388. *The Amino-acid Analogue of Mescaline.*

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Mescaline, or 3,4,5-trimethoxyphenethylamine, is well known as a hallucinogen although it is very much less effective on a weight basis than lysergic acid diethylamide,[1] and both of these compounds are used in the treatment of certain mental disorders.[2] 5-Hydroxytryptophan [3] and 3,4-dihydroxyphenylalanine [4] pass the blood-brain barrier readily in contrast to the amines produced on decarboxylation, and there is much evidence [5] that

[1] Downing, *Quart. Rev.*, 1962, **16**, 133.
[2] Cohen, *J. Nervous and Mental Disease*, 1960, **130**, 30.
[3] Udenfriend, Weissbach, and Bogdanski, *Ann. New York Acad. Sci.*, 1956—1957, **66**, 602.
[4] Carlsson, Lindqvist, and Magnusson, *Nature*, 1957, **180**, 1200.
[5] Dobbing, *Physiol. Rev.*, 1961, **41**, 130.

the blood-brain barrier is rapidly permeable to many amino-acids. The synthesis of the amino-acid analogue of mescaline was therefore undertaken in the hope that it would be a more powerful hallucinogen than the parent compound and have useful therapeutic properties.

3,4,5-Trimethoxybenzaldehyde, under standard conditions,[6] gave poor yields of the corresponding 2-methyl- and 2-phenyl-oxazolones. The latter was hydrogenated and partially hydrolysed to α-benzamido-β-3,4,5-trimethoxyphenylpropionic acid, but subsequent acid hydrolysis gave a mixture which was not successfully resolved. The benzaldehyde readily condensed with nitroacetonitrile [7] yielding β-cyano-3,4,5-trimethoxy-β-nitrostyrene, but selective reduction of the nitro-group and the ethylenic double-bond failed. Attempted acid hydrolysis of the styrene rather surprisingly regenerated the original aldehyde, presumably through consecutive Michael addition and reverse aldol reactions. 3,4,5-Trimethoxyphenylalanine hydrochloride was finally obtained from 3,4,5-trimethoxybenzaldehyde by successive reaction with sodium borohydride, thionyl chloride,[8] diethyl acetamidosodiomalonate, and aqueous hydrochloric acid. The results of pharmacological testing will be reported elsewhere.

Experimental.—*2-Methyl-5-(3,4,5-trimethoxybenzylidene)oxazolone.* 3,4,5-Trimethoxybenzaldehyde (4·0 g.), acetylglycine (3·0 g.), freshly fused sodium acetate (2·0 g.), and acetic anhydride (18 ml.) were heated at 100° for 90 min., cooled, and diluted with water (36 ml.). The precipitate was washed with aqueous acetic acid (33%) and with water, and yielded the *oxazolone* (1·2 g.), which separated from acetone in yellow needles, m. p. 158—159° (Found: C, 60·6; H, 5·4; N, 5·1. $C_{14}H_{15}NO_5$ requires C, 60·6; H, 5·4; N, 5·1%).

α-Acetamido-3,4,5-trimethoxycinnamic acid. The oxazolone (0·5 g.) was refluxed for 30 min. in 50% aqueous ethanol. The *acid* (0·3 g.) separated on cooling and crystallised from the same solvent in needles, m. p. 199·5—200·5° (Found: C, 56·8; H, 5·7; N, 4·8. $C_{14}H_{17}NO_6$ requires C, 56·9; H, 5·8; N, 4·7%).

2-Phenyl-5-(3,4,5-trimethoxybenzylidene)oxazolone.—3,4,5-Trimethoxybenzaldehyde (5·3 g.), hippuric acid (4·2 g.), anhydrous sodium acetate (2·7 g.), and acetic anhydride (27 ml.) were heated in an oil bath at 120° for 30 min. and then at 100° for 3 hr. The mixture was poured into water (200 ml.) and neutralised with sodium carbonate; the precipitate was dried over concentrated sulphuric acid *in vacuo*. Four crystallisations from benzene gave the *oxazolone* (3·3 g.) as yellow needles, m. p. 160° (Found: C, 67·0; H, 5·1; N, 4·4. $C_{19}H_{17}NO_5$ requires C, 67·2; H, 5·0; N, 4·1%).

α-Benzamido-3,4,5-trimethoxycinnamic acid. The last oxazolone (0·5 g.) was refluxed with potassium hydroxide (1·0 g.) in 50% aqueous ethanol (25 ml.) until it dissolved (7 hr.). Evaporation to half volume, and acidification, precipitated the *cinnamic acid*, which crystallised from water in needles (0·4 g.), m. p. 181—182° (Found: C, 63·9; H, 5·3; N, 3·9. $C_{19}H_{19}NO_6$ requires C, 63·8; H, 5·3; N, 3·9%).

α-Benzamido-β-(3,4,5-trimethoxyphenyl)propionic acid. 2-Phenyl-5-(3,4,5-trimethoxybenzylidene)oxazolone (2·6 g.), suspended in aqueous methanol (200 ml.), was shaken under hydrogen over Raney nickel for 12 hr. Filtration and evaporation gave the *acid* (2·5 g.), which separated in needles, m. p. 121—122° (Found: C, 63·2; H, 6·0; N, 3·8. $C_{19}H_{21}NO_6$ requires C, 63·5; H, 5·8; N, 3·9%).

