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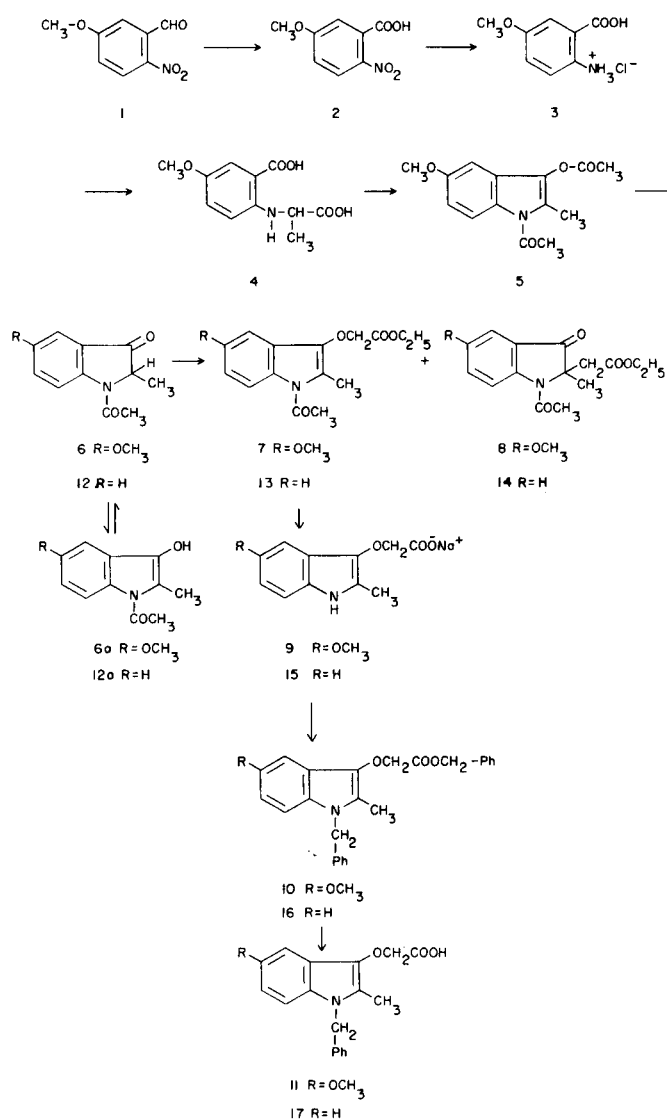
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The synthesis of 1-benzyl-2-methyl-5-methoxyindole-3-oxyacetic acid (**11**) and of 1-benzyl-2-methylindole-3-oxyacetic acid (**17**) was undertaken in the course of a study aimed at the preparation of potential anti-inflammatory agents.

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The synthesis is outlined in the accompanying scheme. Several methods for the preparation of 5-methoxy and 5-hydroxyanthranilic acid are known (1a-d). However, none of these gave satisfactory results when yield and quality of the product were considered. We succeeded in obtaining a good yield of pure 5-methoxyanthranilic acid, isolated as the hydrochloride (**3**), by oxidation of 2-nitro-5-methoxybenzaldehyde (**1**) (**2**) followed by catalytic reduction of the nitroacid (**2**) in the presence of one equivalent of hydrochloric acid. Attempts to condense **3** with 2-bromopropionic acid to give **4** failed, as only tarry products were obtained. However, a high yield of *N*-(2-carboxy-4-methoxyphenyl)-*D,L*-alanine (**4**) was obtained by reacting **3** with methyl 2-bromopropionate and saponifying the monoester so formed.

