V	80	12·5–15	20	0
VI	100	0	—	–
VIII	100*	5	20	0
IX	100*	0	—	–
X	100*	5	40	0
XI	100*	5–6	40	0

* Some mice died at this dose level.

Compound (V) was more active than (IV) in potentiating barbiturate hypnosis, and other compounds were active in this test but the doses required were lethal to some of the mice.

Compounds with an aromatic ring E (V and VIII) possess a more powerful action in potentiating barbiturate hypnosis than those in which ring E is hydrogenated (IV and X).

Only compound IV possessed the power to deplete brain 5–HT and potentiate barbiturate hypnosis, and this is now being subjected to further tests (e.g. hypotensive activity). The other compounds do not justify further testing.

EXPERIMENTAL

Expt. 1. cis-3-*Methoxycyclohexylmethanol.* Methyl *cis*-3-methoxycyclohexanecarboxylate (as prepared by Noyce and others[32]) (13 g.) in ether (100 ml.) was added dropwise to a suspension of $LiAlH_4$ (6·5 g.), in ether (100 ml.), in a three-necked flask (fitted with a condenser and a stirrer) at such a rate that the reaction mixture was just boiling. The mixture was refluxed and stirred for 33 hours. The excess $LiAlH_4$ was destroyed by dropwise addition of ice-cold water and the precipitated inorganic hydroxide was dissolved by dropwise addition of ice-cold 10 per cent sulphuric acid. The acidified mixture was extracted with

ether and the ether removed by distillation. Yield: 9·5 g. (88 per cent), b.p. 110° 18 mm., n_D^{22} 1·4670. Found: C, 65·97; H, 11·48 per cent. $C_8H_{16}O_2$, requires C, 66·66; H, 11·20 per cent.

Expt. 2. cis-3-*Methoxycyclohexylmethyl chloride*. *cis*-3-Methoxycyclohexylmethanol (7 g.) was treated with excess thionyl chloride (25 ml.) and was allowed to reflux for 5 hours. The excess thionyl chloride was removed by distillation with the aid of benzene, and the product distilled *in vacuo*. Yield: 7·32 g. (93 per cent), b.p. 45 to 46°/0·1 mm., n_D^{21} 1·4686. Found: C, 59·0; H, 9·24; Cl, 21·82 per cent. $C_8H_{15}OCl$ requires C, 59·07; H, 9·18; Cl, 22·39 per cent.

Expt. 3. cis-N-(2-*Indol*-3′-*ylethyl*)-*methoxycyclohexanecarboxyamide* (II). Tryptamine, (technical) (0·08 g.) was intimately mixed with methyl *cis*-3-methoxycyclohexanecarboxylate (0·84 g.) and heated at 180 to 190° for 2 hours. The product was dissolved in warm methanol and treated with charcoal. After removal of the charcoal the solution was concentrated. The cold solution was treated with water dropwise until tubid and allowed to stand overnight in the refrigerator. The colourless crystals were separated by filtration. Yield: 0·95 g. (63·3 per cent), m.p. 115 to 117°. Found: C, 71·68; H, 7·82; N, 9·20 per cent. $C_{18}H_{24}O_2N$ requires C, 72·00; H, 8·06; N, 9·33 per cent.

Expt. 4. N-(cis-3-*Methoxycyclohexylmethyl*) *tryptamine* (*III*). *Method* (1). The above amide (200 mg.) was placed in the thimble of a Soxhlet extractor fitted to a flask (250 ml.) containing $LiAlH_4$ (0·5 g.) in ether (200 ml.), the flask also being provided with a mercury-sealed stirrer. The mixture was refluxed for 96 hours under nitrogen and then cooled. The excess $LiAlH_4$ was destroyed by the dropwise addition of ice-cold water and, after inorganic hydroxides had been dissolved by dropwise addition of 10 per cent sulphuric acid, the aqueous layer was extracted thoroughly with ether to remove unchanged amide. The solution was strongly basified with 20 per cent sodium hydroxide solution and then extracted with ether. After drying over anhydrous sodium sulphate, the ether was removed and the residue distilled. Yield: 140 mg. (73·6 per cent), b.p. 190 to 196°/0·1 mm. Found: C, 75·07; H, 9·39; N, 9·99 per cent. $C_{18}H_{26}ON_2$ requires C, 75·45; H, 9·15; N, 9·78 per cent.

