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O-alkylations of indoxylic acid (**2b**) to produce 3-indolyl-alkyl ethers and a synthesis of 5-methoxy-2-carboxyindol-3-oxyacetic acid (**25**) are described.

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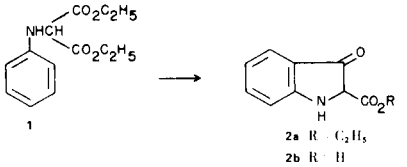
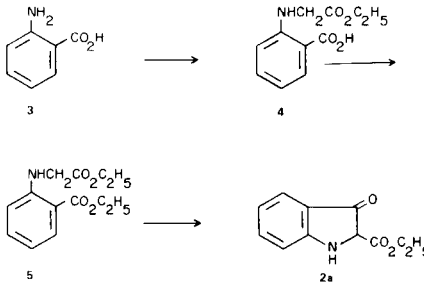
Indoxylic acid (**2b**) has been mentioned frequently in the literature as an intermediate in the synthesis of indigo dyes (1-7,9). In only a few cases (8,10,14) have there been attempts to convert indoxylic acid to its 3-alkoxy ethers. In addition, there are few reports of syntheses of benzene ring substituted indoxylic acid. It was our purpose to synthesize indoxylic acid, its 5-methoxy derivative and the corresponding 3-alkoxy derivatives.

Blanck (2) reported the synthesis of indoxylic acid by heating *N*-phenyldiethylaminomalonate **1**. Upon repeating Blanck's work, we obtained a product that gave an elemental analysis, nmr and ir spectra consistent with **2b**. However, it had a higher melting point and the mass spectrum indicated a higher molecular weight than indoxylic acid synthesized by two different methods (*vide supra*).



Vorländer and Schilling (6) synthesized indoxylic acid starting from anthranilic acid (**3**). When we tried to carry out the esterification step (**4** → **5**) using normal Fisher conditions (catalytic amounts of sulfuric or *p*-toluenesulfonic acid) only starting material was recovered. Only when large amounts of sulfuric acid (*ca.*, mole: mole) were used did we obtain the desired diester (in 75% yield as opposed to 50% reported by Vorländer and Schilling) (6).



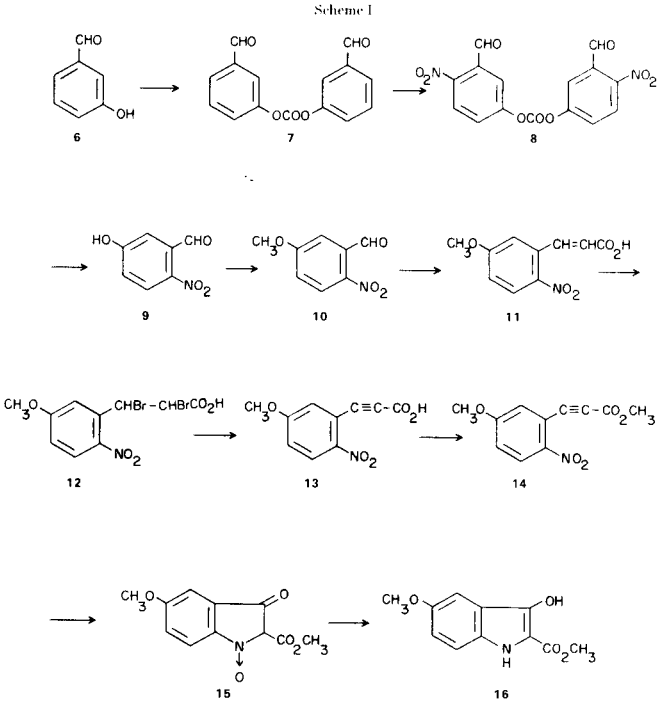
The synthesis of 5-methoxyindoxylic acid methyl ester (**16**) was carried out according to Scheme I. 2-Nitro-5-hydroxybenzaldehyde (**9**) was synthesized by a modification of Mason's (11) procedure. Bromination of 2-nitro-5-methoxycinnamic acid (**11**) to the dibromo derivative (**12**) was unsuccessful with bromine in acetic acid, but proceeded smoothly with pyridine hydrobromide perbromide. Indoxylic acid itself was prepared in a similar manner starting with *o*-nitrobenzaldehyde.

