# POTENTIAL RESERPINE ANALOGUES

## PART II. 3,4,5-TRIMETHOXYBENZOIC ACID DERIVATIVES

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Seven derivatives of 3,4,5-trimethoxybenzoic acid have been prepared and tested for their ability to potentiate barbiturate hypnosis in mice, to deplete the 5-hydroxytryptamine content of rat brain, and to exert a hypotensive action on the cat blood pressure. The only derivative to exert all three actions is the simple anilide, 3,4,5-trimethoxybenzanilide, which is about 8 times less active than reserpine. The anilide, *N*-(3,4-dimethoxyphenethyl)-3,4,5-trimethoxybenzamide, is also about 8 times less active than reserpine in the first two tests but it raises the blood pressure.

THE report of Miller and Weinberg[1] that 3-diethylaminopropyl 3,4,5-trimethoxybenzoate has reserpine-like activity (one-third that of the potency of reserpine) raises the question of the necessity of any of the ring systems of reserpine. A number of similar compounds have recently been prepared by Zdenek and colleagues[3]; Sastry and Lasslo[2] and Perron[4,5] but complete pharmacological tests on the products have not been carried out.

The present work describes the preparation of trimethoxybenzoyl derivatives which retain only the ring A of reserpine, the other rings being represented only by fragments. To this end the compounds indicated in Figure 1 were synthesised. Finally ring A was dispensed with in the *N*-pentyl derivative of trimethoxybenzamide (VII).

### *Pharmacological Data*

The compounds were compared with reserpine for their power (i) to potentiate the hypnosis in mice produced by an intravenous dose of hexobarbitone (50 mg./kg.), (ii) to deplete the 5-hydroxytryptamine (5-HT) content of rat brain, and (iii) to exert a hypotensive action on the arterial blood pressure of a cat anaesthetised with nembutal and chloralose. The standard doses of reserpine were 5 mg./kg. intraperitoneally in test (*a*), 1 mg./kg. intraperitoneally in test (*b*) and 1 mg./kg. subcutaneously in test (*c*). The doses of the new compounds used and their relative activities are shown in Table I.

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.

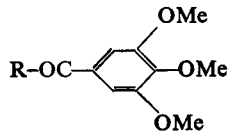
### *Discussion of Pharmacology*

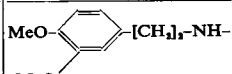
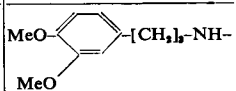
These comparatively simple components are pharmacologically more promising than the tryptamine derivatives discussed in Part I[6]. The

anilide (II) is the only compound so far tested which simulates three of the properties of reserpine (potentiation of barbiturate hypnosis, depletion of brain 5-HT, and hypotensive action). Compound II nevertheless does not appear to act like reserpine even in these three tests, for although

TABLE I

COMPARISON OF THE PHARMACOLOGICAL ACTIVITIES OF VARIOUS DERIVATIVES OF 3,4,5-TRIMETHOXYBENZOIC ACID. (RESERPINE ACTIVITY IS TAKEN AS 100 FOR EACH TEST)




| Trimethoxybenzoic acid derivative | R | Potentiation of barbiturate hypnosis in mice | | Depletion of 5-HT in rat brain | | Action on cat blood pressure | |
|---|---|---|---|---|---|---|---|
| | | Max. dose used (mg./kg.) | Relative activity | Max. dose (mg./kg.) | Relative activity | Dose (mg./kg.) | Effect |
| I | $NH_2$– | 150 | 1 | 40 | 0 | — | — |
| II |  | 40* | 10–16 | 40 | 10–16 | 20 | Hypotension + adrenergic block |
| III |  | 80 | 0 | — | — | 50 | Adrenergic block only |
| IV |  | 80 | 0 | 20 | 0 | 50 | Adrenergic block |
| V |  | 100 | 12 | 20 | 10 | 25 | Hypertension |
| VI |  | 80 | 1 | 20 | 3·5 | 22 | Hypertension |
| VII | Me-$[CH_2]_4$-NH- | 100 | 1–3 | — | — | — | — |

* Some of the mice died at this dose level.

it is a hypotensive agent it also possesses marked anti-adrenaline activity. Alkylation of the N atom in compound II results in compounds which have no activity in tests (i) and (ii) and only adrenergic block activity in test (iii).

When the N atom in compound II does not form part of the aromatic ring system but forms benzamides (as in V, VI and VII), the compounds potentiate barbiturate hypnosis and deplete the brain of 5-HT but exert *hyper*tensive effects on the blood pressure.