Hydrochloride. The above base (5 g.) was dissolved in dry ether and dry hydrogen chloride was passed in. The precipitated hydrochloride was recrystallised from ethanol and ether. Yield: 5·15 g. (92 per cent), m.p. 167 to 168°. Found: C, 67·34; H, 8·52; N, 8·69; Cl, 10·67 per cent. $C_{18}H_{28}ON_2$,HCl requires C, 66·95; H, 8·43; N, 8·68; Cl, 10·97 per cent.

Method (2). Tryptamine (1·6 g.) in tetrahydrofuran (25 ml.) was added drop by drop to a solution of *cis*-3-methoxycyclohexylmethyl chloride (0·85 g.) in tetrahydrofuran (15 ml.) with constant shaking in an atmosphere of nitrogen. Immediate formation of tryptamine hydrochloride was observed. The reaction mixture was then allowed to stand at room temperature for 48 hours and the tryptamine hydrochloride was separated by filtration (0·88 g.). After the solvent had been removed

by distillation under reduced pressure, the residue was distilled and the fraction (200 mg.) boiling at 190 to 196°/0·1 mm. was dissolved in ether, cooled in a refrigerator and then filtered. The filtrate was treated with dry hydrogen chloride The precipitated hydrochloride, after five crystallisations from ethanol and ether, had m.p. 166 to 168° (mixed m.p. with product from Method (1). 166 to 167°). Found: C, 66·65; H, 8·16; N, 8·83; Cl, 10·66 per cent. $C_{18}H_{28}ON_2$,HCl requires C, 66·95; H, 8·43; N, 8·68; Cl, 10·97 per cent.

Expt. 5. *Indol*-3-*yl*-N-(3,4-*dimethoxyphenethyl*)*acetamide* (*VIII*). *Method* (1). Homoveratrylamine (0·9 g.) and 3-indolylacetic acid (0·8 g.) were dissolved in methanol (2 ml.) and the methanol removed by distillation. The mixture was heated at 210 ± 5° for 45 minutes and then dissolved in warm methanol and treated with charcoal; after removal of the charcoal, the solution was concentrated and water added dropwise until a turbidity appeared. On cooling in the refrigerator, colourless crystals were obtained. Yield: 1·2 g. (78 per cent), m.p. 122 to 123°. Found: C, 17·13; H, 6·76; N, 8·35 per cent. $C_{20}H_{22}O_3N_2$ requires C, 70·97; H, 6·56; N, 8·28 per cent.

Method (2). 3-Indolylacetic acid was esterified with freshly prepared diazomethane and the ester (1 g.) dissolved in methanol (2 ml.) together with homoveratrylamine (1 g.). After removal of the methanol the mixture was heated for 3 hours at 170 to 180° and the product worked up as before. Yield: 1·5 g. (84 per cent), m.p. and mixed m.p. with the product from the previous experiment 122 to 123°.

Expt. 6. N-(2-*Indol*-3′-*ylethyl*)-3,4-*dimethoxyphenylacetamide* (*VII*). Homoveratric acid was esterified with freshly prepared diazomethane and the methyl ester (190 mg.) was dissolved in methanol (2 ml.) with tryptamine (160 mg.). After removal of the methanol by distillation the mixture was heated at 180 to 190° for 2½ hours and the product worked up as described in Expt. 5 (1). Yield: 196 mg. (65 per cent), m.p. 65 to 66°. Found: C, 70·44; H, 6·74; N, 8·15 per cent. $C_{20}H_{22}O_2N_2$ requires C, 70·97; H, 6·55; N, 8·28 per cent. It was later found that this amide had been previously prepared by Onda and others[5] by condensing homoveratric acid with tryptamine.

Expt. 7. N-(3,4-*Dimethoxyphenethyl*)*tryptamine* (*IX*). *Method* (1). *N*-(3,4-Dimethoxyphenethyl)-3-indolylacetamide (0·5 g.) dissolved in tetrahydrofuran (25 ml.) was added dropwise to a suspension of $LiAlH_4$ (0·7 g.) in ether (200 ml.) in a 250 ml. flask fitted with a stirrer and a condenser. The mixture was refluxed with stirring in an atmosphere of nitrogen for 72 hours. The excess $LiAlH_4$ was destroyed by the dropwise addition of aqueous tetrahydrofuran with vigorous shaking and the solution filtered. The residue was washed thoroughly with warm tetrahydrofuran and the mixed tetrahydrofuran extracts dried over anhydrous sodium sulphate; after removal of the solvent the residue was distilled under reduced pressure. Yield: 0·35 g. (73 per cent), b.p. 210 to 212°/0·1 mm. Found: C, 74·30; H, 7·49; N, 8·40 per cent. $C_{20}H_{20}O_2N$ requires C, 74·09; H, 7·46; N, 8·63 per cent.