Although reactions of indoxylic acid-3-methyl and 3-ethyl ethers have been reported, (8,10) no details of their syntheses are given. We therefore decided to prepare these compounds before attempting to prepare the 3-*O*-acetic acid derivatives. The synthesis of the two compounds is shown in Scheme II.

The synthesis of the 3-*O*-acetic acid derivatives of indoxylic acid and its 5-methoxy derivative are shown in Scheme II (**22** and **25**, respectively). Although the alkylation proceeds with bromoacetic acid or ethylhaloacetate (bromo or chloro), the latter is preferred since a 70% yield is obtained, whereas the former gives a 20% yield.

Vorländer, *et al.* (12), reported the decarboxylation of 3-acyloxy-2-carboxyindole (**22**) by heating in acetic anhydride. When we tried to repeat the reaction on **22**

Scheme I



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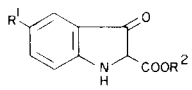
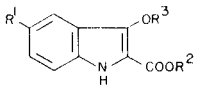
Scheme II

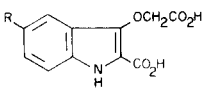


2a R^1 = H; R^2 = C_2H_5
2c R^1 = H; R^2 = CH_3
16 R^1 = OCH_3; R^2 = CH_3

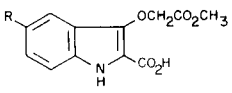


17 R^1 = H; R^2 = C_2H_5; R^3 = CH_3
18 R^1 = R^2 = H; R^3 = CH_3
19 R^1 = H; R^2 = R^3 = C_2H_5
20 R^1 = R^2 = H; R^3 = C_2H_5
21a R^1 = H; R^2 = CH_3; R^3 = CH_2COOH
21b R^1 = H; R^2 = C_2H_5; R^3 = CH_2COOH
22 R^1 = R^2 = H; R^3 = CH_2COOH
24a R^1 = OCH_3; R^2 = CH_3; R^3 = $CH_2COOC_2H_5$
24b R^1 = H; R^2 = C_2H_5; R^3 = $CH_2COOC_2H_5$
25 R^1 = OCH_3; R^2 = H; R^3 = CH_2COOH

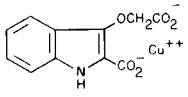
and its 5-methoxy analog **25**, no decarboxylation occurred. Starting material was recovered with an aqueous workup. When a methanol workup was used the methyl ester (**26**) was recovered, indicating that instead of the expected decarboxylation, a mixed acetic-indoxylic anhydride had been formed.



22 R = H
25 R = OCH_3



26a R = OCH_3
26b R = H



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Attempted decarboxylation of the copper salt (**27**) by heating in quinoline was unsuccessful. All other attempts at decarboxylation, including pyrolysis under vacuum, heating in tetralin, decalin, xylene and water gave either starting material or underwent resinification. We believe that an alkoxy group in the 3 position stabilizes the carboxy group at position 2, thus preventing decarboxylation.

The pharmacological properties of the compounds synthesized will be reported elsewhere.

EXPERIMENTAL

Diethyl *N*-phenylaminomalonate (**1**).

This compound was prepared from diethyl bromomalonate according to reference 2.

Cyclization of Diethyl *N*-phenylaminomalonate.

Diethyl *N*-phenylaminomalonate (10 g.) was slowly heated under vacuum (water pump) to 260-265°. During the pyrolysis some starting material distilled at 190°. The residue obtained after cooling was dissolved in hot ethanol and allowed to crystallize. A second crop was isolated from the filtrate (40% total yield), m.p. 120-126°; ir (nujol): 1750, 1700, 1200 cm^{-1}.

Anal. Calcd. for $C_{11}H_{10}NO_3$: C, 64.38; H, 5.40; N, 6.82. Found: C, 64.1; H, 5.3; N, 6.8.

Ethyl *N*-(*o*-Carbethoxyphenyl)glycinate (**5**).