Cyclization of *N*-(2-carboxyphenyl)amino acids seems to be the method of choice for the preparation of *N,O*-diacyl derivatives (to cite only a few examples see (3a-e)). Accordingly, **4** was heated in an acetic anhydride-sodium acetate mixture to afford 1-acetyl-2-methyl-3-acetoxy-5-methoxyindole (**5**). Some contamination with 1-acetyl-2-methyl-5-methoxy-indoxyl (**6**) could be detected by thin layer chromatography. The diacetyl derivative **5** was converted to **6** by selective hydrolysis using aqueous sodium sulfite. The product was found to consist only of the keto form **6** as no trace of the enol form **6a** could be detected by spectral analysis. This fact is probably the cause of the difficulties encountered during the efforts to react **6** with ethyl bromoacetate to form **7**, under various alkylation conditions. It was found that no *O*-alkylation occurred unless enough time was allowed before the addition of the alkylating agent. Development of a dark reddish coloration indicated the formation of the enol salt. Three to four hours were sufficient to enolize **6** in dimethyl sulphoxide as compared to more than ten hours needed in hexamethylphosphoric triamide. An approximately 1:2 mixture of **7** and **8**, respectively was obtained. The isomers were separated by column chromatography and identified by nmr spectra. The spectra were essentially identical except for the chemical shifts of two groups: The 2-methyl in **7** resonates at δ 2.60 as compared to δ 1.56 in **8** and the methylene in the $-O-CH_2-COO-$ group appears as a singlet at δ 4.68 for **7** whereas for **8**, the same methylene exhibits



an AB pattern centered at δ 3.63, resulting from the restricted rotation of the group at this crowded center. Alkaline hydrolysis of **7** produced 2-methyl-5-methoxyindole-3-oxyacetic acid which could be isolated as the sodium salt **9**, since the free acid was unstable. The salt was benzylated by the method of Rubottom and Chabala (**4**) to yield benzyl 1-benzyl-2-methyl-5-methoxyindole-3-

oxyacetate (**10**), which upon saponification afforded the final product **11**.

1-Benzyl-2-methylindole-3-oxyacetic acid (**17**) was synthesized by a similar route, starting with 1-acetyl-2-methylindoxyl (**12**) (**3b**). A higher *O*-versus *C*-alkylation ratio was observed in this case. However, no efforts have been made to change this ratio in either case. Identification of **13** and **14** was also based on the nmr spectra which showed characteristics similar to those of **7** and **8**, respectively.

EXPERIMENTAL

2-Nitro-5-methoxybenzoic Acid (**2**).

A warm solution of potassium permanganate (44.4 g., 0.28 mole) in water (700 ml.) was added in one portion to a suspension of **1** (**2**) (51 g., 0.28 mole) in aqueous potassium hydroxide (1 *M*, 700 ml.) at 60°. The mixture was stirred at the same temperature for 90 minutes, cooled in an ice bath and acidified to pH 1 with 10*N* sulfuric acid. Stirring was continued while hydrogen peroxide (30%) was cautiously added until all the manganese dioxide was reduced. The product was extracted with ether, the ethereal solution washed with water, dried, evaporated and the residue crystallized from ethanol-water to give 51.5 g. (92.7%) of **2** m.p. 131-132° (lit. (**2**) m.p. 132-133°).

5-Methoxyanthranilic Acid Hydrochloride (**3**).

A solution of **2** (49.3 g., 0.25 mole) in methanol (300 ml.) containing hydrochloric acid (32% aqueous, 25 ml.) and 5% palladium on charcoal (0.5 g.) was shaken under a hydrogen atmosphere at 40-70 psi until the gas uptake ceased (1-3 hours). The resulting solution was filtered while still warm, some ether added to the filtrate and the mixture allowed to stand overnight for crystallization. The yield was 41.4 g. (75%), m.p. 210° (lit. (**3c**) m.p. 210°; nmr (DMSO-*d*₆): δ 3.83 (s, methoxy), 7.1-7.8 (m, aromatic), 7.8-8.7 (broad s, ammonium and carboxyl).

Anal. Calcd. for C₈H₁₀ClNO₃: C, 47.14; H, 4.94; Cl, 17.41; N, 6.88. Found: C, 47.31; H, 4.86; Cl, 17.05; N, 6.67.

N-(2-Carboxy-4-methoxyphenyl)-D,L-alanine (**4**).

