the above described experiment by reducing in volume and cooling the hot ethyl acetate filtrate obtained from the extraction of the mixture of diastereoisomers. The white crystalline product XIV which formed was filtered off and washed with cold ethyl acetate. The yield of XIV was 1.4 g., m.p. 173–174°. An analytical sample was recrystallized from ethyl acetate, m.p. 173–174°.

Anal. Calcd. for $C_{12}H_{14}F_3NO_3$: C, 51.98; H, 5.09. Found: C, 52.38; H, 5.24.

threo-2-Amino-1-*p*-trifluoromethylphenyl-1,3-propanediol (XV) was formed by the hydrolysis of three compounds, the *threo*-N-dichloroacetyl compound IX, and the *threo*- and *erythro*-N-acetyl intermediates (XIII and XIV), under conditions similar to those used by Bambas, Troutman and Long[4] for the preparation of the 2-amino-1-*p*-halogenphenyl-1,3-propanediols.

Each of the above three substances was hydrolyzed separately with hot 5% hydrochloric acid to give the same white crystalline product XV, m.p. 123–124° after recrystallization from water. Mixed melting points of any two, as well as of all three, were undepressed.

Anal. Calcd. for $C_{10}H_{12}F_3NO_2$: N, 5.96. Found: N, 5.98.

Dichloroacetylation of XV was effected by treatment with ethyl dichloroacetate in a manner similar to that used by Cutler, Stenger and Suter[5] for the preparation of the *p*-methylmercapto analog of chloramphenicol.

The N-dichloroacetyl derivatives so obtained were identical, m.p. 137.5–138.5°. Mixed melting points of them as well as with the *threo*-2-dichloroacetamido-1-*p*-trifluoromethylphenyl-1,3-propanediol (IX) prepared by the alternate method of synthesis were undepressed.

Acetylation of XV with acetic anhydride followed by selective hydrolysis[14] of any acyloxy groups, was carried out in a manner similar to one of the acylation procedures described by Rebstock[15] for the acylation of the free base of chloramphenicol.

The *threo*-2-acetamido-1-*p*-trifluoromethylphenyl-1,3-propanediol (XIII) so formed melted at 194–195° after recrystallization from methanol.

PHILADELPHIA, PA.

[CONTRIBUTION FROM THE RESEARCH DEPARTMENT, CIBA PHARMACEUTICAL PRODUCTS, INC.]

A Dimethoxy Substituted Harman and Other Compounds Derived from 5,6-Dimethoxyindole

BY CHARLES F. HUEBNER, HYLA AMES TROXELL AND DOROTHY C. SCHROEDER

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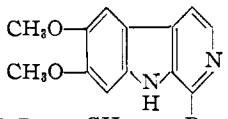
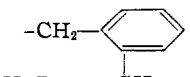
A practical method for the synthesis of 5,6-dimethoxyindole involving the hydrogenation of 3,4-dimethoxy-6,β-dinitrostyrene has been described. This indole has been converted to a dimethoxy substituted harman, yobyrone, heteroauxin and tryptophan by the application of methods used to prepare the parent substances.

In connection with a problem in alkaloid chemistry a dimethoxy substituted harman I, a similarly substituted yobyrine II, and a series of other compounds related to 5,6-dimethoxyindole (III) were required.



