POTENTIAL RESERPINE ANALOGUES

PART III* DERIVATIVES OF 4-ETHOXYCARBONYLOXY-3,5-DIMETHOXYBENZOIC ACID, 3-DIMETHYLAMINOBENZOIC ACID, *p*-HYDROXYBENZANILIDE AND *N*-(3,4-DIMETHOXYPHENETHYL)-3(OR 4)-HYDROXYCYCLOHEXANE CARBOXYAMIDE

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4-Ethoxycarbonyloxy-3,5-dimethoxybenzanilide (I), 3-dimethylaminobenzanilide (II), *N*-(3,4-dimethoxyphenethyl)-4-ethoxycarbonyloxy-3,5-dimethoxybenzamide (III), *N*-(3,4-dimethoxyphenethyl)-3-dimethylaminobenzamide (IV), 4-(3,4,5-trimethoxybenzoyloxy)-benzanilide (V), 4-(4-ethoxycarbonyloxy-3,5-dimethoxybenzoyloxy)-benzanilide (VI), 3-acetoxy-*N*-(3,4-dimethoxyphenethyl)cyclohexanecarboxyamide (VII), 3-anisoyloxy-*N*-(3,4-dimethoxyphenethyl)cyclohexanecarboxyamide (VIII), *N*-(3,4-dimethoxyphenethyl)-3-veratroyloxycyclohexanecarboxyamide (IX), *N*-(3,4-dimethoxyphenethyl)-3-trimethoxybenzoyloxycyclohexanecarboxyamide (X), and *N*-(3,4-dimethoxyphenethyl)-4-trimethoxybenzoyloxycyclohexanecarboxyamide (XI) have been prepared. Eight of the compounds, I–VII and X, were compared with reserpine for their ability to potentiate barbiturate hypnosis in mice and to deplete the 5-hydroxytryptamine content of rat brain. None of them lowered the brain 5-hydroxytryptamine content but several showed barbiturate potentiation. Compound V was the most potent of the series in producing potentiation of barbiturate hypnosis, being about one tenth as action as reserpine.

FOLLOWING the elucidation of the structure of resperine a number of analogues have been synthesised but so far there has been no analogue of reserpine (methyl *O*-3,4,5-trimethoxybenzoylreserpate) prepared that has shown a similar or higher activity on the blood pressure or sedation. Lucas and others (1959) reported two most promising analogues; methyl *O*-3-dimethylaminobenzoylreserpate and syrosingopine [methyl-*O*-(4-ethoxycarbonyloxy-3,5-dimethoxybenzoyl)reserpate; carbethoxy syringoylmethyl reserpate] respectively. Karim, Sharp and Linnell (1960) reported that comparatively simple amides of 3,4,5-trimethoxybenzoic acid appeared to possess promising pharmacological activity and among the compounds reported, 3,4,5-trimethoxybenzanilide showed about one-eighth the activity of reserpine.

It seemed possible, therefore, that new compounds containing a combination of the favoured molecular fragments of the compounds already prepared might reveal increased pharmacological activity. As a result compounds I–XI were prepared. The present work describes the preparation of these compounds.

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Pharmacological

The compounds I–VII and X were dissolved or suspended in solvents such as glycerol formal, or dilutions of ethanol in water, and then compared with reserpine for their ability to potentiate the hypnosis in mice produced by an intravenous dose of hexobarbitone (50 mg./kg.), and to deplete the 5-hydroxytryptamine content of rat brain. The standard intraperitoneal dose of reserpine in the first test was 2 mg./kg., and in the second, 2·5 mg./kg.

Evaluation of these compounds was difficult, because of the lack of suitable solvents. However, none of the compounds reduced the brain 5-hydroxytryptamine content but several potentiated barbiturate hypnosis. Compound V was the most potent in this respect, although other compounds (e.g. VII–X) showed closer structural resemblances to reserpine.

