Infrared absorption: 5.99 μ (C=O). Lit.[3,4] reports the ketone as an oil.

Anal. Calcd. for $C_{16}H_{20}O_4$: C, 69.54; H, 7.30; OCH_3, 33.66. Found: C, 69.28; H, 7.47; OCH_3, 33.76.

The *semicarbazone* formed colorless needles, m.p. 182–183° (dec.) (from methylcyclohexane). Lit.[4] reports 183–184° dec.

Anal. Calcd. for $C_{17}H_{23}N_3O_4$: C, 61.24; H, 6.95; N, 12.61. Found: C, 61.31; H, 6.88; N, 12.51.

The *2,4-dinitrophenylhydrazone* formed orange needles, m.p. 170° (dec.) (from nitromethane). This is β-form which can also be obtained by long refluxing of α-form, m.p. 121–123° with acid.[3]

Anal. Calcd. for $C_{22}H_{24}N_4O_7$: C, 57.89; H, 5.30; N, 12.28. Found: C, 57.93; H, 5.13; N, 12.64.

2-(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).

Anal. Calcd. for $C_{17}H_{25}N_3O_4$: C, 60.88; H, 7.51; N, 12.53. Found: C, 60.72; H, 7.49; N, 12.51.

The *2,4-dinitrophenylhydrazone* formed orange crystals, m.p. 152° (from ethanol–ethyl acetate). Lit.[4,9] reports m.p. 153–154°.

2-(5′-Bromo-2′,3′,4′-trimethoxyphenyl)tropone. 2-(2′,3′,4′-trimethoxyphenyl)cyclohept-2-enone (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 bezene 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 *bromotropone* 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 (w), 1100 (vs), 1065 (m).

Anal. Calcd. for $C_{16}H_{15}O_4Br$: C, 54.70; H, 4.27; Br, 22.79; OCH_3, 26.50. Found: C, 54.66; H, 4.21; Br, 22.20; OCH_3, 25.80.

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

Anal. Calcd. for $C_{22}H_{19}BrN_4O_7$: C, 49.72; H, 3.58; N, 10.54. Found: C, 49.42; H, 3.26; N, 10.18.

Hydrogenation of the bromotropone. The bromotropone (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°.

HAIFA, ISRAEL

[CONTRIBUTION FROM BATTELLE MEMORIAL INSTITUTE AND THE FELS RESEARCH INSTITUTE]

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

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Received July 15, 1957

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-β-phenethylamines,[3–5] we have synthesized several new alkoxyindole 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]

2,3,4-Trimethoxyaniline (VI) was selected as the starting compound for the new series of indole compounds and a number of routes were investigated for its preparation. As a first approach, it was planned to prepare VI from 2,3,4-trimethxoybenzamide *via* the Hoffmann reaction.[6] However, in attempting to convert 2,3,4-trimethoxyacetophenone[7] to the corresponding benzoic acid *via* the hypohalite oxidation of the side chain,[8] it was noted that considerable nuclear halogenation occurred; the resulting product was believed to be either 5- or 6-chloro-2,3,4-tri-

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(1) Battelle Memorial Institute.

(2) The Fels Research Institute.

(3) F. Benington, R. D. Morin, and L. C. Clark, *J. Org. Chem.*, **20**, 1454 (1955).

(4) F. Benington, R. D. Morin, and L. C. Clark, *J. Org. Chem.*, **20**, 1292 (1955).

(5) F. Benington, R. D. Morin, and L. C. Clark, *J. Org. Chem.*, **22**, 331 (1957).

(6) C. Grabe and M. Suter, *Ann.*, **340**, 227 (1905).

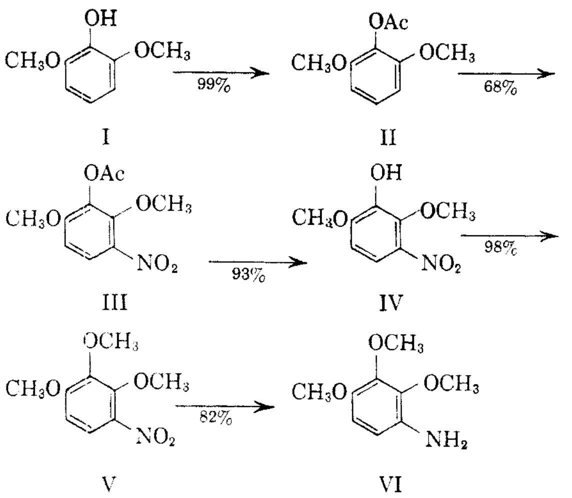
(7) M. Blumberg and S. V. Kostanecki, *Ber.*, **36**, 2191 (1903).