I, R = $-CH_3$

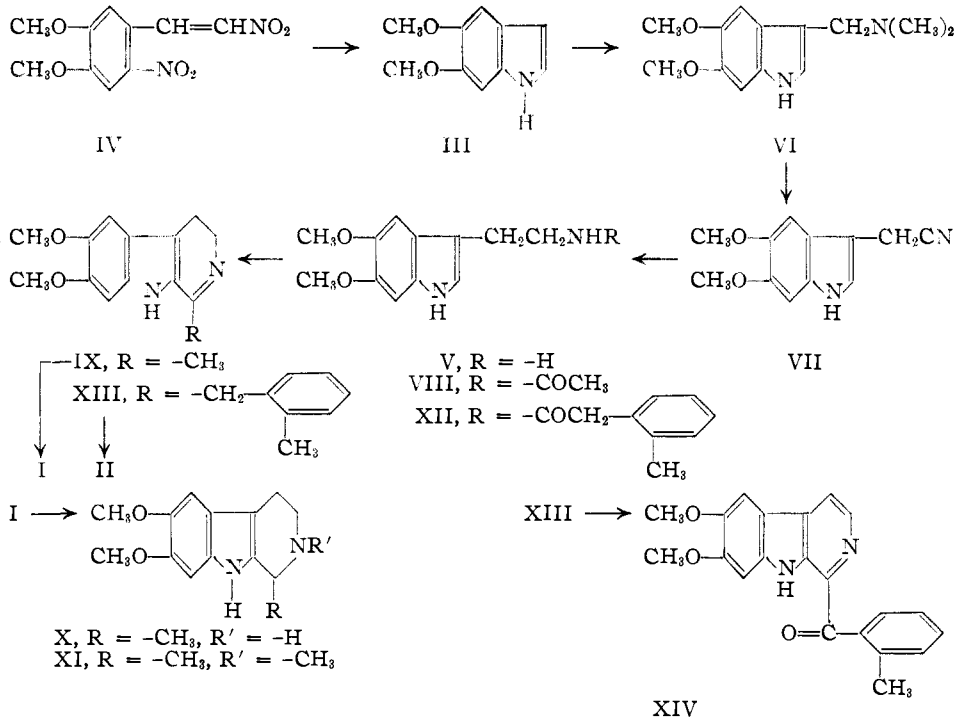


II, R = CH_3

An attempt to prepare I by Perkin and Rubenstein[1] in 1926 by the Fischer indole method was abandoned because of the extreme instability of the intermediate 3,4-dimethoxyphenylhydrazine. The synthesis of 5,6-dimethoxyindole (III) from 6-nitrohomoveratrole by the Reissert method has been reported by Oxford and Raper.[2] In seeking a more convenient route to III, the starting point for our further transformations, we investigated the Nenitzescu synthesis which has been successfully exploited by Robertson and co-workers[3] in a study of the chemistry of melanins. Nitration of veratraldehyde in the 6-position[4] and conversion to 3,4-dimethoxy-6,β-dinitrostyrene (IV) by reaction with nitromethane proceeded easily and in satisfactory yield. The reduction and ring closure of IV to produce the indole III, when carried out in the usual manner, employing iron powder and a large excess of acetic acid, worked satisfactorily only on the small scale (2 g.) used by Robertson.[3] Increasing the scale caused a drop in yield and made the work-up of the reaction mixture excessively tedious. We investigated the optimum conditions for the conversion of IV to III by catalytic reduction, a hitherto undescribed variation of the Nenitzescu synthesis. Using palladium-on-carbon as a catalyst in an ethyl acetate–ethanol solvent mixture in the presence of four molar equivalents of acetic acid to remove the ammonia formed, 60% yields of III were obtained regardless of the scale of the reaction.

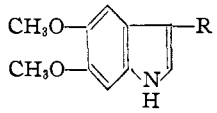
The route from III to 3-(2-aminoethyl)-5,6-dimethoxyindole (V) followed the sequence used by Thesing and Schülde[5] in their excellent tryptamine synthesis. Thus, III was converted successively to 3-(dimethylaminomethyl)-5,6-dimethoxyindole (VI), to the quaternary salt of VI and to 5,6-dimethoxyindole-3-acetonitrile (VII). High pressure catalytic reduction of VII gave the substituted tryptamine (V). Transformation of V to I proceeded according to the pattern of the harmala synthesis of Späth and Lederer.[6] Ring closure with phosphorus pentoxide of VIII (obtained either by acetylation of V or by the reduction of VII in acetic anhydride over platinum) afforded 3,4-dihydro-6,7-dimethoxy-1-methyl-9H pyrid[3,4-b]-indole (IX). In the final step 6,7-dimethoxy-1-methyl-9H-pyrid[3,4-b]indole (I) (7,8-dimethoxy-2-methyl-β-carboline) was obtained by catalytic dehydrogenation of IX. Compounds were also required in which the pyridine ring of I was completely reduced. Two of these (X and XI) were obtained by catalytic reduction of IX and by so-