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TABLE I

COMPARISON OF THE PHARMACOLOGICAL ACTIVITIES OF VARIOUS COMPOUNDS

	Potentiation of barbiturate hypnosis in mice		Depletion of 5-hydroxytryptamine in rat brain	
Compound No.	Maximum dose (mg./kg.)	Relative activity	Maximum dose (mg./kg.)	Relative activity
I	80	0·5	—	—
II	80	0·8	—	—
III	8	2·5	20	0·5
IV	20	2·0	20	0·5
V	10	10	10	0·1
VI	40	0·4	10	1·0
VII	—	—	40	0
X	10	8·0	20	0·5

EXPERIMENTAL

4-*Ethoxycarbonyloxy*-3,5-*dimethoxybenzoic acid.* Ethyl choroformate (16 g.) was added gradually to an ice-cold mechanically stirred solution of syringic acid (20 g.) in N aqueous sodium hydroxide (240 ml.). When the odour of the ester was no longer perceptible (left overnight), the solution was acidified with dilute hydrochloric acid, the precipitate collected, washed with water and dried in a vacuum desiccator. The crude acid was recrystallised twice from 50 per cent aqueous acetone. M.p. 178–181°. Yield 26 g. (95 per cent). Found C, 53·4; H, 4·8 per cent. $C_{12}H_{14}O_7$ requires C, 53·3; H, 5·1 per cent.

4-*Ethoxycarbonyloxy*-3,5-*dimethoxybenzanilide* (*I*). Freshly prepared 4-ethoxycarbonyloxy-3,5-dimethoxybenzoyl chloride (6 g.) (obtained from 4-ethoxycarbonyloxy-3,5-dimethoxybenzoic acid and thionyl chloride) was dissolved in ether (50 ml.) and added to an ice-cold mechanically

stirred solution of redistilled aniline (4 g.) in ether (50 ml.). The ethereal layer, after treatment with dilute hydrochloric acid and water, was dried with anhydrous magnesium sulphate. The solvent was removed and the solid residue was dissolved in benzene, treated with animal charcoal and crystallised by the addition of light petroleum (60–80°); after leaving in the refrigerator pale yellow needle-shaped crystals were obtained. Yield 4·5 g. (30 per cent), m.p. 165–166°. Found C, 62·6; H, 5·4, N, 3·9 per cent $C_{18}H_{19}NO_6$ requires C, 62·6; H, 5·5; N, 4·0 per cent.

N-(3,4-*Dimethoxyphenethyl*)-4-*ethoxycarbonyloxy*-3,5-*dimethoxybenzamide* (III). To 4-ethoxycarbonyloxy-3,5-dimethoxybenzoyl chloride (2·25 g.) dissolved in tetrahydrofuran (50 ml.) was added redistilled homoveratrylamine (1·81 g.) dissolved in tetrahydrofuran (50 ml.) over 1 hr. The reaction mixture was mechanically stirred for 1 hr. and the precipitated hydrochloride was removed by filtration. The solvent was removed under reduced pressure to leave gum, which was crystallised from tetrahydrofuran and ether, after treatment with animal charcoal and leaving overnight in the refrigerator. Further recrystallisation from 50 per cent ethanol gave colourless, long, needle-shaped crystals. Yield 1·7 g. (39 per cent), m.p. 93–94°. Found C, 59·3; H, 6·2; N, 3·2 per cent. $C_{22}H_{27}NO_8$ requires C, 60·4; H, 6·2; N, 3·3 per cent.

3-*Dimethylaminobenzanilide* (II). 3-Dimethylaminobenzoic acid was esterified with diazomethane and the ester (4·5 g.) was heated with aniline (3 ml.) on a metal bath at 200–210° for 7 hr. The reaction mixture was dissolved in benzene and refluxed with decolorising charcoal for 30 min. and filtered. To the filtrate was added light petroleum (60–80°). After one day silvery, shining clusters of crystals were obtained. Yield 2·5 g. (62 per cent); m.p. 133–134°. Found C, 75·0; H, 6·4; N, 11·5 per cent. $C_{15}H_{16}N_2O$ requires C, 75·0; H, 6·6; N, 11·7 per cent.

