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MESCALINE ANALOGS. IV. SUBSTITUTED 4,5,6-TRIMETHOXYINDOLES

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In a further study of compounds derived from physiologically active polyalkoxy-β-phenethylamines (1–3), we have undertaken the synthesis of several trimethoxyindole compounds related to noradrenolutin trimethyl ether (3,5,6-trimethoxyindolin). This paper describes the preparation of 2-carbethoxy-4,5,6-trimethoxyindoxyl (III), 2-carbethoxy-3,4,5,6-tetramethoxyindole (IV), and 4,5,6-trimethoxy-3-hydroxy-3-carbethoxyindole (V). 3,4,5-Trimethoxyaniline (I) served as a starting material for the synthesis of all of these substances.

By reaction of I with bromomalonic ester, in accordance with the procedure of Balsiger, *et al.* (4), N-(3,4,5-trimethoxyphenyl)aminomalonic ester (II) was obtained. Thermal cyclization of II in Nujol at 245° resulted in a 14% yield of the corresponding indoxyl (III); neither concentrated sulphuric acid nor phosphorous pentoxide were effective in bringing about this cyclization at lower temperatures. Treatment with methyl sulphate and alkali transformed the enol form of III to 3,4,5,6-tetramethoxy-2-carbethoxyindole (IV).

Although the Martinet reaction (5) has been used to prepare a variety of substituted dioxindoles from the corresponding anilines and oxomalonic ester, only a single instance is reported for the reaction having taken place with an alkoxyaniline (6). By following a slight modification of Langenbeck's procedure (7), I reacted smoothly with oxomalonic ester in glacial acetic acid to give 4,5,6-trimethoxy-3-hydroxy-3-carbethoxyoxindole (V) in 87% yield. The structure of V was established by oxidation to the bright orange-red 4,5,6-trimethoxyisatin (VI); this oxidation product gave the characteristic blue color reaction (8, 9) of an isatin compound with thiophene and sulphuric acid.

Several unsuccessful attempts were made to prepare 4,5,6-trimethoxy-2,3-dihydroindole. For example, refluxing I with ethylene chlorobromide gave N,N′-bis-(3,4,5-trimethoxyphenyl) piperazine (VII) rather than the desired indole. N-(3,4,5-trimethoxyphenyl)chloracetamide (VIII) underwent extensive demethylation during all attempts to cyclize this material to 4,5,6-trimethoxyoxindole in the presence of aluminum chloride according to a modification of the procedure described by Smith (10).

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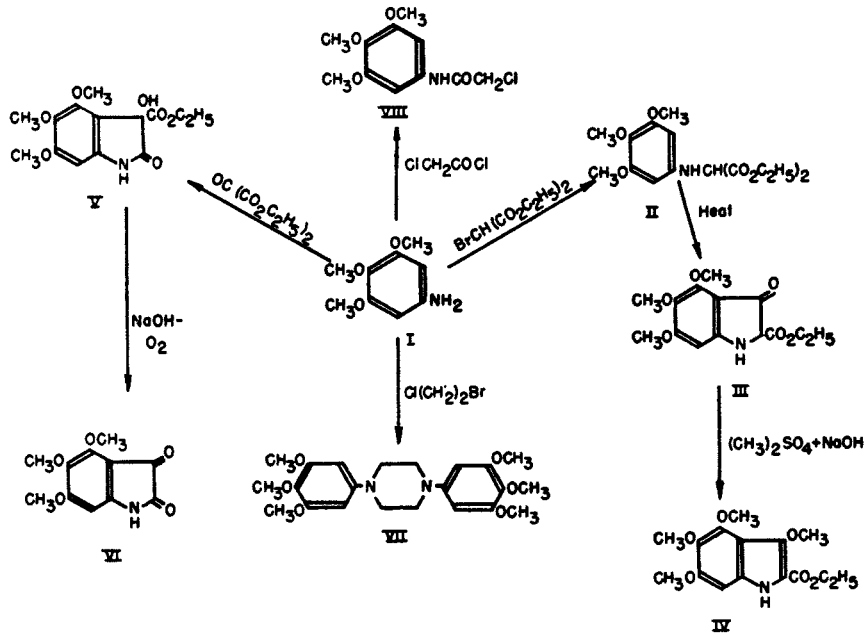

CHART I

EXPERIMENTAL

(All melting points uncorrected).

3,4,5-Trimethoxyaniline (I). Gallic acid was converted to trimethylgallic acid in 80% yield by methylation with methyl sulphate (11). Trimethylgalloyl chloride was obtained in 81% yield by the action of phosphorus pentchloride on trimethylgallic acid (12). Treatment of a cold benzene solution of the acid chloride with an excess of gaseous ammonia gave a nearly quantitative yield of 3,4,5-trimethoxybenzamide (13).