To a solution of **3** (30.5 g., 0.15 mole) in water (90 ml.) containing sodium hydroxide (12 g., 0.3 mole), was added anhydrous carbonate (15.9 g., 0.15 mole) and a solution of methyl 2-bromopropionate (25 g., 0.15 mole) in methanol (90 ml.). The mixture was stirred overnight at 80°. A solution of sodium hydroxide (12 g., 0.3 mole) in water (50 ml.) was added and the mixture refluxed for 90 minutes. Most of the methanol was evaporated. The resulting aqueous solution was cooled, acidified to pH 3 with concentrated hydrochloric acid and extracted with ethyl acetate (3 × 150 ml.). The combined extracts were washed with water, dried and evaporated to yield 33.4 g. (93%) of **4**. The product was pure enough to be used in the next step without further purification. A sample was recrystallized from ethyl acetate-petroleum ether (60-80°), m.p. 174-177°; nmr (acetone-*d*₆): δ 1.50 (d, methyl), 3.75 (s, methoxy), 4.25 (q, H-2), 6.6-7.5 (m, aromatic), 9.2 (broad s, N-H and carboxyls).

Anal. Calcd. for C₁₁H₁₃NO₅: C, 55.22; H, 5.47; N, 5.85. Found: C, 55.27; H, 5.30; N, 5.58.

1-Acetyl-2-methyl-3-acetoxy-5-methoxyindole (**5**).

A mixture of **4** (31.7 g., 0.133 mole) and sodium acetate (40 g.) in acetic anhydride (170 ml.) was refluxed for one hour. The solvent was evaporated under reduced pressure and the residue partitioned between water and chloroform. The organic layer was successively washed with water, bicarbonate solution, water, dried and evaporated. The residue was crystallized from methanol to yield 7.9 to 11.0 g. (25-35%) of **5**. The yield could be increased by 2-4% by purifying the residue obtained upon evaporation of the mother liquor by chromatography on an alumina column eluted with dichloromethane-petroleum ether (60-80°) (a 1:1 mixture). Thin layer chromatography revealed that the product was con-

taminated by small amounts of **6**. Recrystallization from methanol yielded the pure compound, m.p. 116-118°; nmr (deuteriochloroform): δ 2.35 (s, acetyl), 2.40 (s, acetyl), 2.60 (s, methyl), 3.78 (s, methoxy), 6.75 (m, aromatic), 7.85 (d, aromatic); ir (nujol): 1735, 1670 cm⁻¹.

Anal. Calcd. for C₁₄H₁₅NO₄: C, 64.35; H, 5.78; N, 5.36. Found: C, 64.27; H, 5.88; N, 5.41.

1-Acetyl-2-methyl-5-methoxyindoxyl (**6**).

A hot solution of sodium sulfite (4.2 g. 33.3 mmoles) in water (140 ml.) was added to a boiling solution of **5** (7.6 g., 29.1 mmoles) in ethanol (70 ml.). Heating was continued for ten minutes, the mixture cooled, most of the ethanol evaporated and the resulting aqueous solution extracted with chloroform (3 × 50 ml.). The combined organic extracts were washed with water, dried and evaporated. The syrup was crystallized from ethanol to afford 5.1 g. (80%) of **6**, m.p. 125-126°; nmr (deuteriochloroform): δ 1.57 (d, methyl), 2.35 (s, acetyl), 3.81 (s, methoxy), 4.26 (q, H-2), 7.25-8.40 (m, aromatic); ir (nujol): 1690, 1645 cm⁻¹.

Anal. Calcd. for C₁₃H₁₅NO₃: C, 65.74; H, 5.97; N, 6.38. Found: C, 65.76; H, 5.99; N, 6.51.

Ethyl 1-Acetyl-2-methyl-5-methoxyindole-3-oxyacetate (**7**) and Ethyl 1-Acetyl-2-methyl-5-methoxy-3-indolinone-2-acetate (**8**).