N-(3,4-*Dimethoxyphenethyl*)-3-*dimethylaminobenzamide* (*IV*). Redistilled homoveratrylamine (1·71 g.) and methyl *m*-dimethylaminobenzoate (1·64 g.) were heated together on a metal bath at 160–180° for 3 hr. The brown-coloured transparent reaction product was treated as in the previous experiment and recrystallised from benzene and light petroleum (60–80°) to give needle-shaped crystals, m.p. 100–101°, Yield 2·6 g. (84 per cent). Found C, 69·8; H, 7·2; N, 8·8 per cent. $C_{19}H_{24}N_2O_3$ requires C, 69·5; H, 7·3; N, 8·5 per cent.

4-(3,4,5-*Trimethoxybenzoyloxy*)*benzanilide* (*V*). *p*-Hydroxybenzanilide (0·24 g.) was dissolved in dry pyridine (5 ml.) at room temperature. 3,4,5-Trimethoxybenzoyl chloride (0·32 g.) (obtained by inter-reaction of 3,4,5-trimethoxybenzoic acid and thionyl chloride) was slowly added with shaking. The mixture was left for 1 hr., poured into ice-cold water (50 ml.), and vigorously stirred when a precipitate was deposited. The precipitate was removed by filtration washed first with 1 per cent Na_2CO_3 solution and then with cold water, dried and recrystallised thrice from benzene. Yield 0·357 g. (77 per cent); m.p. 200–201°. Found C, 68·1; H, 5·3; N, 4·0 per cent. $C_{23}H_{21}NO_6$ requires C, 67·8; H, 5·1; N, 3·6 per cent.

4-(4-*Ethoxycarbonyloxy*-3,4-*dimethoxybenzoyloxy*)*benzanilide* (*VI*). This was similarly prepared from *p*-hydroxybenzanilide (0·21 g.) and 4-ethoxycarbonyloxy-3,5-dimethoxybenzoyl chloride (0·32 g.) in pyridine (6 ml.). The crude product was crystallised from benzene and light petroleum (60–80°). Yield 0·34 g. (74 per cent); m.p. 162–163°. Found C, 64·9; H, 5·0; N, 3·0 per cent. $C_{25}H_{23}NO_8$ requires C, 64·5; H, 4·9; N, 3·0 per cent.

N-(3,4-*Dimethoxyphenethyl*)-3-*hydroxycyclohexanecarboxyamide* (*XII*). *Method* (*a*). 3-Hydroxycyclohexanecarboxylic acid (as prepared by Noyce and Denney (1952) (0·49 g.) and homoveratrylamine (0·615 g.) were heated together on a metal bath at 200–210° for 1½ hr. The reaction product (a gum) was dissolved in warm benzene (100 ml.) and refluxed with decolorising charcoal for 2 hr., filtered and the volume reduced to about 10 ml. On addition of light petroleum (40–60°) and leaving aside for three days a solid substance was obtained. After three crystallisations from benzene a constant melting-point was obtained. Yield 0·35 g. (17 per cent); m.p. 117–118°. Found C, 65·9; H, 8·2; N, 4·8 per cent. $C_{17}H_{25}NO_4$ requires C, 66·4; H, 8·1; N, 4·6 per cent.

Method (*b*). Ethyl 3-hydroxycyclohexanecarboxylate (as prepared by Ungnade and Morriss, 1948) (1·14 g.) and homoveratrylamine (1·15 g.) were similarly treated for 3 hr. and the reaction product was recrystallised four times from benzene to yield the crystalline amide, m.p. 117–118°. Yield 0·98 g. (50 per cent). Mixed m.p. with the product of Method (a) 117–118·5°.