(1) W. H. Perkin, Jr., and L. Rubenstein, *J. Chem. Soc.*, 357 (1926).
(2) A. E. Oxford and H. S. Raper, *ibid.*, 417 (1927).
(3) R. J. S. Beer, K. Clarke, H. F. Davenport and A. Robertson, *ibid.*, 2029 (1951).
(4) A. H. Salway, *ibid.*, **95**, 1155 (1909).
(5) J. Thesing and F. Schülde, *Ber.*, **85**, 324 (1952).
(6) E. Späth and E. Lederer, *ibid.*, **63**, 2101 (1930).



dium borohydride reduction of the methiodide of IX, respectively.

A final substance needed in connection with our alkaloid problem was the substituted yobyrine II. (Yobyrine is a selenium dehydrogenation product of yohimbine.) However, in attempting the preparation of II (*via* XII and XIII) in a manner similar to that used by Julian[7] and coworkers for the synthesis of yobyrine, we could obtain only the corresponding yobyrone (XIV). It is evidently formed by the ready air oxidation of II. Julian[7] reports the tendency for this to occur in the yobyrine series; however, it is much more marked in the present case of the methoxylated analog. Ring closure to the expected and desired position in the indole nucleus in IX and XIII was demonstrated by the disappearance of the strong Ehrlich reaction displayed by all our indole derivatives unsubstituted in the 2-position.



XV, R = $-CH_2COOH$
XVI, R = $-CH_2CHNH_2COOH$
XVII, R = $-CH_3$

Two new substances of potential physiological interest, 5,6-dimethoxyindole-3-acetic acid (XV) and 5,6-dimethoxytryptophan (XVI) were synthesized during this study. Alkaline hydrolysis of the nitrile VII afforded XV. XV was of additional interest because it could be decarboxylated to yield the substituted skatole, an as yet undescribed substance XVII. XVI was obtained by the series of reactions described by Snyder[8] and others for the synthesis of tryptophan. The condensation product of IV with diethyl acetaminomalonate was converted in three steps to 5,6-dimethoxytryptophan (XVI). Difficulty was experienced in the isolation of an absolutely ash-free preparation of XVI because of its great solubility in water and inability to crystallize from that solvent.

Mention should be made of a characteristic of all the indole derivatives in this series in which the 2-position was unsubstituted. Aqueous solutions of these compounds are quickly oxidized by air to indigo-like dyes. Especially bad in this regard are 3-(2-aminoethyl)-5,6-dimethoxyindole (V), 5,6-dimethoxyindole-3-acetic acid (XV), and 5,6-dimethoxytryptophan (XVI). The color can be discharged with hydrosulfite. These same compounds give a dark green coloration with ferric chloride, a reaction first described by Oxford and Raper[2] for 5,6-dimethoxyindole (III). Although these authors state: "This indole quickly darkens on keeping and is very sensitive to oxidizing agents in the presence of acids," we found III to be reasonably stable, although it is difficult to purify because of unfavorable coefficients of solubility in organic solvents. This property is generally true for most of the compounds we have encountered in this series.

It is a pleasure to acknowledge the helpful advice of Dr. E. Schlittler, who suggested this problem. We also wish to thank Mr. Louis Dorfman and staff for the microanalyses and physical measurements and Mrs. Katheryn Oney and Miss M. Connolly for technical assistance.