The procedure described by Buck and Ide for the preparation of 4-aminoveratrole (14) proved to be most satisfactory for conversion of the benzamide to I. To a cold solution of sodium hypochlorite, prepared by the addition of 28.3 g. of chlorine to 590 ml. of water containing 95 g. of sodium hydroxide and 360 g. of crushed ice, 80 g. of 3,4,5-trimethoxybenzamide was added in one portion. The temperature of the mixture was allowed to increase gradually to 65–70° within one hour after adding the amide. A solution of 130 g. of NaOH in 130 ml. of water then was added to the mixture; stirring and heating were continued for an additional hour. The nearly white crystalline amine which separated was collected and washed with several portions of water. The crude product, weighing 46 g. (66%), melted at 116–118° [lit. (15) m.p. 113–114°].

N-(3,4,5-Trimethoxyphenyl)aminomalonic ester (II). A mixture of 36.6 g. of I, 125 ml. of dry benzene, and 23.9 g. of diethyl bromomalonate (16) was refluxed for four hours and then cooled; the precipitated hydrobromide of I (24 g.) was recovered by filtration. The dark filtrate was concentrated to a small volume under reduced pressure and then was diluted with a large volume of 30–60° petroleum ether. Upon cooling, there was obtained 23.7 g. (70%) of crude II as a purple crystalline solid. Recrystallization from methanol-water gave 17.1 g. (50%) of purified II as small white prisms melting at 103–104°.

Anal. Calc'd for $C_{16}H_{23}NO_7$: C, 56.3; H, 6.75; N, 4.11.

Found: C, 56.3; H, 6.86; N, 4.02.

4,5,6-Trimethoxyindoxyl-2-carboxylic ester (III). To 46 ml. of mineral oil (Nujol) which had been preheated to 245–250°, was added 9.9 g. of the aminoester (II) while maintaining vigorous stirring; the temperature of the mixture was held at 240–250° for 0.75 hour. Upon

cooling, the dark-brown semisolid product which had separated was recovered by decantation of the oil layer. This crude cyclization product was taken up in ether, filtered and evaporated. Two subsequent recrystallizations of the dark-brown residue from benzene-ligroin gave 1.2 g. (14%) of III melting at 168–170°. Sublimation *in vacuo* gave yellow prisms; m.p. 168–169°.

Anal. Calc'd for $C_{14}H_{17}NO_6$: C, 57.0; H, 5.8.

Found: C, 57.3; H, 5.9.

3,4,5,6-Tetramethoxy-2-carbethoxyindole (IV). To an ice-cold solution of 0.7 g. of III in 3.5 ml. of 2 *N* KOH was added 1.8 g. of dimethyl sulphate. Although no reaction occurred at 0°, warming the mixture to 35–40° caused a rapid consumption of the dimethyl sulphate. The resulting clear yellow solution was extracted with several portions of ether. Evaporation of the ether extract gave a residue of 0.3 g. (41%) of green-white needles; m.p. 135–136°, after recrystallization from benzene-petroleum ether.

Anal. Calc'd for $C_{15}H_{19}NO_6$: C, 58.2; H, 6.15.

Found: C, 58.7; H, 6.17.

4,5,6-Trimethoxy-3-hydroxy-3-carbethoxyoxindole (V). A solution of 1.8 g. of 3,4,5-trimethoxyaniline in 10 ml. of glacial acetic acid was treated with 1.9 g. of ethyl oxomalonate (dihydrate). The resulting olive-green solution was heated on the steam-bath for 10 minutes and then kept for two hours at room temperature. Diluting the solution with 125 ml. of water and then adding solid ammonium carbonate to give a final *p*H of 8 caused the carbethoxyoxindole (V) to precipitate as a light-tan solid. The crude product, weighing 2.7 g. (86.8%), melted at 187–189°. Recrystallization from a mixture of ether-benzene-petroleum ether afforded V as colorless prisms; m.p. 189–190°.

Anal. Calc'd for $C_{14}H_{17}NO_7$: N, 4.50. Found: N, 4.47.

Alkaline oxidation of V. A solution of 450 mg. of V in 5 ml. of 5% aqueous sodium hydroxide was heated on a water-bath and a stream of air was passed through the solution for 10 minutes. The resulting light-yellow solution was brought to *p*H 4 by the dropwise addition of 95% formic acid. The orange microcrystalline solid which separated was collected and washed with water. Recrystallization from ethanol-water afforded 100 mg. of orange platelets of VI; m.p. 194–195° (dec). The addition of a dilute solution of the compound in commercial benzene (containing thiophene) to a few ml. of concentrated sulphuric acid produced a blue-violet coloration which is typical of isatin compounds.