A mixture of **6** (3.17 g., 14.5 mmoles), triethylamine hydrochloride (3.3 g.) and finely ground anhydrous potassium carbonate (< 60 μ particles, 12 g.) in dry dimethyl sulphoxide (87 ml.) was stirred under a nitrogen atmosphere at 30-35° for 3.5 hours, by which time a red coloration had developed. Ethyl bromoacetate (3.64 g., 21.8 mmoles) was added in one portion and stirring was continued at the same temperature overnight. The solvent was evaporated under reduced pressure and the residue partitioned between water and ethyl acetate. The aqueous layer was extracted once again and the combined organic layers were washed and dried. The residue obtained after evaporation of the solvent was chromatographed on an alumina column and eluted with ether-petroleum ether (60-80°) (2:3). The *O*-alkylated product (**7**) was eluted first. Evaporation of the appropriate fractions yielded 0.75 g. (17%) of **7** as a syrup; nmr (deuteriochloroform): δ 1.32 (t, ethyl), 2.60 (s, 2-methyl), 2.64 (s, acetyl), 3.91 (s, methoxy), 4.30 (q, ethyl), 4.68 (s, *O*-methylene), 7.0 (m, aromatic), 8.1 (d, aromatic). The *C*-alkylated product (**8**) was obtained as crystals from ether-petroleum ether (60-80°) (1.28 g., 29%), m.p. 75-78°; nmr (deuteriochloroform): δ 0.99 (t, ethyl), 1.56 (s, 2-methyl), 2.52 (s, acetyl), 3.63 (AB q, Δν 32 Hz, J = 14 Hz, nonequivalent protons of the 2-methylene group), 3.88 (s, methoxy), 3.92 (q, ethyl), 7.00-8.00 (m, aromatic).

Anal. Calcd. for C₁₆H₁₉NO₅: C, 62.93; H, 6.27; N, 4.55. Found: C, 62.85; H, 6.35; N, 4.73.

Benzyl 1-Benzyl-2-methyl-5-methoxyindole-3-oxyacetate (**10**).

To a stirred solution of **7** (1 g., 3.3 mmoles) in ethanol (15 ml.) under nitrogen was added a solution of sodium hydroxide (0.26 g., 6.6 mmoles) in water (3 ml.). The mixture was stirred at room temperature for 4 hours, evaporated to dryness and vacuum dried over phosphorus pentoxide. The dry residue was dissolved in dimethyl sulphoxide (10 ml.) and sodium hydride (0.17 g. of a 50% dispersion in mineral oil) added under nitrogen. The dark mixture was stirred for 5 hours. Benzyl chloride (1.7 g., 13.2 mmoles) was added in one portion and stirring was continued overnight. The resulting mixture was evaporated to dryness, the residue dissolved in benzene, washed twice with water and dried. The solvent was evaporated and the product crystallized from ether-petroleum ether (60-80°) to yield 1.2 g. (88.1%), m.p. 81-82°; nmr (deuteriochloroform): δ 2.35 (s, 2-methyl), 3.52 (s, methoxy), 4.75 (s, *O*-methylene), 5.20 and 5.24 (2s, two benzylic methylenes), 6.7-7.4 (m, aromatic).

Anal. Calcd. for C₂₆H₂₅NO₄: N, 3.37. Found: N, 3.27.

1-Benzyl-2-methyl-5-methoxyindole-3-oxyacetic acid (**11**).

A solution of **10** (0.52 g., 1.25 mmoles) in 50% ethanol (25 ml.) containing sodium hydroxide (0.7 g., 17.5 mmoles) was refluxed under nitrogen for 1 hour. Most of the ethanol was evaporated. The sodium salt of **11**, which separated as a white solid was dissolved by the addition of some

water and the acid was precipitated by acidification with dilute hydrochloric acid. The product was recrystallized from ethyl acetate-petroleum ether (60-80°) to yield 0.35 g. (88%) of **11**, m.p. 124-125°; nmr (deuteriochloroform): δ 2.36 (s, 2-methyl), 3.90 (s, methoxy), 4.77 (s, *O*-methylene), 5.25 (s, benzylic methylene), 6.8-7.4 (m, aromatic).