The results indicate that the actions of comparatively simple derivatives of 3,4,5-trimethoxybenzoic acid mimic those of reserpine in a few tests, and the indole nucleus is not so important for reserpine-like activity as has been suggested by other authors.

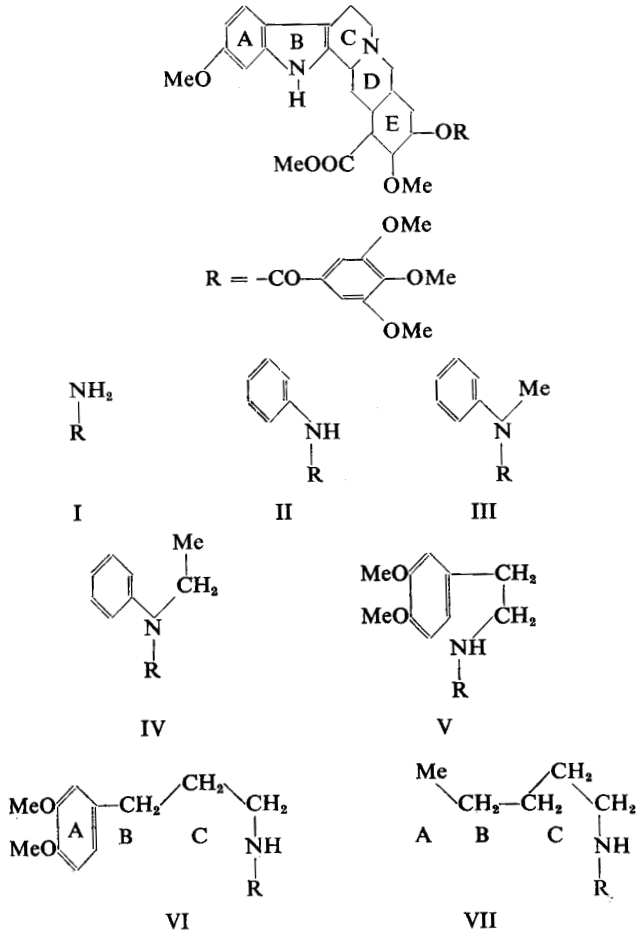



FIG. 1

## EXPERIMENTAL

*Expt.* 1. 3-(3,4-*Dimethoxyphenyl*)*propylamine.* β-(3,4-Dimethoxyphenyl)propionamide (prepared according to the method of Buck and Perkin[7] (8 g.) in tetrahydrofuran (150 ml.) was added dropwise to a boiling suspension of $LiAlH_4$ (3 g.) in ether (150 ml.). The reaction mixture was refluxed for 72 hours and cooled. The excess $LiAlH_4$ was destroyed by the dropwise addition of aqueous tetrahydrofuran with vigorous shaking and 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: 6·3 g. (85 per cent), b.p. 125 to 130°/1·5 mm., $n_D^{22}$ 1·5338.

*Hydrochloride.* The above amine (2·1 g.) in ether (100 ml.) was treated with dry hydrogen chloride and the precipitated hydrochloride recrystallised from ethanol and ether. Yield: 1·8 g. (72 per cent), m.p. 162 to 163°. Found: C, 57·05; H, 7·86; N, 6·29; Cl, 14·93; per cent. $C_{11}H_{17}O_2N$,HCl requires C, 57·10; H, 7·79; N, 6·06; Cl, 15·15 per cent.

*Expt.* 2. 3,4,5-*Trimethoxybenzamide* (*I*). 3,4,5-Trimethoxybenzoyl chloride (10 g.) in ether (50 ml.) was cooled below 10° and excess ammonia (sp.gr. 0·88) (50 ml.) added dropwise with constant stirring. The reaction mixture was stirred well for about 30 minutes at the same temperature and then allowed to stand at room temperature for another 30 minutes with occasional shaking. The precipitated amide was recrystallised from benzene. Yield: 8·09 g. (88 per cent), m.p. 176 to 177° (lit. 176 to 177°).

*Expt.* 3. 3,4,5-*Trimethoxybenzanilide* (*II*). 3,4,5-Trimethoxybenzoyl chloride (4·6 g.) in tetrahydrofuran (15 ml.) was added dropwise to a cooled solution (below 10°) of aniline (3·72 g.) in ether (50 ml.). The mixture was stirred at room temperature for about an hour and then allowed to stand for a further 2 hours. The precipitated aniline hydrochloride was removed and the solvent removed by distillation under reduced pressure. The solid residue was recrystallised from methanol. Yield: 4·9 g. (85 per cent) m.p. 137 to 139°. Found: N, 4·90 per cent, requires N, 4·87 per cent.