(8) M. S. Newman and H. L. Holmes, *Org. Syn.*, Coll. Vol. II, 428 (1943).

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 nitration product saponified to give 4-nitropyrogallol. The nitro compound, however, failed to give the expected 2,3,4-trimethoxynitrobenzene 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 —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

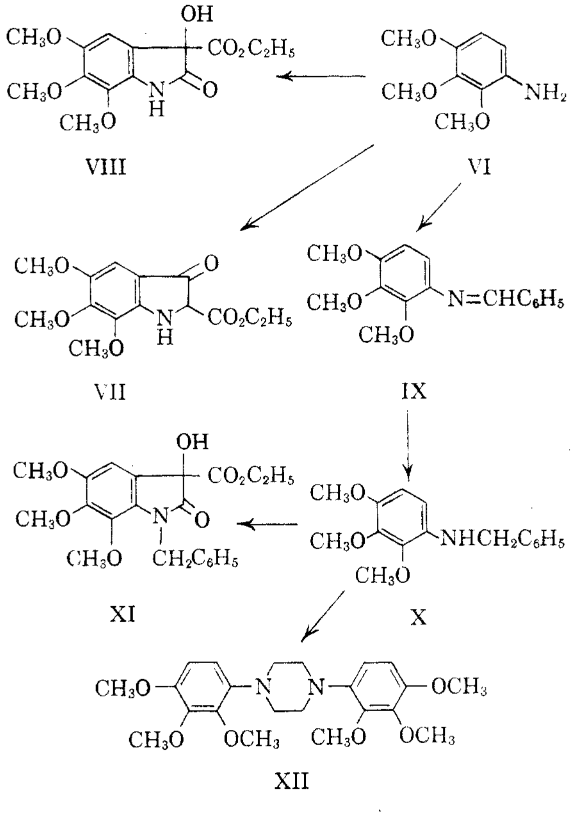


The resulting 3-nitro-2,6-dimethoxyphenyl acetate (III) was saponified to the monohydrate of the free phenol (IV). Methylation of IV with methyl sulfate and alkali yielded 2,3,4-trimethoxynitrobenzene (V) which, in turn, was reduced to 2,3,4-trimethoxyaniline (VI) by employing stannous chloride. Since 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 trimethoxyindoles 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*-(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 oxomalonate dihydrate to give an 87 per cent yield of 4,5,6-trimethoxy-3-hydroxy-3-carbethoxyoxindole. 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-carbethoxyoxindole (VIII).

In order to investigate the possibility of using a monofunctional secondary amine as a means of improving the syntheses of 5,6,7-trimethoxyindole 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 oxomalonate to give a 53 per cent yield of 1-benzyl-3-carbethoxy-5,6,7-trimethoxydioxindole (XI).

CHART II



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

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(9) A. Einhorn, *Ber.*, **37**, 100 (1904).

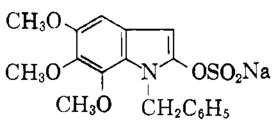
(10) K. Brand and H. Collishorn, *J. Prakt. Chem.* (2) **103**, 329 (1922).

(11) R. W. Balsieger, R. W. Fischer, and E. Giovannini, *Helv. Chim. Acta*, **36**, 710 (1953).

(12) W. H. Hartung and R. Simonoff, *Org. Reactions*, **VII**, 275 (1953).

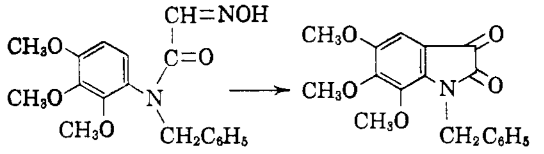
trimethoxy-2,3-dihydroindole. Hydrogenolysis of this compound should yield 5,6,7-trimethoxy-2,3-dihydroindole which has been hypothesized as a possible oxidative cyclization product of mescaline.[5] However, the reaction of X with ethylene chlorobromide did not give the expected 2,3-dihydroindole; instead, 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,[13] it was found that only unreacted X was present in the reaction mixture after a suitably long reflux period.



