Infrared absorption: 5.99 μ (C=O). Lit.4 reports the ketone as an oil.

Anal. Caled. for C_{12}H_{16}O: C, 69.54; H, 7.30; OCH_{3}, 23.16. Found: C, 69.25; H, 7.42; OCH_{3}, 23.39.

The semicarbazono formed colorless needles, m.p. 123° (dec.) (from nitromethane). This is α-form which can also be obtained by long refluxing of α-form, m.p. 121-123° with acid.3

Anal. Caled. for C_{12}H_{16}N_{2}O: C, 61.31; H, 6.88; N, 12.64. Found: C, 61.25; H, 6.92; N, 12.60.

The 2,4-dinitrophenylhydrazone formed deep red clusters of needles, m.p. 132-134° (from ethanol-ethyl acetate). Lit.4 reports m.p. 135-137°.

2-β-(2',3',4'-trimethoxyphenyl)cycloheptanone. The unsaturated ketone (1.3 g.) in ethanol (50 ml.) was reduced in the presence of 10% palladium-charcoal at room temperature and atmospheric pressure. One mole of hydrogen was absorbed during 20 min. Removal of the catalyst and solvent afforded the saturated ketone (1.3 g.), as a pale yellow oil, b.p. 160° (0.2 mm.). It was characterized as the semicarbazone, colorless plates, m.p. 148° (dec.) (from ethanol). Lit.3 reports m.p. 145° (1903).

Anal. Caled. for C_{12}H_{16}N_{2}O: C, 60.72; H, 7.49; N, 12.51. Found: C, 60.72; H, 7.49; N, 12.53.

The 2,4-dinitrophenylhydrazone formed orange crystals, m.p. 152° (from ethanol-ethyl acetate). Lit.4 reports m.p. 153-154°.

2-(2',3',4'-Trimethoxyphenyl)tropono. 2-(2',3',4'-trimethoxyphenyl)cyclohept2-ene (3 g.), N-bromosuccinimide (5.8 g.), and a catalytic amount of dibenzoyl peroxide were heated under reflux in carbon tetrachloride (50 ml.). The reaction was over after 3 hr. and some spontaneous dehydrobromination was observed. The succinimide was removed by filtration and the solvent was removed in vacuo (water pump). Collidine (20 ml.) was added to the residue and the mixture was heated under reflux for 4 hr. After cooling, the precipitated collidine hydrobromide was removed by filtration, the collidine remaining was removed in vacuo, and the residue was taken up in benzene. The benzene extract was washed with dilute hydrochloric acid, with water, dried over sodium sulfate, and the solvent was removed.

A benzene solution of the residue was chromatographed over acid-washed alumina (Merck), using benzene and finally benzene-chloroform (4:1) for elution. Five distinct bands could be observed on the column and these fractions were worked up separately. Infrared spectra and analyses showed that these were apparently bromo-enones and bromo-dienones but it was not possible to purify these sufficiently for characterization. Fortunately, however, one of these fractions turned out to be the bromotropane derivative. The compound was an oil (300 mg.), distilled at bath temp. 190° (0.05 mm.). Infrared absorption (cm.⁻¹): 1700 (m), 1675 (m), 1625 (s), 1585 (s), 1488 (vs), 1305 (m), 1270 (m), 1228 (v), 1100 (vs), 1065 (m).

Anal. Caled. for C_{12}H_{16}Br_{2}O: C, 54.70; H, 4.27; Br, 22.79; OCH_{3}, 25.80. Found: C, 54.66; H, 4.21; Br, 22.20; OCH_{3}, 25.80.

Hydrogenation of the bromotropane. The bromotropane (60 mg.) was reduced in ethanol with 10% palladium-charcoal at room temperature and atmospheric pressure. Four moles of hydrogen were absorbed during 6 hr. and working up yielded a 2,4-dinitrophenylhydrazone, melting point and mixed melting point with an authentic specimen of the corresponding derivative of 2-(2',3',4'-trimethoxyphenyl)cycloheptanone, 152°.