Experimental

3,4-Dimethoxy-6,β-dinitrostyrene (IV).—To a cooled, stirred suspension of 494 g. of 6-nitroveratraldehyde (prepared from veratraldehyde in 78% yield in essentially the manner described by Salway[4]) in 6 l. of methanol and 126 ml. of nitromethane was added 196 ml. of 50% (w./v.) solution of sodium hydroxide. The temperature was kept at about 15° during the addition (45 minutes). After standing 15 minutes, the reaction mixture was added with stirring to solution of 1.5 l. of concd. hydrochloric acid in 2 l. of water. The yellow crystalline mass was filtered, washed well with water and finally with a little ethanol. The melting point (118–145°) of the crude material indicated it to be a mixture of the desired styrene and the α-nitromethylbenzyl alcohol. Dehydration was completed by heating on a steam-bath for 15 minutes with 400 ml. of acetic anhydride and 100 g. of sodium acetate. This mixture was poured into 2 l. of ice-water and filtered after one hour. After washing well with water and drying, 374 g. of IV (63%) was obtained, m.p. 166–169°. This product was of sufficient purity to use in the next step. Recrystallization does not raise the melting point.

Anal. Calcd. for $C_{10}H_{10}N_2O_6$: N, 11.02. Found: N, 10.99.

(7) P. L. Julian, W. J. Karpel, A. Magnani and E. W. Meyer, THIS JOURNAL, **70**, 180 (1948).

(8) E. E. Howe, A. J. Zambito, H. R. Snyder and M. Tishler, *ibid.*, **67**, 38 (1945); H. R. Snyder and C. W. Smith, *ibid.*, **66**, 350 (1944).

5,6-Dimethoxyindole (III).—Twenty grams of the nitrostyrene IV was hydrogenated at 50 p.s.i. over 2 g. of 10% palladium-on-charcoal in a solvent mixture of 225 ml. of ethyl acetate, 25 ml. of ethanol and 28 ml. of acetic acid. The addition of the ethanol was essential to keep the ammonium acetate formed during the reduction from precipitating and flocculating the catalyst. The reduction was complete in 45 minutes. Slower reduction causes a decrease in yield. After removal of the catalyst, the filtrate was washed with a suspension of 20 g. of sodium bicarbonate in 75 ml. of water. The organic layer was dried over sodium sulfate and concentrated to a small volume *in vacuo*, and the 5,6-dimethoxyindole (III) allowed to crystallize. Several crops were collected, and the combined crude material recrystallized from ethyl acetate, yield 8.4 g. (60%), m.p. 149–152°. Recrystallization from benzene–petroleum ether raised the melting point to 152–153°; λ_{max}^{EtOH} 220 mμ (log ε 4.30), 272 mμ (log ε 3.67), 294 mμ (log ε 3.85), 300 mμ (log ε 3.85). Oxford and Raper[2] record a melting point of 154–155°. III in ethanol solution exhibits a blue fluorescence under ultraviolet light.

Anal. Calcd. for $C_{10}H_{11}NO_2$: N, 7.91. Found: N, 7.95.

3-(Dimethylaminomethyl)-5,6-dimethoxyindole (VI).—Twenty-five grams of powdered III was added over several minutes with external cooling (the temperature should be kept at 60°) to a mixture of 28.6 ml. of 22.3% aqueous dimethylamine, 25 ml. of acetic acid and 10.9 ml. of 36% aqueous formaldehyde. After one hour the brown solution was diluted with 25 ml. of water and made neutral by the slow addition of 10% sodium carbonate. The pink amorphous powder separating during this addition was filtered off. This acid-insoluble by-product is probably a formaldehyde–indole condensation product. Although reaction conditions were varied, we never succeeded in preventing the formation of this substance. The filtrate from above was made strongly basic with sodium hydroxide and the claret-colored solution extracted several times with ethyl acetate. The ethyl acetate phase was washed with water, dried over sodium sulfate and concentrated *in vacuo* to a small volume and chilled in the ice-box for 18 hours to yield 16.4 g. (50%) of VI, m.p. 121–126.5°. Recrystallization from ethyl acetate sharpened the melting point to 125–125.5°.