XIII

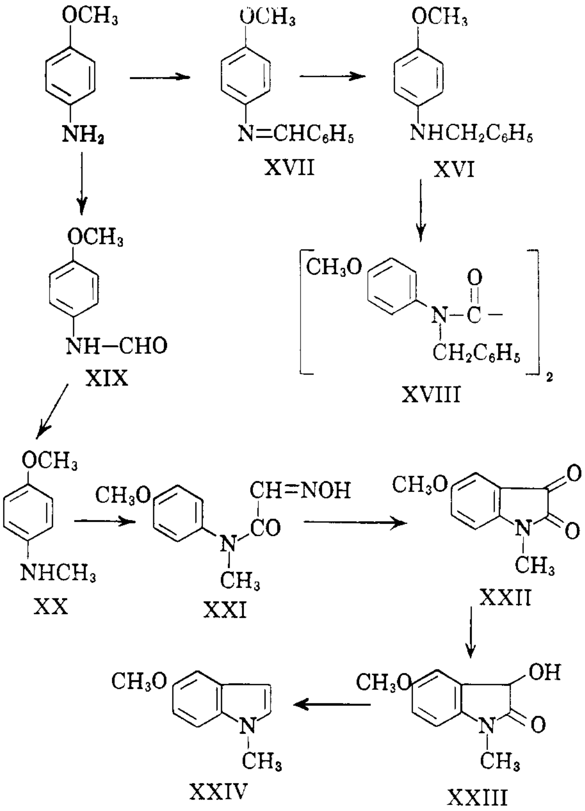
N-Benzyl-2,3,4-trimethoxyaniline (X) was next subjected to reaction with chloral hydrate and hydroxylamine in an attempt to form an intermediate isonitrosoacetanilide (XIV) which should cyclize in the presence of sulfuric acid to form 1-benzyl-5,6,7-trimethoxyisatin (XV). When this reaction was carried out in an analogous manner to that described by Marvel and Hiers.[14] an intractable tar was formed, from which none of the desired compound could be isolated.



XIV XV

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.[15,16] The product is believed to be the tetrasubstituted oxamide XVIII.

CHART III



In contrast to XVI, *N*-methyl-*p*-anisidine, prepared by reducing *N*-formyl-*p*-anisidine (XIX) with lithium aluminum hydride, gave the desired isonitrosoacetanilide (XXI) in 52 per cent yield. Ring closure of XXI to 1-methyl-5-methoxyisatin (XXII) took place smoothly in concentrated sulfuric acid, giving an 81 per cent yield of the product. Compound XXII gave a characteristic isatin color reaction[15,16] 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.*[17] obtained from the reduction of 1-methyl-5-methoxyindole with the same reagent.

EXPERIMENTAL[18]

Attempted methylation of 4-nitropyrogallol. Pyrogallol carbonate, obtained in 19 per cent yield from the action of phosgene on pyrogallol in xylene-pyridine solution,[9] 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,[9] 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 2,3,4-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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(13) H. Burton, *J. Chem. Soc.*, 546 (1932).

(14) C. S. Marvel and G. S. Hiers, *Org. Syntheses*, **Coll. Vol. I,** 321 (1932).

(15) L. Kalb and E. Berer, *Ber.*, **57,** 2105 (1924).

(16) A. A. Morton, *Chemistry of Heterocyclic Compounds*, McGraw Hill, New York, 1953, p. 46.

(17) J. W. Cook, J. D. Loudon, and P. McCloskey, *J. Chem. Soc.*, 1203 (1951).

(18) All melting points uncorrected.

oil (3.5 g.) was soluble in dilute sodium hydroxide and therefore was an incompletely methylated product.