Haiifa, Israel

[CONTRIBUTION FROM BATTEN LE MEMORIAL INSTITUTE AND THE FELS RESEARCH INSTITUTE]

Mescaline Analogs. VIII. Substituted 5-Methoxy- and 5,6,7-Trimethoxyindoles

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Several 5-methoxy- and 5,6,7-trimethoxyindole derivatives have been synthesized by the cyclization of appropriately substituted open chain amines. Convenient syntheses of 1-benzyl-3-hydroxy-3-carboethoxy-5,6,7-trimethoxyindole and of 1-methyl-5-methoxyindole are described.

In a continuation of our studies of indole compounds related to the physiologically active polyalkoxy-phenethyamines,1-4 we have synthesized several newwotalkoxyindole derivatives. The present work was undertaken with the idea of synthesizing a number of intermediates which might be used in the preparation of certain key compounds needed for further examining the indole hypothesis of psychotomimetic drug activity.5

(1) Battelle Memorial Institute.
(2) The Fels Research Institute.
(7) M. Blumberg and S. V. Kostanecki, Ber., 36, 2191 (1903).
methoxybenzoic acid. Accordingly, this approach to the preparation of VI was abandoned. In an alternative route, pyrogallol carbonate was nitrated in accordance with the directions given by Einhorn,\(^9\) and the nitrification product saponified to give 4-nitropyrogallol. The nitro compound, however, failed to give the expected 2,3,4-trimethoxynitrobenezene when treated with methyl sulfate and alkali;\(^9\) reaction of 4-nitropyrogallol with ethereal diazomethane similarly failed to give a completely methylated product. In both instances, the solubility of the reaction product in dilute sodium hydroxide solution was indicative of the presence of free phenolic \(-\mathrm{OH}\) groups.

The synthetic route which was finally chosen for the preparation of VI is outlined in Chart I. 2,6-Dimethoxyphenyl acetate (II), obtained from I by the action of acetic anhydride, was nitrated by employing a mixture of concentrated and white fuming nitric acids.\(^10\)

![CHART I](chart.png)

The resulting 3-nitro-2,6-dimethoxyphenyl acetate (III) was saponified to the monohydrate of the free phenol (IV). Methylolation of IV with methyl sulfate and alkali yielded 2,3,4-trimethoxynitrobenezene (V) which, in turn, was reduced to 2,3,4-trimethoxyaniline (VI) by employing stannous chloride. Since Brand and Collishorn\(^10\) failed to report the stepwise yields in their synthesis of V, we have included our yield data in Chart I. It may be seen that each is satisfactorily high and that the over-all yield from 2,6-dimethoxyphenol (I) is about 50 per cent.

Chart II indicates the routes which were followed in preparing the various trimethoxyniroles from VI. Reaction of VI with bromomalonic ester under similar conditions to those outlined by Balsieger \(et\ al.\)\(^11\) resulted in the formation of crude \(N-\)

\[\text{V} \rightarrow \text{VI} \]

(2,3,4-trimethoxyphenyl)aminomalonic ester (not isolated) which was thermally cyclized to 5,6,7-trimethoxyindoxyl-2-carboxylic ester (VII) in very low yield. In an earlier phase of this investigation,\(^3\) we had shown that 3,4,5-trimethoxyaniline can be condensed smoothly with ethyl oxomalanate dihydrate to give an 87 per cent yield of 4,5,6-trimethoxy-3-hydroxy-3-carbethoxynirole. It was somewhat surprising to find that a similar condensation reaction carried out between 2,3,4-trimethoxyaniline (VI) and the above ester gave only a 23 per cent yield of 5,6,7-trimethoxy-3-hydroxy-3-carbethoxynirole (VIII).