Anal. Calcd. for $C_{13}H_{18}N_2O_2$: C, 66.64; H, 7.74; N, 11.96. Found: C, 66.42; H, 7.45; N, 11.70.

(5,6-Dimethoxy-3-indolylmethyl)-trimethylammonium Methyl Sulfate.—A solution of 41.8 g. of VI and 2.55 ml. of acetic acid in 250 ml. of dry, peroxide-free tetrahydrofuran was added with stirring and cooling (10–15°) over a period of 30 minutes to a solution of 84 ml. of dimethyl sulfate and 2.55 ml. of acetic acid in 100 ml. of tetrahydrofuran. After one hour in the ice-box, the pinkish quaternary salt was filtered and washed well with ether, yield 64 g. (99%), m.p. 154–161°. Attempted recrystallization of this substance brings about decomposition with the loss of trimethylamine. It is advisable to use this substance directly because it begins to turn dark blue after a few days.

Anal. Calcd. for $C_{15}H_{24}N_2O_6S$: N, 8.89. Found: N, 8.63.

5,6-Dimethoxyindole-3-acetonitrile (VII).—A solution of 71 g. of the quaternary salt of VI in 385 ml. of a 10% aqueous solution of potassium cyanide was heated one hour at 65–75°. Trimethylamine was evolved almost immediately, and the nitrile VII began to separate, first as an oil and later as a white crystalline material. Crude VII was filtered, washed with water, dried *in vacuo* and recrystallized from a benzene–hexane mixture, from which it separated in plates, yield 27.0 g. (64%), m.p. 120–125°.

Anal. Calcd. for $C_{12}H_{12}N_2O_2$: C, 66.65; H, 5.59; N, 12.96. Found: C, 67.13; H, 5.68; N, 12.80.

3-(2-Aminoethyl)-5,6-dimethoxyindole (V).—Sixteen grams of VII was hydrogenated at 1500 p.s.i. and room temperature in 300 ml. of methanol saturated with ammonia at 0° over 3 teaspoons of Raney nickel catalyst. Hydrogen uptake was complete in about an hour. The catalyst was filtered and the solvent distilled off *in vacuo* to yield crude V. Because of the instability of this substance toward oxidation, it was used directly in its crude form for further chemical transformations. It could be distilled in a sublimation apparatus at 0.02 mm. and a bath temperature of 180°. The resinous distillate on the cold finger soon crystallized, m.p. 90–92°. We were unable, however, to find a suitable solvent for recrystallization.

Anal. Calcd. for $C_{12}H_{16}N_2O_2$: C, 65.43; H, 7.27; N, 12.73. Found: C, 65.45; H, 7.18; N, 12.59.

We were also unable to prepare any water soluble crystalline salts of V. Due to oxidation, solutions of V rapidly became progressively bluer. Small amounts of sodium hydrosulfite slowed up this process. The **picrate of V** is a satisfactory derivative. It forms in highly insoluble, tiny, dark red needles from ethanol, m.p. 225° dec. (with darkening beginning at 200°).

Anal. Calcd. for $C_{12}H_{16}N_2O_2 \cdot C_6H_3N_3O_7$: C, 48.11; H, 4.26; N, 15.59; OCH_3, 13.79. Found: C, 48.48; H, 4.48; N, 15.20; OCH_3, 14.53.

N-[2-(5,6-dimethoxy-3-indolyl)-ethyl]-acetamide (VIII).—Four grams of crude V was stirred into 10 ml. of acetic anhydride with cooling. The solution soon set solid with the crystalline acetate VIII. It was filtered, washed with a little ethanol and recrystallized from ethanol, m.p. 179–181°, yield 3.4 g., λ_{max}^{EtOH} 242 mμ (log ε 4.41), 297 mμ (log ε 3.83).

Anal. Calcd. for $C_{14}H_{18}N_2O_3$: C, 64.10; H, 6.92; N, 10.68; OCH_3, 23.64. Found: C, 64.14; H, 7.17; N, 10.43; OCH_3, 24.10.