A solution of ethyl *N*-(*o*-carboxyphenyl)glycinate (**4**)(6)(80 g.) in absolute ethanol (800 ml.) containing concentrated sulphuric acid (60 ml.) was heated under reflux for 16 hours. The reaction mixture was cooled and poured into an excess of sodium carbonate solution in ice water. The precipitate was filtered, washed with water and crystallized from ethanol-water (yield 73.5%), m.p. 73-74°, lit., (**6**) m.p. 75°.

Some unreacted starting material can be recovered from the basic aqueous filtrate.

2-Carbethoxyindoxyl (**2a**).

A solution of sodium (8.5 g.) in absolute ethanol (120 ml.) was added rapidly to a solution of **5** (50 g.) in boiling dry ether (150 ml.). The mixture was refluxed for 1 hour, cooled, water (500 ml.) was added and the aqueous phase extracted twice with ether to remove color and undissolved material. The aqueous phase was neutralized with gaseous carbon dioxide, the precipitate filtered and triturated with 30% aqueous ethanol (yield: 75%), m.p. 113-114°, lit., (6) m.p. 116°.

3-Methoxy-2-carbethoxyindole (**17**).

Dimethyl sulphate (3.0 g.) was added dropwise to a solution of **2a** (3.0 g.) in dilute potassium hydroxide (1.0 g. in 20 ml. of water). After stirring for 5 hours at room temperature, the product was filtered and crystallized from petroleum ether 60-80°, (yield 47%), m.p. 88°; ir (nujol): 1720, 1130, 1100 cm^{-1}; nmr (deuteriochloroform): δ 9.15 (broad s, NH), 6.8-7.7 (m, aromatic) 4.42 (q, ethyl), 4.0 (s, methoxy), 1.22 (t, ethyl); ms: m/e M^+ 219.

Anal. Calcd. for $C_{12}H_{13}NO_3$: C, 65.7; H, 6.0; N, 6.4; OCH_3, 14.2; OC_2H_5, 20.5. Found: C, 65.8; H, 6.0; N, 6.8; OCH_3, 13.8; OC_2H_5, 20.1.

3-Methoxy-2-carboxyindole (**18**).

A solution of **17** (2 g.) in a mixture of methanol (20 ml.) and water (20 ml.) containing potassium hydroxide (2 g.) was refluxed for 1 hour, the methanol evaporated and the residual aqueous solution extracted twice with ether and acidified to precipitate **18**. The product was filtered, washed with water and dried (yield 86.5%), m.p. 127-130°; ir (nujol) 3300, 1700, 1100 cm^{-1}; nmr (deuteriochloroform): δ 7.5-6.8 (m, aromatic) 4.1 (s, methoxy). The spectrum contains a peak with variable chemical shift (from *ca.*, 4.7 to 7.0). This peak disappears after treatment with deuterium oxide and is due to water of crystallization.

3-Ethoxy-2-carbethoxyindole (**19**).

Ethyl iodide (7 g.) in acetone (50 ml.) was added to a solution of **2a** (10 g.) in aqueous potassium hydroxide (2.8 g. in 200 ml. of water). The mixture was stirred overnight at room temperature. The precipitate obtained after the evaporation of the acetone was recrystallized from ethanol-water (yield 37%), m.p. 81-83°; ir (nujol): 3310, 1730, 1140, 1116 cm^{-1}; nmr (deuteriochloroform): δ 9.3 (broad s, NH), 7.8-7.0 (m, aromatic), 4.10-4.50 (d, q, *O*-ethyl and ethyl), 1.35 (t, *O*-ethyl).

Anal. Calcd. for $C_{13}H_{15}NO_3$: C, 66.9; H, 6.5; N, 6.0; OC_2H_5, 38.6. Found: C, 67.0; H, 6.4; N, 6.2; OC_2H_5; 39.1.

3-Ethoxy-2-carboxyindole (**20**).