In order to investigate the possibility of using a monofunctional secondary amine as a means of improving the syntheses of 5,6,7-trimethoxynirole derivatives, the aniline VI was converted to \(N\)-benzyl-2,3,4-trimethoxyaniline (X) by low pressure hydrogenation of the benzylidene compound (IX) in the presence of Adams' catalyst. Selection of the \(N\)-benzyl intermediate was prompted by the fact that this group may be selectively removed from many compounds by hydrogenolysis.\(^12\) In contrast to VI, the secondary amine X condensed smoothly with ethyl oxomalanate to give a 53 per cent yield of 1-benzyl-3-carbethoxy-5,6,7-trimethoxynirole (XI).

An attempt was made to prepare 1-benzyl-5,6,7-

\[\text{XI} \rightarrow \text{XII} \]

\[\text{XII} \]

trimethoxy-2,3-dihydroindole. Hydrogenolysis of this compound should yield 5,6,7-trimethoxy-2,3-dihydroindole which has been hypothesized as a possible oxidative cyclization product of mescaline. However, the reaction of X with ethylene chloro- bromide did not give the expected 2,3-dihydroindole; instead, the N,N'-diaryl-1,4-diazine (XII), accompanied by benzyl chloride and/or bromide, was found to be the main reaction product.

In attempting to convert the amine X to the sodium 5,6,7-trimethoxy-1-benzylindolyl-2-sulfite (XIII) through reaction with the sodium bisulfite addition compound of glyoxal, it was found that only unreacted X was present in the reaction mixture after a suitably long reflux period.

N-Benzyl-2,3,4-trimethoxyaniline (X) was next subjected to reaction with chloral hydrate and hydroxylamine in an attempt to form an intermediate isonitrosoacetanilide (XIV) which should cyclize in the presence of sulfuric acid to form 1-benzyl-5,6,7-trimethoxyisatin (XV). When this reaction was carried out in an analogous manner to that described by Marvel and Hiers, an intractable tar was formed, from which none of the desired compound could be isolated.

Both N-methyl- and N-benzyl-p-anisidine were also examined in connection with their tendencies to form isatins which might, in turn, be converted to indole derivatives. As shown in Chart III, the N-benzylamine (XVI), obtained through the hydrogenation of the Schiff base XVII, when subjected to the action of chloral hydrate and hydroxylamine, gave a product which failed to give the characteristic isatin color reaction with thiophene and sulfuric acid. The product is believed to be the tetrasubstituted oxamide XVIII.

Compound XXII gave a characteristic isatin color reaction and was reduced with aqueous sodium hydrosulfite solution to give a nearly quantitative yield of 1-methyl-5-methoxydioxindole (XXIII). Further reduction of XXIII with lithium aluminum hydride gave an 85.6 per cent yield of crude 1-methyl-5-methoxyindole (XXIV) which after purification was found to be identical with the compound which Cook, et al. obtained from the reduction of 1-methyl-5-methoxyindole with the same reagent.

EXPERIMENTAL

Attempted methylation of 4-nitropyrogallol. Pyrogallol carbonate, obtained in 19 per cent yield from the action of phosgene on pyrogallol in xylene-pyridine solution, was nitrated by Einhorn's procedure. The resulting "nitropyrogallol carbonate" afforded a quantitative yield of 4-nitropyrogallol by hydrolysis in hot water; m.p. 167-168° (reported, 162°). Treatment of 4-nitropyrogallol with a large excess of dimethyl sulfate and aqueous alkali, as described by Einhorn, failed to give the alkali insoluble 2,3,5-trimethoxynitrobenzene.

To a stirred ether solution containing 3 g. of diazomethane, there was added 3 g. of 5-nitropyrogallol. After nitrogen evolution had stopped, the clear solution was decolorized with Norit and then evaporated. The light brown residual

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(15) L. Kalb and E. Berer, Ber., 57, 2105 (1924).
(18) All melting points uncorrected.
ether and the extract dried over anhydrous magnesium sulfate. Following filtration, the collected solid was recrystallized from ethanol-water to afford 11.8 g. (98%) of pure IX as yellow needles melting at 104-105°.