2,3,4-Trimethoxyaniline (VI). A mixture of 130 g. of 2,6-dimethoxyphenol (I) and 155 ml. of acetic anhydride was refluxed for 3.5 hr. After removing the unreacted anhydride and acetic acid at diminished pressure, the residual oil was distilled *in vacuo;* 163.2 g. (99%) of pure II was obtained; b.p. 118–119°/1–2 mm. (reported,[10] m.p. 53.5°). To a cold mixture of 195 ml. of concentrated and 21.7 ml. of white fuming nitric acid, there was added during 40 min. 65 g. of II; the mixture was kept between 13–16° during the reaction. After stirring for an additional 10 min., the mixture was poured into 1080 ml. of ice and water containing urea. The precipitate of crude III was collected and dried; yield 54.2 g. (68%) of green-yellow crystals, m.p. 90–92°. Recrystallization from aqueous ethanol gave pure III as yellow-orange prisms, m.p. 94–95° (reported,[10] 93–95°). To a solution of sodium hydroxide (2*N*) was added 47 g. of III and the resulting mixture refluxed for 0.5 hr. Upon cooling and acidification with 225 ml. of 10 per cent hydrochloric acid, 39.3 g. (93%) of the phenol IV (dihydrate) melting at 67–69° (reported,[10] 67–68°) precipitated. A solution of 39.3 g. of IV in 50 ml. of ethanol was methylated by first adding 65 ml. of methyl sulfate, cooling, and then gradually adding 35 g. of sodium hydroxide in 40 ml. of water. After diluting with 500 ml. of cold water and further cooling in an ice bath, 38 g. (98%) of 2,3,4-trimethoxynitrobenzene (V) was obtained melting at 44–45° (reported,[10] 44°).

To a cold, stirred mixture of 160 g. of stannous chloride dihydrate and 160 ml. of concentrated hydrochloric acid there was added 37.9 g. of V. The temperature was allowed to rise to 97° and then cooling to room temperature was affected by means of an ice bath. The cool reaction mixture was treated with 285 g. of sodium hydroxide and then diluted with a large volume of water. After exhaustively extracting the aqueous mixture with ether, the water layer was discarded and the ether layer dried over anhydrous magnesium sulfate. Following filtration, the ether solution was evaporated at reduced pressure and the residue distilled *in vacuo;* b.p. 111–114°/0.8 mm. (reported,[6] 150°/2 mm.) 26.9 g. (82%) of 2,3,4-trimethoxyaniline as a light yellow oil.

2-Carboethoxy-5,6,7-trimethoxyindoxyl (VII). A mixture of 34.7 g. of VI, 100 ml. dry C.P. benzene and 22.7 g. of ethyl bromomalonate[19] 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 residue was a tar from which the desired phenylaminomalonic 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. Calcd. for $C_{14}H_{16}NO_6$: N, 4.7. Found: N, 4.7.

5,6,7-Trimethoxy-3-hydroxy-3-carboethoxyoxindole (VIII). A solution of 1.8 g. of VI in 10 ml. of glacial acetic acid was treated with 1.9 g. of ethyl oxomalonate (dihydrate). The resulting green solution was heated on a steam bath for 10 min. and then kept at room temperature for 2 hr. Diluting the solution with 125 ml. of water and then adding solid ammonium carbonate to give a final *p*H of 8 caused the product to separate as an oil. The product was taken up in ether and the extract dried over anhydrous magnesium sulfate. Evaporation of the solvent gave a crystalline residue which, after recrystallization from ether–petroleum ether (30–60°), formed tan prisms; m.p. 142–143°; yield of pure product, 700 mg. (23%).

Anal. Calcd. for $C_{14}H_{17}NO_7$: C, 54.0; H, 5.5; N, 4.5. Found: C, 54.2; H, 5.6; N, 4.5.

N-Benzylidene-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 free 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. Calcd. for $C_{16}H_{17}NO_3$: C, 70.8; H, 6.3; N, 5.2. Found: C, 70.8; H, 6.4; N, 5.1.

N-Benzyl-2,3,4-trimethoxyaniline (X). In the reaction bottle of a Parr hydrogenation apparatus there was placed 11 g. of IX, 66 ml. of dioxane (technical grade which had been freed of peroxides by prehydrogenation over Raney nickel), and *ca.* 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 *in vacuo*, diluted with 125 ml. of water, and finally extracted with ether. The dry ether extract (anhydrous magnesium sulfate) was evaporated and the 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. Calcd. for $C_{16}H_{19}NO_3$: C, 70.4; H, 6.6; N, 5.3. Found: C, 70.4; H, 6.9; N, 5.13.

1-Benzyl-3-carbethoxy-5,6,7-trimethoxydioxindole (XI). A mixture of 2.0 g. of X, 1.22 g. of ethyl oxomalonate (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. Calcd. for $C_{21}H_{23}NO_7$: 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 chlorobromide 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 distilland when all of the excess ethylene chlorobromide had distilled. After making the clear distilland strongly alkaline with 20% sodium hydroxide, the product was extracted with three portions of ether. 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 176–177° by sublimation in a high vacuum.