Picrate. The above base (0·35 g.) in ethanol (20 ml.) was treated with a saturated ethanolic solution of picric acid at room temperature and heated on a water bath for 5 minutes; the solid deposited on cooling was recrystallised from ethanol. Yield: 0·45 g. (75 per cent), m.p. 158 to 158·5°. Found: C, 56·03; H, 4·97; N, 12·40 per cent. $C_{26}H_{27}O_9N_5$ requires C, 56·14; H, 4·88; N, 12·65 per cent.

Method (2). *N*-(3-Indolylethyl)-3,4-dimethoxyphenylacetamide (0·5g). was reduced in exactly the same way as the isomeric amide in *Method* (1). Yield: 0·32 g. (66 per cent), b.p. 210 to 212°/0·1 mm., m.p. picrate 158 to 159·5°, mixed m.p. with picrate from *Method* (1) 158 to 159·5°.

Hydrochloride. The hydrochloride was prepared as described in Expt. 4 and recrystallised from acetone; m.p. 175 to 176°. Found: C, 68·54; H, 7·32; N, 7·60 per cent. $C_{20}H_{24}O_2N_2$, HCl requires C, 66·54; H, 6·98; N, 7·76 per cent.

Expt. 8. cis-N-(2-*Indol*-3′-*ylethyl*)-N-3-*methoxycyclohexylmethylacetamide* (*IV*). *cis-N*-(3-Methoxycyclohexylmethyl)tryptamine (425 mg.) was dissolved in pyridine (45 ml.) and acetyl chloride (200 mg.) was added dropwise. Spontaneous formation of a coloured precipitate was observed, which was removed by filtration. The filtrate was allowed to stand overnight (the colour changed to dark yellow) and after distillation of the solvent the residue was dissolved in methanol and treated with charcoal. After removal of the charcoal, the solution was concentrated and allowed to stand in the refrigerator for 4 days, when a white precipitate was deposited. This was recrystallised from aqueous methanol (also from aqueous ethanol). Yield: 200 mg. (41 per cent), m.p. 88 to 90°. Found: C, 73·72; H, 8·65; N, 8·53 per cent. $C_{20}H_{28}O_2N_2$ requires C, 73·10; H, 8·58; N, 8·53 per cent.

Expt. 9. 3,4,5-*Trimethoxybenzoyl chloride.* 3,4,5-Trimethoxybenzoic acid (10 g.) and thionyl chloride (20 g.) were mixed together and allowed to stand at room temperature for 3 hours and then refluxed for 1 hour. The excess thionyl chloride was removed with the aid of dry benzene. Yield: 10·31 g. (95 per cent), m.p. 77 to 78°. (lit. m.p. 77 to 78°).

Expt. 10. N-(2-*Indol*-3′-*ylethyl*)-3,4,5-*trimethoxybenzamide* (*V*). Tryptamine (1·9 g.) in tetrahydrofuran (25 ml.) was added dropwise to a cooled well-stirred solution of 3,4,5-trimethoxybenzoyl chloride (1·4 g.) in tetrahydrofuran (30 ml.) and the stirring continued for 30 minutes. The mixture was allowed to stand overnight under dry nitrogen.

The precipitated tryptamine hydrochloride (0·98 g.) was removed by filtration and the solvent by distillation under reduced pressure. The residue was dissolved in absolute methanol and treated with charcoal. After removal of the charcoal the solution was concentrated to about 20 ml. and allowed to stand in the refrigerator. The colourless crystals deposited were recrystallised from methanol. Yield: 1·70 g. (65 per cent), m.p. 200 to 202°. Found: C, 68·00; H, 6·44; N, 7·89 per cent. $C_{20}H_{22}O_4N_2$ requires C, 67·79; H, 6·24; N, 7·90 per cent.

Expt. 11. N-(3,4,5-*Trimethoxybenzyl*)*tryptamine* (*VI*). The above amide (0·5 g.) was placed in the thimble of a Soxhlet extractor, fitted to a flask (250 ml.) containing $LiAlH_4$ (1·0 g.) in tetrahydrofuran (200 ml.) and provided with a mercury-sealed stirrer. The mixture was then refluxed for 72 hours in an atmosphere of nitrogen and then the procedure described in Expt. 7 (1) was followed. Yield: 0·3 g. (66 per cent), b.p. 215 to 217°/0·2 mm. Found: C, 71·04; H, 7·08; N, 8·20 per cent. $C_{20}H_{24}O_3N$ requires C, 70·58; H, 7·08; N, 8·23 per cent.