Anal. Calcd. for $C_{13}H_{19}NO_4$: C, 70.13; H, 5.88; N, 4.30. Found: C, 69.97; H, 6.09; N, 4.03.

Ethyl 1-Acetyl-2-methylindole-3-oxyacetate (**13**) and Ethyl 1-Acetyl-2-methyl-3-indolinone-2-acetate (**14**).

A mixture of **12** (3b) (13.2 g., 70 mmoles), triethylamine hydrochloride (15.8 g.) and finely ground potassium carbonate (< 60 μ particles, 57.9 g.) was reacted with ethyl bromoacetate (17.55 g., 105 mmoles) as described for the preparation of **7** and **8**. Yields of **13** ranged between 5-12 g. (26-62%). The product was obtained as a syrup; nmr (deuteriochloroform): δ 1.28 (t, ethyl), 2.58 (s, 2-methyl), 2.65 (s, acetyl), 4.25 (q, ethyl), 4.65 (s, *O*-methylene), 7.0-8.4 (m, aromatic). The *C*-alkyl product (**14**) was crystallized from ether-petroleum ether (60-80°) to give 4 to 10 g. (20.8-50.4%) of crystals, m.p. 79-80°; nmr (deuteriochloroform): δ 0.88 (t, ethyl), 1.35 (s, 2-methyl), 2.53 (s, acetyl), 3.29 (AB q, $\Delta\nu = 35$ Hz, $J = 16$ Hz, unequivalent protons of the 2-methylene group), 3.85 (q, ethyl), 7.0-8.0 (m, aromatic).

Anal. Calcd. for $C_{15}H_{17}NO_4$: C, 65.44; H, 6.20; N, 5.10. Found: C, 65.50; H, 6.10; N, 5.0.

Sodium 2-Methyl-indole-3-oxyacetate (**15**).

A solution of sodium hydroxide (3.5 g., 88.5 mmoles) in water (12 ml.) was added to a solution of **13** (12.2 g., 44.3 mmoles) in ethanol (75 ml.). The mixture was stirred at 25° for one hour. The solvents were evaporated, the residue dissolved in absolute ethanol (25 ml.) and the sodium salt (**15**) precipitated by the slow addition of acetone. The yield was 8.7 g. (86.5%).

Benzyl 1-Benzyl-2-methylindole-3-oxyacetate (**16**).

The sodium salt **15** (8.5 g. 37.5 mmoles) was reacted with sodium hydride (1.8 g. of a 50% dispersion in mineral oil) in dimethyl sulfoxide

(64 ml.) under nitrogen at 30-35° until a reddish coloration had developed (about 4 hours). Benzyl chloride (9.37 g., 74 mmoles) was added in one portion and the mixture stirred overnight at the same temperature. The work up was as described for **10**. The product was crystallized from ethyl acetate-petroleum ether (60-80°) to give 4.0 g. (19.5%) of **16**, m.p. 96-98°; nmr (deuteriochloroform): δ 2.26 (s, 2-methyl), 4.63 (s, *O*-methylene), 5.1 (s, four benzylic protons), 6.5-7.5 (m, aromatic).

Anal. Calcd. for $C_{25}H_{23}NO_3$: C, 77.90; H, 6.01; N, 3.60. Found: C, 78.20; H, 5.90; N, 3.70.

1-Benzyl-2-methylindole-3-oxyacetic Acid (**17**).

The dibenzyl derivative **16** (3.0 g., 7.7 mmoles) was saponified as described for the preparation of **11**. The product was recrystallized from ether-petroleum ether to yield 2.0 g. (87.0%) of the acid (**17**), m.p. 123-124°; nmr (deuteriochloroform): δ 2.25 (s, 2-methyl), 4.60 (s, *O*-methylene), 5.22 (s, benzylic methylene), 6.8-7.8 (m, aromatic).

Anal. Calcd. for $C_{18}H_{17}NO_3$: C, 73.20; H, 5.80; N, 4.70. Found: C, 73.10; H, 5.70; N, 4.60.

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