Prepared in the same manner as the 3-methoxy derivative (**18**), (yield 90%), m.p. 142-144°; ir (nujol): 1700 cm^{-1}; nmr (deuteriochloroform): δ 9.3 (broad s, NH), 7.8-7.0 (m, aromatic), 4.25 (q, *O*-ethyl), 1.35 (t, *O*-ethyl and ethyl).

Anal. Calcd. for $C_{11}H_{11}NO_3$: N, 6.8. Found: N, 6.5.

2-Carbomethoxyindol-3-oxyacetic Acid (**21a**).

Bromoacetic acid (16.8 g.) was added in portions to a hot (80°) solution of 2-carbomethoxyindoxyl (10 g.) in aqueous potassium hydroxide (14 g. in 200 ml. of water). Heating was continued until the *p*H dropped to 7. The reaction mixture was cooled, acidified with dilute hydrochloric acid and extracted with chloroform. After drying (magnesium sulphate) the chloroform

was evaporated and the product crystallized from ether (yield 24%), m.p. 168-170°; nmr (deuteriochloroform): δ 7.8-7.0 (m, aromatic), 4.88 (s, *O*-methylene), 3.86 (s, methyl).

Anal. Calcd. for $C_{12}H_{11}NO_5$: C, 57.8; H, 4.4; N, 5.6. Found: C, 57.5; H, 4.3; N, 6.0.

2-Carbethoxyindol-3-oxyacetic Acid (**21b**).

Prepared in the same manner as **21a** from **2a** (yield 22%), m.p. 151-153°; ir (nujol): 1720, 1700, 1140, 1110 cm^{-1}; nmr (deuteriochloroform): δ 7.8-7.0 (m, aromatic), 4.85 (s, *O*-methylene), 4.32 (q, ethyl), 1.35 (t, ethyl).

2-Carboxyindol-3-oxyacetic Acid (**22**).

The hydrolysis of **21a** and **21b** was carried out as described for **18** (yield 90%), m.p. 156°; ir (nujol): 3310, 1690, 1140 cm^{-1}; nmr (deuteriochloroform): δ 7.6-7.0 (m, aromatic), 5.0 (s, O-methylene); ms: M^+ 235.

Anal. Calcd. for $C_{11}H_9NO_5$: N, 5.9. Found: N, 5.8.

Ethyl 2-Carbethoxyindole-3-oxyacetate (**24b**).

A solution of ethyl bromoacetate (11.4 g.) in acetone (100 ml.) was added to a solution of **2a** in aqueous potassium hydroxide (4.1 g. in 300 ml. of water). The reaction mixture was stirred until a *p*H of 7 was reached. The acetone was evaporated and the oily product was extracted with chloroform. The organic layer was washed with a 10% potassium hydroxide solution, water and dried over magnesium sulphate. The product was crystallized from ether-petroleum ether (60-80°) (yield 45%), m.p. 75°; ir (nujol): 3310, 1710, 1050, 1020 cm^{-1}; nmr (deuteriochloroform): δ 7.95-7.15 (m, aromatic), 4.95 (s, *O*-methylene), 4.55-4.15 (*two* q, ethyls), 1.35 (t, ethyls); ms: M/e M^+ 291.

Anal. Calcd. for $C_{15}H_{17}NO_5$: C, 61.8; H, 5.9; N, 4.8. Found: C, 62.0; H, 5.8; N, 5.2.

2-Nitro-5-hydroxybenzaldehyde (**9**).

Phosgene was bubbled through a stirred solution (1000 ml. of water) of *m*-hydroxybenzaldehyde (100 g.) containing sodium carbonate decahydrate (80 g.), sodium hydroxide (32.5 g.) and sodium chloride (512 g.) at room temperature until no additional gas was absorbed. The precipitated carbonate was filtered, dispersed in water (500 ml.), refiltered, washed with glacial acetic acid (100 ml.) followed by isopropyl alcohol (100 ml.) then finally air dried.