VIII is also formed by the following but less desirable process. The nitrile VII (0.4 g.) was hydrogenated at atmospheric pressure in 4 ml. of acetic anhydride over 0.1 g. of platinum oxide. Hydrogenation was complete in four hours. The catalyst was separated and the solvent removed *in vacuo*. The residue was recrystallized from ethanol to yield 0.14 g. of VIII.

3,4-Dihydro-6,7-dimethoxy-1-methyl-9H-pyrid[3,4-b]-indole (IX).—One gram of VIII was dissolved in 200 ml. of refluxing dry xylene. Phosphorus pentoxide (10 g.) was added portionwise over 30 minutes and refluxing continued for an hour. The brown insoluble residue was filtered, washed with ether and slowly added to 200 g. of ice-water. Five ml. of concd. hydrochloric acid was added to bring about complete solution of the phosphate salts. The green solution was washed once with ether and then made basic by the slow addition of solid potassium hydroxide; IX does not separate from the basic solution because of its moderate water solubility. It may be extracted, however, with ether. Removal of the ether leaves a crystalline residue of IX which recrystallizes from ethyl acetate in almost colorless prisms, m.p. 180–181°, yield 0.5 g., λ_{max}^{EtOH} 337 mμ (log ε 4.28).

Anal. Calcd. for $C_{14}H_{16}N_2O_2$: C, 68.83; H, 6.60; N, 11.47. Found: C, 69.06; H, 6.57; N, 11.55.

6,7-Dimethoxy-1-methyl-9H-pyrid[3,4-b]indole (I)—IX (30 mg.) was mixed intimately with 10 mg. of a 30% palladium on carbon dehydrogenation catalyst[9] in a small test-tube and placed in an oil-bath at 200° for two minutes. The catalyst was extracted with acetone and the latter evaporated to yield crystalline I. Recrystallization from acetone gave 13 mg. of I as faintly yellow, granular crystals, m.p. 225–226°, λ_{max}^{EtOH} 238 mμ (log ε 4.53), 304 mμ (log ε 4.27). Solutions of I exhibit intense yellow-green fluorescence under ultraviolet light in contrast to the dihydro compound IX, which shows no fluorescence.

Anal. Calcd. for $C_{14}H_{14}N_2O_2$: C, 69.40; H, 5.83; N, 11.56. Found: C, 69.04; H, 5.61; N, 11.74.

I and IX are considerably less stable than the parent compounds lacking the methoxy groups. For this reason the dehydrogenation of IX must be carried out as rapidly as possible to obtain maximum amounts of I.

1,2,3,4-Tetrahydro-6,7-dimethoxy-1-methyl-9H-pyrid-[3,4-b]indole (X).—IX (160 mg.) was hydrogenated at atmospheric pressure in 15 ml. of ethanol over 50 mg. of platinum oxide. One molar equivalent of hydrogen was absorbed in 10 minutes. The solid resulting from removal of the catalyst and solvent was recrystallized from acetone–water to yield 75 mg. of X, m.p. 180–181°, λ_{max}^{EtOH} 226 mμ (log ε 4.45), 303 mμ (log ε 3.98). A mixture of IX and X showed a depression in melting point (150–160°).

Anal. Calcd. for $C_{14}H_{18}N_2O_2$: C, 68.27; H, 7.37; N, 11.37. Found: C, 68.25; H, 7.46; N, 11.20.

(9) R. P. Linstead and S. L. S. Thomas, *J. Chem. Soc.*, 1127 (1940).

1,2,3,4-Tetrahydro-6,7-dimethoxy-1,2-dimethyl-9H-pyrid[3,4-b]indole (XI).—IX (200 mg.) was refluxed with 0.1 ml. of methyl iodide in 10 ml. of methanol for one hour. The crystals separating during the reaction were recrystallized from water to give 250 mg. of short yellow needles of the methiodide of IX, m.p. 270–274° dec.