Anal. Caled. for C_{16}H_{14}NO: C, 70.8; H, 6.1; N, 5.1.

N-Benzilene-2,3,4-trimethoxyaniline (X). In the reaction bottle of a Parr hydrogenation apparatus there was placed 11 g. of IX, 60 ml. of dioxane (technical grade which had been freed of peroxides by hydrogenation over Raney nickel), and 5-8 g. of Raney nickel catalyst. Hydrogenation was initiated at a gas pressure of 30 p.s.i.g. and the theoretical uptake of hydrogen was complete within 13-15 min. After filtering free of the spent catalyst, the dioxane solution of the product was concentrated to vacuo, diluted with 125 ml. of ice bath, 39 g. (98%) of colorless residual oil solidified. The crude amine, m.p. 62-64°, gave 9.5 g. (86%) of colorless prisms after recrystallization from ethanol containing a little water; m.p. 63-64°.

Anal. Caled. for C_{16}H_{14}NO: C, 70.4; H, 6.6; N, 5.3. Found: C, 70.4; H, 6.9; N, 5.13.

1-Benzyl-3-carbethoxy-2,6,7-trimethoxydioxindole (XI). A mixture of 2.0 g. of X, 1.22 g. of ethyl oxalaluate (dihydrate), and 8 ml. of glacial acetic acid was warmed on a steam bath for 10 min. and then allowed to stand for 20 min. The light red-brown reaction mixture was worked up by the same procedure used for VIII. The pink, crystalline product which was collected melted over a range of 65-70°. Recrystallization from ethanol (Norit) afforded 2.8 g. (54%) of XI; m.p. 185-186°.

Anal. Caled. for C_{16}H_{14}NO: C, 62.8; H, 5.7; N, 3.5. Found: C, 62.8; H, 5.7; N, 3.5.

N,N'-Bis(2,3,4-trimethoxyphenyl)piperazine (XII). A solution of 3.0 g. of X in 15 ml. of ethylene chlorohydrin was refluxed for 15 hr.; hydrogen halide was evolved during the reaction period. Treatment of the resulting reaction mixture with 10% hydrochloric acid followed by steam distillation gave a clear distillate which was further purified by recrystallization from ethanol (Norit). The clear distillate was collected and dried; m.p. 104-105°. Evaporation of the solvent layer afforded 250 mg. of nearly white prisms; m.p. 172-173°. The melting point of the product was increased to 175-177° by sublimation in a high vacuum.

Anal. Caled. for C_{16}H_{14}NO: C, 62.8; H, 5.7; N, 3.5. Found: C, 62.8; H, 5.7; N, 3.5.

The product was then cooled to room temperature overnight. The precipitated hydrobromide of VI (16.5 g.) was recovered by filtration. Concentration of the solution in vacuo gave an additional 3.6 g. of the amine hydrobromide. The resulting nearly black reaction mixture from which the malonic ester could not be isolated in pure form. Distillation of the tarry product in a high vacuum resulted in cyclization, and a small amount of yellow crystalline condensate was obtained. After recrystallization from benzene-ligroin, the purified product, consisting of light yellow flakes, weighed 700 mg.; m.p. 118-119°.

Anal. Caled. for C_{16}H_{14}NO: N, 4.7. Found: N, 4.7.

2-Carbethoxy-5,6,7-trimethoxydioxindole (VIII). A mixture of 34.7 g. of VI, 100 ml. dry n-p. benzene and 22.7 g. of ethyl bromomalonalate was refluxed for 4 hr. and allowed to stand at room temperature overnight. The precipitated hydrobromide of VI (16.5 g.) was recovered by filtration. Concentration of the solution in vacuo gave an additional 3.6 g. of the amine hydrobromide. The resulting nearly black reaction mixture from which the malonic ester could not be isolated in pure form. Distillation of the tarry product in a high vacuum resulted in cyclization, and a small amount of yellow crystalline condensate was obtained. After recrystallization from benzene-ligroin, the purified product, consisting of light yellow flakes, weighed 700 mg.; m.p. 118-119°.