N,N'-bis(3,4,5-trimethoxyphenyl)piperazine (VII). A mixture of 1.4 g. of 3,4,5-trimethoxyaniline (I) and 7.3 ml. of ethylene chlorobromide was refluxed for 40 hours. Treatment of the resulting mixture with dilute hydrochloric acid followed by steam-distillation gave a clear distilland. After adding a large excess of 20% sodium hydroxide, the solution was extracted with several portions of an ether-chloroform mixture. Evaporation of the solvent layer afforded 400 mg. of colorless prisms; m.p. 201–202°, after recrystallization from the same solvent mixture.

The purified substance failed to undergo either benzoylation or acetylation by the usual methods; the absence of halogen was demonstrated by a negative Beilstein test and further confirmed by the absence of a silver halide precipitate upon refluxing the compound with alcoholic silver nitrate.

Anal. Calc'd for $C_{22}H_{30}N_2O_6$: C, 63.2; H, 7.2; N, 6.7; Mol. wt., 418.

Found: C, 62.7; H, 6.5; N, 6.4; Mol. wt., 403 (Ebullioscopic in *n*-butanol).

N-(3,4,5-Trimethoxyphenyl)chloracetamide (VIII). A mixture of 7.2 g. of I, 4.8 g. of chloracetyl chloride, and 60 ml. of C.P. acetone was refluxed for 72 hours and then poured into a large volume of dilute hydrochloric acid. The oily crude product which separated was extracted with several portions of ether. Concentration of the solvent layer to a small volume followed by cooling yielded 7.0 g. (68%) of VIII as colorless prisms, m.p. 97–98°, after recrystallization from ether. After remaining in air for several hours, the crystals lost the solvent of crystallization; they melted at 119–120°.

Anal. Calc'd for $C_{11}H_{14}ClNO_4$: N, 5.5; Cl, 13.7.

Found: N, 5.34; Cl, 13.7.

SUMMARY

1. The synthesis of 2-carbethoxy-4,5,6-trimethoxyindoxyl, 2-carbethoxy-3,4,5,6-tetramethoxyindole, and 3-carbethoxy-3-hydroxy-4,5,6-trimethoxyindole from 3,4,5-trimethoxyaniline is described.

2. 3,4,5-Trimethoxyaniline reacted with ethylene chlorobromide to give N,N′-bis(3,4,5-trimethoxyphenyl)piperazine rather than 4,5,6-trimethoxy-2,3-dihydroindole. Similarly, N-(3,4,5-trimethoxyphenyl)chloracetamide failed to undergo a catalytic cyclization to the 2,3-dihydroindole.

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REFERENCES

(1) BENINGTON, MORIN, AND CLARK, *J. Org. Chem.*, **19,** 11 (1954).
(2) BENINGTON, MORIN, AND CLARK, *J. Org. Chem.*, **20,** 102 (1955).
(3) BENINGTON, MORIN, AND CLARK, *J. Org. Chem.*, **20,** 1292 (1955).
(4) BALSIGER, FISCHER, HIRT, AND GIOVANNINI, *Helv. Chim. Acta*, **36,** 710 (1953).
(5) MARTINET, *Compt. rend.* 362 (1913).
(6) HALBERKANN, *Ber.*, **54,** 3080 (1921).
(7) LANGENBECK, HELLRUNG AND JUTTEMANN, *Ann.*, **512,** 276 (1934).
(8) KALB AND BERRER, *Ber.*, **57,** 2105 (1924).
(9) MORTON, *Chemistry of Heterocyclic Compounds*, 1st Ed., p. 46, McGraw-Hill, 1953.
(10) SMITH AND YU, *J. Am. Chem. Soc.*, **74,** 1096 (1952).
(11) MAUTHNER, *Org. Syntheses*, Coll. Vol. 1, 2nd Ed., 537 (1941).
(12) SLOTTA AND HELLER, *Ber.*, **63,** 3029 (1930).
(13) JONES, ZOMLEFER, AND HAWKINS, *J. Org. Chem.*, **9,** 507 (1944).
(14) BUCK AND IDE, *Org. Syntheses*, Coll. Vol. II, 44 (1943).
(15) GRAEBE AND SUTER, *Ann.*, **340,** 222 (1905).
(16) PALMER AND MCWHERTER, *Org. Syntheses*, Coll. Vol. 1, 2nd Ed., 245 (1941).