Anal. Calcd. for $C_{22}H_{30}N_2O_6$: N, 6.8. Found: N, 6.5.

Attempted conversion of 4-methoxy-N-benzylaniline to 4-methoxy-N-benzylisonitrosoacetanilide. To a solution of 24.6 g. of *p*-anisidine in 20 ml. of ethanol was added 21.2 g. of benzaldehyde. After warming on the steam bath for 10 min., the reaction mixture was cooled in order to cause the crude XVII to crystallize. The solid Schiff base was collected and recrystallized from ethanol. Pure XVII (34.5 g.; 82%) was obtained as nearly colorless prisms; m.p. 73–74° (reported,[20] 72°). The previously obtained Schiff base XVII was hydrogenated in dioxane solution using Raney nickel catalyst in the same manner which was described for the preparation of X. From 33.2 g. of XVII there was obtained 31.3 g. (94%) of XVI, m.p. 50–51° (reported,[21] 52°). A solution of 3.0 g. of XVI in 8.4 ml. of water containing 1.5 ml. of concentrated hydrochloric acid

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(19) C. S. Palmer and P. W. McWherter, *Org. Syntheses*, 2nd Ed., Coll. Vol. 1, 245 (1941).

(20) W. Von Miller, J. Plöchl, and P. Scheitz, *Ber.*, **31**, 2706 (1898).

(21) E. Frölich and E. Wedekind, *Ber.*, **40**, 1009 (1907).

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 5*N* 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'*-bisbenzyloxamide (XVIII).

Anal. Calcd. for $C_{30}H_{28}N_2O_4$: N, 5.84. Found: N, 5.83.

N-Methyl-p-anisidine (XX). *p*-Methoxyformanilide (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,[21] 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 1 hr. 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°/0.2 mm. was the desired XX (27.8 g.; 81%). The product eventually solidified; m.p. 35°. (Reported,[21] 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.; 55%) 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°.

Anal. Calcd. for $C_{10}H_{12}N_2O_3 \cdot H_2O$: C, 53.2; H, 6.2; N, 12.4. Found: C, 53.2; H, 6.1; N, 12.5.

1-Methyl-5-methoxyisatin (XXII). Concentrated sulfuric acid (40 ml.) was heated to 50° on a steam bath and then 9.6 g. of the isonitroso compound (XXI) was added at such a rate that the mixture temperature did not exceed 60–70°. The resulting blue-violet solution was then kept at 80° for a period of 10 min. After cooling to room temperature, the reaction mixture was poured onto 450 g. of cracked ice and the deep maroon solid which separated was collected and washed with water until free of acid. The air dried product weighed 7.2 g. (81%); m.p. 175–176°. An analytical specimen was obtained by recrystallization from methanol-water; red-brown prisms melting at 176°.

Anal. Calcd. for $C_{10}H_9NO_3$: N, 7.3. Found: N, 7.3.

1-Methyl-5-methoxydioxindole (XXIII). To a stirred suspension of the isatin XXII in 30 ml. of boiling water was added 7.0 g. of sodium hydrosulphite. The solution became clear and after standing overnight in a refrigerator, crude XXIII was deposited. The dry crude product weighed 4.9 g. (98%) and melted at 158–160°. After recrystallization from boiling water, pure XXIII was obtained as colorless prisms, m.p. 165°.

Anal. Calcd. for $C_{10}H_{11}NO_3$: C, 62.1; H, 5.7. Found: C, 62.0; H, 5.6.

1-Methyl-5-methoxyindole (XXIV). To an efficiently stirred slurry of 1.9 g. of lithium aluminum hydride in 100 ml. of dry ether was added 3.3 g. of the dioxindole XXIII in about 120 ml. of dry benzene. The mixture was then refluxed for 3³/₄ hours, cooled in an ice bath, and then hydrolyzed by the addition of a limited quantity of water. The organic layer was filtered free of lithium metaluminate and dried over anhydrous magnesium sulphate. After treatment with Norite, the ether-benzene filtrate was evaporated *in vacuo* and the oily green residue cooled to induce crystallization. There was obtained 2.2 g. (85%) of yellow-green prisms melting at 75–80°. The crude product was recrystallized from ether-petroleum ether (30–60°) with poor recovery. Purified XXIV (900 mg.) was obtained as yellow prisms melting at 104–105° (reported,[17] 103–104°). The picrate of XXIV melted at 98–100° (reported,[24] 97–98°).

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