N-Benzilene-2,3,4-trimethoxyaniline (IX). An aqueous solution of VI hydrobromide, prepared from 13.2 g. of the salt in 30 ml. of water, was treated with 25 ml. of 25 per cent sodium hydroxide, and then the base was extracted with ether. The solvent layer, after drying over calcium chloride, was evaporated in a nitrogen stream and the residue of VI treated with 5.3 g. of benzaldehyde and 6 ml. of ethanol. Reacting under reflux for about 12 min. followed by cooling caused the crude Schiff base IX to separate. After filtration, the collected solid was recrystallized from ethanol-water to afford 11.8 g. (98%) of pure IX as yellow needles melting at 104-105°.

Anal. Caled. for C_{16}H_{14}NO: C, 70.8; H, 6.3; N, 5.2. Found: C, 70.8; H, 6.4; N, 5.1.
was poured into a second solution prepared by dissolving 3.0 g. of chloral hydrate and 31 g. of sodium sulphate (decahydrate) in 33 ml. of water. After adding to this mixture a third solution of 3.1 g. of hydroxylamine hydrochloride in 14 ml. of water, the final mixture was heated for 20 min. on a steam bath. During the heating period a very dark oil separated from the aqueous phase. After cooling and decanting the aqueous layer from the oil, the former was made alkaline with 5N sodium hydroxide. Since no unreacted amine was precipitated, the water layer was discarded. The oily layer was taken up in ethyl acetate, treated with Norit, filtered, and concentrated. Upon cooling, light tan needles separated which were again recrystallized from ethyl acetate; the product (200 mg.) melted at 179–180°.

This reaction product was not the expected isonitrosoacetanilide since it failed to form an isatin on warming in concentrated sulfuric acid. It is thought that the substance is likely N,N′-bis(4-methoxyphenyl)-N,N′-bisbenzoylumamide (XVIII).


N-Methyl-p-anisidine (XX). p-Nitroanisidine (XIX) was obtained in 91% yield by the N-formylation of p-anisidine with 90% formic acid.22 The distilled product (b.p. 156–159°/0.5 mm.) solidified and melted at 84–85° (reported,22 80–81°). To a slurry of 14.2 g. of lithium aluminum hydride in 250 ml. of dry ether was gradually added 37.8 g. of XIX in 150 ml. of hot dry benzene. After completing the addition, the mixture was refluxed for 38/4 hours, cooled in an ice bath, and then hydrolyzed by the addition of a limited amount of water.23 The organic layer was filtered free of suspended lithium metaluminate and then dried over anhydrous magnesium sulfate. The residue obtained after removing the solvents was distilled in vacuo. The fraction boiling at 80–84/2°/0.2 mm. was the desired XX (27.8 g.; 81%). The product eventually solidified; m.p. 35°. (Reported,24 37°.)

N-Methyl-4-methoxyisonitrosoacetanilide (XXI). To a solution of 18 g. of chloral hydrate and 260 g. of sodium sulfate (decahydrate) in 240 ml. of water was added a solution of 13.7 g. of XX in 60 ml. of water containing 8.6 ml. of concentrated hydrochloric acid. A third solution containing 22 g. of hydroxylamine hydrochloride in 100 ml. of water was next added and the resulting mixture heated on a steam bath for 15–20 min. After cooling, the dark product (11.5 g.; 85%) which separated was collected and dried. The crude product was recrystallized by dissolving in ethyl acetate (Norit) and adding enough petroleum ether (30–60°) to initiate crystallization of the product. The product was obtained as heavy colorless plates melting at 116–117°.

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