Picrate. M.p. 147·5 to 149°. Found: N, 12·77 per cent. $C_{26}H_{27}O_{10}N_5$ requires N, 12·32 per cent.

Hydrochloride. M.p. 229 to 231°. Found: C, 64·01; H, 6·43; N, 7·42; Cl, 9·39 per cent. $C_{20}H_{24}O_3N_2,HCl$ requires C, 63·72; H, 6·66; N, 7·43; Cl, 9·42 per cent.

Expt. 12. 4-*Methoxycyclohexylacetotryptamide* (*X*). *Method* (1). Tryptamine (technical) (1·6 g.) in tetrahydrofuran (20 ml.) was cooled to below 10° and to this cooled and stirred mixture, 4-methoxycyclohexylacetyl chloride (0·95 g.) in tetrahydrofuran (15 ml.) was added dropwise. The mixture was stirred at room temperature for 30 minutes and then allowed to stand overnight. The precipitated tryptamine hydrochloride was removed by filtration and the solvent by distillation under reduced pressure. The residue was dissolved in excess benzene and washed with 5 per cent sodium hydroxide solution followed by 3N hydrochloric acid. The benzene extract was dried over anhydrous sodium sulphate and the solvent removed. The residue solidified on standing in the refrigerator and was then recrystallised from benzene. Yield: 1·0 g. (69 per cent), m.p. 96 to 101°, b.p. 300°/0·2 mm. Found: C, 73·11; H, 8·36; N, 8·89 per cent. $C_{19}H_{26}O_2N_2$ requires C, 72·65; H, 8·35; N, 8·92 per cent.

Method (2). Tryptamine (1·0 g.) in benzene (50 ml.) and 4 per cent sodium hydroxide solution (40 ml.) were mixed. To the mixture, 4-methoxycyclohexylacetyl chloride (1·3 g.) in benzene (10 ml.) was added dropwise. Stirring was continued at room temperature for about an hour, after which the benzene layer was washed with 5 per cent. caustic soda solution followed by 3N hydrochloric acid. The benzene extract was dried over anhydrous sodium sulphate and the benzene removed. The rest of the procedure follows that described in Method (1). Yield: 0·98 g. (46 per cent), m.p. and mixed m.p. with the product of Method (1) 95·5 to 100·5° (mixture of stereoisomers).

Method (3). Methyl 4-methoxycyclohexylacetate (1·0 g.) and tryptamine (0·8 g.) were mixed together and heated at 180 to 190° for 3 hours. The reacted product was dissolved in warm benzene and washed with 5 per cent sodium hydroxide solution followed by 3N hydrochloric acid. The benzene layer was separated and dried over anhydrous sodium sulphate and the benzene removed. The residue was allowed to stand in the refrigerator for about three months and then recrystallised from benzene.

Yield: 0·25 g., m.p. and mixed m.p. with the product of Method (1) 95·5 to 100·5°.

Expt. 13. *N*-[2-(4-*Methoxycyclohexyl*)*ethyl*]*tryptamine* (*XI*). 4-Methoxycyclohexylacetotryptamide (0·5 g.) in tetrahydrofuran (20 ml.) was added dropwise to a boiling suspension of $LiAlH_4$ (1·0 g.) in ether (100 ml.) in a flask (250 ml.) fitted with a mercury-sealed stirrer and a condenser (calcium chloride guard tube). The mixture was refluxed with stirring in an atmosphere of nitrogen for about 56 hours. The rest of the procedure followed that described in Expt. 7 (1). Yield: 0·305 g. (65 per cent), b.p. 180 to 182°/0·05 mm. Found: C, 75·82; H, 9·63; N, 9·57 per cent. $C_{19}H_{28}ON$ requires C, 75·97; H, 9·36; N, 9·33 per cent.

Hydrochloride. The above base (about 250 mg.) was dissolved in tetrahydrofuran (3 ml.) and ether (25 ml.) was added. The solution was treated with dry hydrogen chloride The precipitated hydrochloride was recrystallised from ethanol, m.p. 205 to 210°. Found: C, 67·75; H, 8·40; N, 8·34; Cl, 10·55 per cent. $C_{19}H_{28}ON,HCl$ requires C, 68·36; H, 8·38; N, 8·32; Cl, 10·38 per cent.

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