Anal. Calcd. for $C_{15}H_{19}IN_2O_2$: N, 7.25. Found: N, 7.09.

The methiodide of IX (200 mg.) was suspended in 5 ml. of methanol and 80 mg. of sodium borohydride added in portions. A rapid exothermic reaction took place. After standing for five minutes, the methanol was concentrated, the residue rubbed with 5% aqueous sodium hydroxide and extracted with ethyl acetate. The residue, after removal of the ethyl acetate, was recrystallized twice from ethanol to yield XI, m.p. 169–170°.

Anal. Calcd. for $C_{15}H_{20}N_2O_2$: C, 69.20; H, 7.74; N, 10.76. Found: C, 69.44; H, 7.80; N, 10.50.

N-[2-(5,6-Dimethoxy-3-indolyl)-ethyl]-*o*-methylphenylacetamide (XII).—To a solution of 2 g. of V in 10 ml. of pyridine was added with cooling, 2.75 ml. of *o*-tolylacetyl chloride (2 molar equivalents). After 15 minutes the solution was poured into ice and the crystalline amide XII separated. It was recrystallized from benzene–hexane to yield 1.4 g. of platelets of XII, m.p. 146–147°.

Anal. Calcd. for $C_{21}H_{24}N_2O_3$: C, 71.57; H, 6.86; N, 7.95. Found: C, 71.83; H, 7.14; N, 7.97.

1-(*o*-Toluyl)-5,6-dimethoxy-9H-pyrid[3,4-b]indole (XIV).—A solution of 1.1 g. of XII in 200 ml. of refluxing xylene was treated with 10 g. of phosphorus pentoxide as described for the preparation of IX. The reaction mixture was worked up in a similar manner, and the residue remaining after the removal of the ether was recrystallized from ethyl acetate to yield 0.6 g. of bright orange plates, m.p. 194–195°, λ_{max}^{EtOH} 300 mμ (log ε 4.04), 370 mμ (log ε 3.96). A strong carbonyl band was present at 1667 cm.$^{-1}$.

Anal. Calcd. for $C_{21}H_{18}N_2O_3$: C, 72.82; H, 5.24; N, 8.09. Found: C, 72.53; H, 5.51; N, 7.83.

The properties of XIV, *i.e.*, its orange color and its inability to fluoresce, are consonant with those reported by Scholz[10] for yobyrone.

In another trial to prepare II and prevent the oxidation to the ketone XIV, peroxide-free ether was used to extract the product resulting from ring closure. The ether was removed under nitrogen and the residue recrystallized from ethanol to yield colorless needles of **3,4-dihydro-5,6-dimethoxy-1-(*o*-methylbenzyl)-9H-pyrid[3,4-b]indole (XIII)**, m.p. 168–170°.

Anal. Calcd. for $C_{21}H_{22}N_2O_2$: N, 8.38. Found: N, 8.16.

However, during the dehydrogenation and subsequent work-up of the product, XIV was obtained again.

5,6-Dimethoxyindole-3-acetic Acid (XV).—One gram of the nitrile VII was refluxed under nitrogen with 11 ml. of 20% aqueous potassium hydroxide containing a trace of sodium hydrosulfite. By the second hour the nitrile had completely dissolved. After refluxing for an additional hour the reaction mixture was cooled and carefully made slightly acid with acetic acid. Crude XV (0.6 g.) separated as plates. It could be recrystallized only with difficulty, water being the best solvent, m.p. 136–138°.

Anal. Calcd. for $C_{12}H_{13}NO_4$: C, 61.27; H, 5.57; N, 5.96. Found: C, 61.50; H, 5.58(2); N, 6.01.

5,6-Dimethoxy-3-methylindole (XVII).—XV (100 mg.) was heated under nitrogen at 200° for five minutes, by which time frothing due to carbon dioxide evolution stopped. The green gummy material solidified on cooling. A portion of this crude material was converted to the **picrate**. It was recrystallized from ethanol and separated in fine red-brown needles.