*Expt.* 4. 3,4,5-*Trimethoxy*-N-*methylbenzanilide* (*III*). *N*-Methylaniline (2·3 g.) in ether (25 ml.) was added dropwise to a cooled solution (below 10°) of 3,4,5-trimethoxybenzoyl chloride (2 g.) in tetrahydrofuran (10 ml.). The mixture was stirred well at room temperature for 1 hour. The precipitated hydrochloride was removed and the solution was washed with 3N hydrochloric acid. The extract was dried over anhydrous sodium sulphate and the solvent removed. The residue was recrystallised from methanol. Yield: 1·65 g. (63 per cent), m.p. 80·5 to 82°, b.p. 178 to 180°/0·3 mm. Found: C, 66·94; H, 6·37; N, 4·62 per cent. $C_{17}H_{19}O_4N$ requires C, 67·74; H, 6·34; N, 4·62 per cent.

*Expt.* 5. N-*Ethyl*-3,4,5-*trimethoxybenzanilide* (*IV*). 3,4,5-Trimethoxybenzoyl chloride (2·3 g.) in dry ether (25 ml.) was added dropwise to a cooled solution (below 10°) of *N*-ethylaniline (2·45 g.) in ether (25 ml). with constant shaking. Immediate formation of *N*-ethylaniline hydrochloride was observed. The mixture was stirred at room temperature for 30 minutes and then allowed to stand for 40 hours. The *N*-ethylaniline hydrochloride was removed by filtration and the solvent by distillation under reduced pressure. The residue was distilled *in vacuo*. Yield: 2·8 g. (87 per cent), b.p. 165 to 170°/0·2 mm., m.p. 70·5 to 72° (aqueous methanol). Found: C, 68·50; H, 6·96; N, 4·37 per cent. $C_{18}H_{22}O_4N$ requires C, 68·40; H, 6·96; N, 4·43 per cent.

*Expt.* 6. N-(3,4-*Dimethoxyphenethyl*)-3,4,5-*trimethoxybenzamide* (*V*). 3,4,5-Trimethoxybenzoyl chloride (1·2 g.) in tetrahydrofuran (20 ml.) was added dropwise to a cooled and well stirred solution of homoveratrylamine (1·8 g.) in ether (25 ml.). The mixture was stirred at room temperature for 20 minutes and then allowed to stand overnight.

The precipitated homoveratrylamine hydrochloride was separated by filtration, the solution was dried over anhydrous sodium sulphate, and the solvent removed by distillation under reduced pressure. The solid residue was recrystallised from aqueous methanol. Yield: 1·5 g. (74 per cent), m.p. 134 to 135°. Found: C, 64·00; H, 6·65; N, 3·73 per cent. $C_{20}H_{25}O_6N$ requires C, 63·98; H, 6·69; N, 3·73 per cent.

*Expt.* 7. N-[3-(3,4-*Dimethoxyphenyl*)*propyl*]-3,4,5-*trimethoxybenzamide* (*VI*). 3,4,5-Trimethoxybenzoyl chloride (1·5 g.) in tetrahydrofuran (15 ml.) was added dropwise to a cooled (below 10°) solution of 3-(3,4-dimethoxyphenyl)propylamine (1·95 g.) in tetrahydrofuran (20 ml.) with constant stirring. The reaction mixture was allowed to stand overnight at room temperature and the precipitated hydrochloride of 3-(3,4-dimethoxyphenyl)propylamine removed by filtration and the solvent by distillation under reduced pressure. The solid residue was recrystallised from ether. Yield: 1·5 g. (75 per cent), m.p. 105 to 106°. Found: C, 64·66; H, 7·27; N, 3·61 per cent. $C_{21}H_{27}O_6N$ requires C, 64·80; N, 6·97; N, 3·60 per cent.

*Expt.* 8. 3,4,5-*Trimethoxy*-N-*pentylbenzamide* (*VII*). 3,4,5-Trimethoxybenzoyl chloride (2·3 g.).) in tetrahydrofuran (10 ml.) was added dropwise to a cooled (below 10°) stirred solution of pentylamine (1·74 g.) in ether (35 ml.). The reaction mixture was strongly acidified with hydrochloric acid and extracted with ether. The ether extract was dried over anhydrous sodium sulphate and the solvent removed. The solid residue was recrystallised from ether. Yield: 1·85 g. (66 per cent), m.p. 108 to 110°. Found: C, 64·31; H, 8·01; N, 4·88 per cent. $C_{15}H_{23}O_4N$ requires C, 64·15; H, 8·23; N, 4·98 per cent.

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