3-*Acetoxy*-N-(3,4-*dimethoxyphenethyl*)*cyclohexanecarboxyamide* (*VII*). *N*-(3,4-Dimethoxyphenethyl)-3-hydroxycyclohexanecarboxyamide (XII) (0·195 g.) and acetyl chloride (1 ml.) were warmed for 5 min. on a very low flame and on cooling the reaction mixture was poured into water (10 ml.). The white precipitate obtained was washed with water, dried and recrystallised from benzene and light petroleum (40–60°) to yield needle-shaped crystals. Yield 0·23 g. (82 per cent), m.p. 108–109°. Found C, 65·4; H, 8·1; N, 3·9 per cent. $C_{19}H_{27}NO_5$ requires C, 65·3; H, 7·7; N, 4·0 per cent.

3-*Anisoyloxy*-N-(3,4-*dimethoxyphenethyl*)*cyclohexanecarboxyamide* (*VIII*). The amide (XII) (0·175 g.) was dissolved in dry pyridine (3 ml.). To this was added anisoyl chloride (0·5 g.). The mixture was refluxed for 30 min. and left aside for three days. It was then poured into ice-cold water, vigorously stirred and extracted with benzene. The benzene extracts were refluxed with decolorising charcoal, filtered, dried over anhydrous magnesium sulphate, and the solvent removed under reduced pressure on a water-bath leaving a pale yellow viscous substance. This crystallised from ether and light petroleum and two crystallisations yielded white granular crystals. Yield 0·15 g. (38 per cent); m.p. 128–130° (softens at 125°). Found C, 68·6; H, 7·0 per cent. $C_{25}H_{31}NO_6$ requires C, 68·0; H, 7·0 per cent.

N-(3,4-*Dimethoxyphenethyl*)-3-*veratroyloxycyclohexanecarboxyamide* (*IX*). On treating similarly the amide (XII) (0·31 g.) with veratroyl chloride (0·395 g.) in pyridine (4 ml.) a white flocculent precipitate was

obtained. Two recrystallisations from benzene and light petroleum (60–80°) gave a substance melting at 97–98°. Yield 0·285 g. (60 per cent). Found C, 66·4; H, 7·1; N, 3·0 per cent. $C_{26}H_{33}NO_7$ requires C, 66·2; H, 7·0; N, 3·0 per cent.

N-(3,4-*Dimethoxyphenethyl*)-3-*trimethoxybenzoyloxycyclohexanecarboxyamide* (*X*). 3,4,5-Trimethoxybenzoyl chloride (0·275 g.) was treated similarly with the amide (XII) (0·305 g.) in pyridine (5 ml.) to give a white precipitate. After two recrystallisations from benzene and light petroleum (40–60°) granular crystals melted at 140–142°. Yield 0·16 g. (32 per cent.) Found C, 65·0; H, 7·1; N, 2·6 per cent. $C_{27}H_{35}NO_8$ requires C, 64·7; H, 7·0; N, 2·8 per cent.

N-(3,4-*Dimethoxyphenethyl*)-4-*hydroxycyclohexanecarboxyamide* (*XIII*). Homoveratrylamine (1·3 g.) and ethyl 4-hydroxycyclohexanecarboxylate (as prepared by Ungnade and Morriss, 1948) (1·295 g.) were heated together on a metal bath at 200–220° for 3 hr. After working up the reaction product as in the preparation of the amide (XII), four recrystallisations from benzene gave needle-shaped crystals. Yield 0·81 g. (37 per cent), m.p. 98–99°. Found C, 66·8; H, 8·1; N, 4·3 per cent. $C_{17}H_{25}NO_4$ requires C, 66·4; H, 8·1; N, 4·6 per cent.

N-(3,4-*Dimethoxyphenethyl*)-4-*trimethoxybenzoyloxycyclohexanecarboxyamide* (*XI*). The amide (XIII) (0·100 g.) was treated exactly in the same way as for the amide (XII) with 3,4,5-trimethoxybenzoyl chloride (0·145 g.) in pyridine (1 ml.) to give a substance melting at 144–145°. Yield, 0·080 g. (49 per cent). Found C, 64·5; H, 7·0 per cent. $C_{27}H_{35}NO_8$ requires C, 64·7; H, 7·0 per cent.

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