A solution of nitric acid (97%, 42 ml.) in concentrated sulphuric acid (175 ml.) was added portionwise and with cooling (ice-salt bath) to a solution of the carbonate (112 g.) in concentrated sulphuric acid (1100 ml.), keeping the reaction temperature below 5°. The cooled reaction mixture was stirred for a further hour, poured onto crushed ice (4 kg.) and left overnight. The precipitate was filtered, washed with water followed by isopropyl alcohol. The resulting wet nitrocarbonate was added to a hot (water bath) stirred sodium hydroxide solution (4%; 750 ml.). Some sodium hydroxide pellets were added to effect complete solution. The reaction mixture was cooled and acidified to *p*H 4 with glacial acetic acid. The precipitate **9** was filtered, washed with water and air dried (yield 73%), m.p. 132°.

2-Nitro-5-methoxybenzaldehyde (**10**).

A dispersion of **9** (100 g.) in a mixture of water (1000 ml.) and dimethyl sulphate (240 ml.) at 40° was treated with a potassium hydroxide solution (200 g. in 600 ml. of water) at such a rate as to keep the *p*H between 8 and 10. Some cooling was necessary during this process to keep the temperature at 40°. After the *p*H kept steady at 9-10, the mixture was stirred for another hour, cooled, filtered and the product washed with water (yield 80%), m.p. 78-79°, lit. (15) m.p. 82°.

2-Nitro-5-methoxycinnamic Acid (**11**).

A mixture of **10** (35 g.), malonic acid (21.4 g.), dry pyridine (5.2 ml.) and absolute ethanol (55 ml.) was refluxed for 8 hours. The resulting mass was broken up, the mixture cooled and the product filtered, washed with ethanol (2 x 10 ml.) and ether (10 ml.). The acid was dispersed in ethanol (40 ml.), heated for 2 hours, cooled and filtered (yield 65%), m.p. 234°.

2,3-Dibromo-3-(2nitro-5-methoxyphenyl)propionic Acid (**12**).

A hot solution of pyridine hydrobromide perbromide (34 g.) in acetic acid (100 ml.) was added to a stirred hot solution of **11** (21 g.) in glacial acetic acid (150 ml.). After heating was continued for another 0.75 hour, the mixture was cooled and water was added. The product was filtered and crystallized from benzene-petrol ether (60-80°) (yield 72%), m.p. 130-135°; nmr (deuteriochloroform): δ 10 (s, carboxyl), 8.1-6.9 (m, aromatic), 6.25 (d, -CHBr-), 5.3 (d, -CHBr-), 3.85 (s, methoxy).

3-(2-Nitro-5-methoxyphenyl)propiolic Acid (**13**).

A solution of **12** (28 g.) in aqueous potassium hydroxide (28 g. in 840 ml. of water) was stirred at room temperature for 24 hours. The mixture was acidified with hydrochloric acid, the precipitate was filtered and redissolved in aqueous potassium hydroxide (28 g. in 560 ml. of water) and stirred for an additional 24 hours. The solution was again acidified, the product filtered, washed with water and dried (yield 75%), m.p. 146-148° dec.; ir (nujol): 3400, 2220, 1695 cm^{-1}; nmr (deuteriochloroform): δ 7.2-6.7 (m, aromatic); 3.8 (s, methoxy).

Anal. Calcd. for $C_{10}H_7NO_5$: C, 54.3; H, 3.2; N, 6.3. Found: C, 54.3; H, 3.2; N, 6.1.

Methyl 3-(2-Nitro-5-methoxyphenyl)propiolate (**14**).

A solution of **13** in methanolic hydrogen chloride (3%; 150 ml.) was stirred in a closed vessel in the dark, at room temperature, overnight. The yellow precipitate was filtered, the mother liquor concentrated and a second crop was isolated (combined yield 85%), m.p. 97-99°; ir (nujol): 2220, 1725 cm^{-1}; nmr (deuteriochloroform): δ 8.1-7.9 (d, aromatic); 7.1-6.9 (m, aromatic): 3.7 (s, methyl); 3.6 (s, methoxy).

Anal. Calcd. for $C_{11}H_9NO_5$: C, 56.2; H, 3.9; N, 5.9. Found: C, 56.0; H, 3.9; N, 5.9.

2-Carbomethoxy-5-methoxyisatogen (**15**).