Anal. Calcd. for $C_{11}H_{13}NO_2 \cdot C_6H_3N_3O_7$: N, 13.33. Found: N, 13.26.

The free skatole derivative XVII was difficult to crystallize but could be purified by the concentration of a hexane extract (300 ml.) of the crude substance described above. Small colorless platelets separated from the hexane during the concentration, m.p. 133–136°.

Anal. Calcd. for $C_{11}H_{13}NO_2$: C, 69.09; H, 6.85; N, 7.33. Found: C, 69.31; H, 6.77; N, 7.64.

Diethyl Acetamido-(5,6-dimethoxy-3-indolylmethyl)-malonate.—A mixture of 4 g. of VI and 3.7 g. of diethyl acetamidomalonate was refluxed in 40 ml. of dry xylene in the presence of 0.2 g. of powdered sodium hydroxide. Dry nitrogen was passed through the mixture till dimethylamine was no longer evolved (5 hours). The hot solution was filtered, and, on cooling, an oil separated which crystallized on rubbing. On recrystallization from ethyl acetate–hexane, 4.7 g. was obtained, m.p. 125–127°.

Anal. Calcd. for $C_{20}H_{28}N_2O_7$: C, 59.10; H, 6.45; N, 6.89. Found: C, 59.21; H, 6.54; N, 7.00.

5,6-Dimethoxytryptophan (XVI).—The substituted ethyl malonate described above (1.35 g.) was hydrolyzed under nitrogen in 13.5 ml. of 25% aqueous sodium hydroxide for two hours. The solution was diluted with 20 ml. of water, treated with norite and filtered through a sintered glass funnel. The filtrate was carefully made acid by the slow addition of concd. hydrochloric acid. Extraction with four portions of ethyl acetate (50 ml.) and removal of the ethyl acetate yielded 0.78 g. of the semi-crystalline malonic acid. Decarboxylation was brought about by heating the malonic acid dissolved in 4 ml. of water in a sealed tube under nitrogen at 105° for three hours. Effervescence was noted on opening the tube. Concentration to dryness yielded 0.6 g. of the acetyl tryptophan. This substance was obtained as a glass. The acetyl group was removed by hydrolysis in a sealed tube under nitrogen with 14 ml. of 0.35 *N* barium hydroxide for 12 hours. After opening the tubes, 14 ml. of 0.35 *N* sulfuric acid was added. Upon removing the barium sulfate it was noted that a small excess of sulfate was present, due to the consumption of barium hydroxide by the glass. This was balanced out by the addition of a few tenths ml. of 0.35 *N* barium hydroxide. The sirupy residue remaining after removal of the barium sulfate and concentration *in vacuo* was reduced to a crystalline powder by rubbing with absolute ethanol. The crystals were collected with a small amount of absolute ethanol. Purification was effected by dissolving in 10 ml. of hot 90% ethanol, removal of a small amount of solid material and concentration to a small volume to yield 0.3 g. of XVI as a bluish-tinted powder, m.p. 248–251°. A small amount of ash was present, but correcting for this an acceptable analysis was obtained.

Anal. Calcd. for $C_{13}H_{16}N_2O_4$: C, 59.08; H, 6.10; N, 10.60. Found: C, 58.85; H, 6.34; N, 10.29.

XVI gives a ninhydrin reaction, and an aqueous solution quickly becomes blue. Paper chromatography under nitrogen using a mixture of *t*-butyl alcohol–acetic acid–water (2:1:1) indicated XVI to have an R_f value of 0.41. Glycine in the same system showed the same R_f value. When the chromatogram was attempted without replacing the air in the chamber by nitrogen, ink-blue spots became evident in a few hours, due to oxidation of XVI.

SUMMIT, NEW JERSEY

(10) C. Scholz, *Helv. Chim. Acta*, **18**, 923 (1935).