3,4,5-Trimethoxy-α-methylcinnamic acid. 3,4,5-Trimethoxybenzaldehyde (10 g.) in ethyl propionate (55 ml.) was added with stirring during 30 min. to a mixture of powdered sodium (1·5 g.), ethyl propionate (25 ml.), and ethanol (0·2 ml.) at 0—5°. Ethanol (10 ml.) was then added and after 12 hr. at room temperature the mixture was poured into water (200 ml.), and the ether-soluble fraction collected and refluxed for 30 min. with sodium hydroxide (10 g.) in water (30 ml.) and ethanol (20 ml.). Acidification, evaporation, and cooling precipitated the *acid* (7·9 g.) which crystallised from light petroleum (b. p. 60—80°) in needles, m. p. 155—156° (Found: C, 61·7; H, 6·5. $C_{13}H_{16}O_5$ requires C, 61·9; H, 6·4%).

α-Methyl-β-(3,4,5-trimethoxyphenyl)propionic acid. The previous acid (7·0 g.) in 2N-sodium

[6] Carter, *Org. Reactions*, 1946, **3**, 198.
[7] Ried and Köhler, *Annalen*, 1957, **598**, 145.
[8] Cook, Graham, Cohen, Lapsley, and Lawrence, *J.*, 1944, 322.

hydroxide was shaken under hydrogen over Raney nickel for 8 hr. Filtration, acidification at 100°, and cooling precipitated the *propionic acid* (6·2 g.) which separated from water as prisms, m. p. 116—117° (Found: C, 61·8; H, 7·2. $C_{13}H_{18}O_5$ requires C, 61·4; H, 7·1%).

β-Cyano-3,4,5-trimethoxy-β-nitrostyrene. 3,4,5-Trimethoxybenzaldehyde (1·9 g.) and nitroacetonitrile (1·7 g.) were heated in ethanol (10 ml.) with the addition of a few drops of aqueous sodium carbonate containing methylamine hydrochloride. The precipitate, which formed rapidly, crystallised from carbon tetrachloride, to give the *nitro-compound* (2·55 g.) as orange needles, m. p. 180° (Found: C, 54·7; H, 4·6; N, 10·8; OMe, 34·7. $C_{12}H_{12}N_2O_5$ requires C, 54·5; H, 4·5; N, 10·6; OMe, 35·2%), $\nu_{max.}$ (Nujol paste) 2240 (C≡N), and 1570 and 1310 cm.$^{-1}$ (NO_2).

The nitro-compound (2·5 g.), concentrated hydrochloric acid (40 ml.), water (110 ml.), and ethanol (50 ml.) were refluxed for 8 hr., the ethanol evaporated, and the residue extracted with ether. Addition of light petroleum (b. p. 40—60°) to the dried extract precipitated 3,4,5-trimethoxybenzaldehyde (0·73 g.) which was identical (m. p. and infrared spectrum) with an authentic specimen.

The nitro-compound (0·85 g.) and 2,4-dinitrophenylhydrazine (0·64 g.) were refluxed in concentrated hydrochloric acid (30 ml.), water (100 ml.), and ethanol (225 ml.) for 2 hr., and after cooling the precipitate was collected. Crystallisation from glacial acetic acid gave 3,4,5-trimethoxybenzaldehyde 2,4-dinitrophenylhydrazone (1·27 g.), m. p. and mixed m. p. identical with that of an authentic specimen, 242—244° (decomp.) (lit.,[9] 242—246°).

3,4,5-Trimethoxybenzyl alcohol. 3,4,5-Trimethoxybenzaldehyde (8·3 g.) in ethanol (250 ml.) was added dropwise to a stirred suspension of potassium borohydride (8·15 g.) in ethanol (200 ml.), and the mixture subsequently refluxed for 7 hr. When cool, the mixture was acidified with dilute sulphuric acid, the ethanol evaporated *in vacuo*, and the residue extracted with ether. Evaporation of the washed, dried extract gave the alcohol as an oil (6·9 g.), which was characterised as the 3,5-dinitrobenzoate, m. p. 146° (lit.,[8] 147—148°)

Diethyl α-acetamido-α-3,4,5-trimethoxybenzylmalonate. Diethyl acetamidomalonate (0·55 g.) and 3,4,5-trimethoxybenzyl chloride (0·5 g.) were added to a solution of sodium (0·059 g.) in ethanol (5 ml.) and, after refluxing for 2 hr., most of the ethanol was removed *in vacuo* and water added. Extraction with ether and evaporation of the dried extract gave the *ester* (0·72 g.) which separated from light petroleum (b. p. 80—100°) as flakes, m. p. 116° (Found: C, 57·6; H, 6·8; N, 3·6; " OMe," 39·3. $C_{19}H_{27}NO_8$ requires C, 57·4; H, 6·8; N, 3·5; OMe and OEt calculated as " OMe," 39·1%).

3,4,5-Trimethoxyphenylalanine hydrochloride. The above acetamidomalonic ester (0·3 g.) was refluxed with 5N-aqueous hydrochloric acid (10 ml.) for 4 hr., and the *hydrochloride* separated on cooling. It crystallised from the same solvent in needles (0·14 g.), m. p. *ca.* 242° (decomp.) (Found: C, 49·5; H, 6·4; Cl, 12·1. $C_{12}H_{17}NO_5$,HCl requires C, 49·4; H, 6·2; Cl, 12·2%). It gave a purple colour with ninhydrin, and travelled as a single material of R_F 0·54 and 0·49 in n-butanol–acetic acid–water (4 : 1 : 1 v/v), and propan-2-ol–ammonia (*d* 0·88)–water (8 : 1 : 1), respectively.

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[9] Milletti, *Ann. Chim.* (*Italy*), 1955, **45**, 1211.