A solution of **14** (11.5 g.) in dry pyridine (23 ml.) was heated in a boiling water bath. The reaction mixture was cooled, the crystals filtered, washed with water, triturated with methanol and dried (yield 78%), m.p. 216-218°.

Anal. Calcd. for $C_{11}H_9NO_5$: C, 56.2; H, 3.9; N, 6.0. Found: C, 56.4; H, 4.0; N, 6.0.

2-Carbomethoxy-5-methoxyindoxyl (**16**).

Phenyl hydrazine (8.5 ml.) was added dropwise to a dispersion of **15** (8.5 g.) in ethanol (85 ml.). When the exothermic reaction ceased, the mixture was heated for an additional 4 minutes, cooled, the ethanol evaporated and the residue triturated with methanol, filtered and dried (yield 74%), m.p. 136-140°.

Anal. Calcd. for $C_{11}H_{11}NO_4$: C, 59.7; H, 5.0; N, 6.3. Found: C, 59.9; H, 5.2; N, 6.3.

Ethyl 2-Carbomethoxy-5-methoxyindole-3-oxyacetate (**24a**).

A mixture of **16** (5.1 g.), ethyl chloroacetate (3.32 g.) and anhydrous potassium carbonate (1.9 g.) in ethanol (20 ml.) was

stirred at 70° for 2 hours. The solvent was evaporated, the residue partitioned between water and chloroform, the organic layer washed with a 10% potassium hydroxide solution, followed by water and dried. The product was crystallized from ether-petroleum ether (60-80°) (yield 43%), m.p. 80-83°; ir (nujol): 3340, 1710, 1300, 1060 cm^{-1}; nmr (deuteriochloroform): δ 9.9 (broad s, NH), 7.15-6.6 (m, aromatic), 4.65 (s, *O*-methylene), 3.95 (q, ethyl), 3.7 (s, methyl), 3.6 (s, methoxy), 0.98 (t, ethyl).

Anal. Calcd. for $C_{15}H_{17}NO_6$: C, 58.6; H, 5.6; N, 4.6. Found: C, 58.7; H, 5.8; N, 4.6.

5-Methoxy-2-carboxyindol-3-oxyacetic Acid (**25**).

A mixture of **24a** (2.5 g.), sodium hydroxide (1.5 g.), ethanol (12.5 ml.) and water (30 ml.) was refluxed for 90 minutes. The ethanol was evaporated and the aqueous solution was extracted with chloroform, acidified and the product filtered and crystallized from ethyl acetate-petroleum ether (60-80°) (yield 97%), m.p. 180-182°; ir (nujol): 3400, 1700; nmr (deuteriochloroform): δ 7.2-6.65 (m, aromatic), 4.7 (s, *O*-methylene), 3.7 (s, methoxy).

Anal. Calcd. for $C_{12}H_{11}NO_6$: C, 54.3; H, 4.2; N, 5.3. Found: C, 54.3; H, 4.3; N, 5.3.

Methyl 5-Methoxy-2-carboxyindole-3-oxyacetate (**26a**).

A solution of **25** (4.2 g.) in acetic anhydride was stirred at 80°, under nitrogen, for 3 hours. The mixture was cooled, methanol added and stirring continued overnight at room temperature. Ice water was added after the evaporation of the solvents and the mixture was stirred until the product solidified. The precipitate was dissolved in a sodium hydrogen carbonate solution (saturated, 100 ml.), the solution extracted twice with chloroform, acidified and extracted with dichloromethane. The organic layer was dried over magnesium sulphate and concentrated to a small volume from which the product crystallized (yield 35%), m.p. 158-160°; nmr (deuteriochloroform): δ 7.4-6.8 (m, aromatic), 4.8 (s, *O*-methylene), 3.8 (s, methoxy), 3.7 (s, methyl).

Methyl 3-Carboxyindole-3-oxyacetate (**26b**).

Prepared in the same manner as the 5-methoxy derivative **26a** (yield 59%), m.p. 138-142°; nmr (deuteriochloroform): δ 7.5-6.8 (m, aromatic), 4.9 (s, *O*-methylene), 3.76 (s, methyl).

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