Carboxylation and Acylation of 4,7-Dimethoxyindoles and a Study of the Corresponding Dealkylated Derivatives

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Treatment of 4,7-dimethoxyindoles **1** and **9** with ethylmagnesium bromide and ethyl chloroformate in refluxing dry ether gives the corresponding indole-1-carboxylic acid ethyl esters **3** and **10** as major products, together, with minor amounts of indole-3-carboxylic acid ethyl esters **2** and **11**. Similar treatment of 4,7-dimethoxyindole (**1**) with ethylmagnesium bromide and chloroacetyl chloride affords the related 3-chloroacetyl derivative **13**. All of the new 4,7-dimethoxyindole compounds were dealkylated with anhydrous aluminium chloride in refluxing dry benzene. Transformation of these demethylated indoles into other interesting derivatives, in view of possible antimicrobial activity is also reported.

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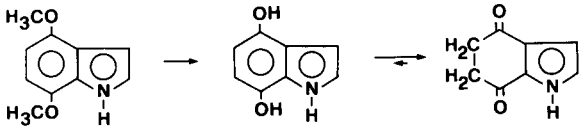
Introduction.

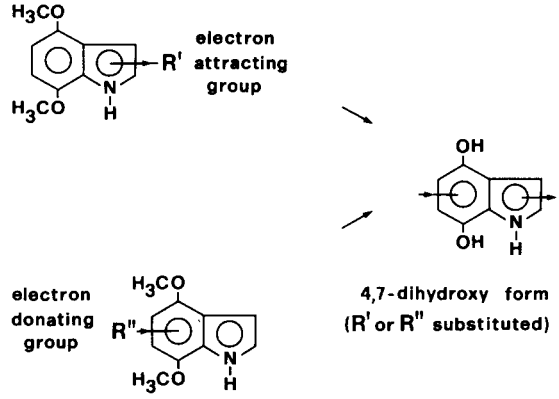
The point of departure of this study was our previous observation that 4,7-dimethoxyindole, subjected to demethylation in refluxing benzene solution with anhydrous aluminium chloride, instead of yielding the expected 4,7-dihydroxyindole, produced the partly dearomatizated diketo isomer 4,7-dioxo-4,5,6,7-tetrahydroindole (1,2).



On the other hand, demethylation worked out with the usual inorganic acids, afforded a complex mixture of black linear polymers, the structure and formation mechanism of which has been widely studied (3,4). More recently, we found that a phenol-keto equilibrium appeared to exist between 4,7-dihydroxy- and 4,7-dioxo-4,5,6,7-tetrahydroindole (5).

Sometime ago we reported that the presence of electron-withdrawing groups at C-2 or C-3 positions of 4,7-dimethoxyindole led to the obtaining of the demethylated 4,7-dihydroxy species in a remarkable yield, in consequence of demethylation carried out with the usual Lewis acid in benzene (6,7). It was possible, therefore, to suggest a reasonable explanation for the behaviour of the demethylation products and for the role of the substituents in preventing an otherwise easy isomerization towards the diketo forms (6).

We have recently prepared some 4,7-dimethoxyindole derivatives bearing various electron-donating groups at C-5 and C-6 positions, which were demethylated under the experimental conditions previously indicated. In this case too, the presence of such substituents made possible the isolation of the corresponding stable dihydroxy structures (8).



All of the previous studies were aimed at determining which electronic characteristics of the substituents in the various possible positions of the indole nucleus were important for chemical stability of the dihydroxy species, with the aim of testing the probable chemotherapeutic properties exhibited by these 4,7-dihydroxyindoles and related indole-4,7-diones.

Therefore, in continuing our research program, the present paper reports the preparation, identification and study of the chemical properties of new carboxylated and acylated 4,7-dimethoxyindoles and corresponding demethylation products, as well as their transformation into significative derivatives as potential antimicrobial agents.

The experimental data with regard to the microbiological tests will be published elsewhere (9).

Chemistry.

As shown in Scheme 1, the reaction of 4,7-dimethoxyindole (**1**) with magnesium ethyl bromide in dry ether gave 4,7-dimethoxyindolylmagnesium bromide which, by treatment at reflux with ethyl chloroformate, afforded a mixture of indole carboxylated esters **2** and **3** (17.9% and

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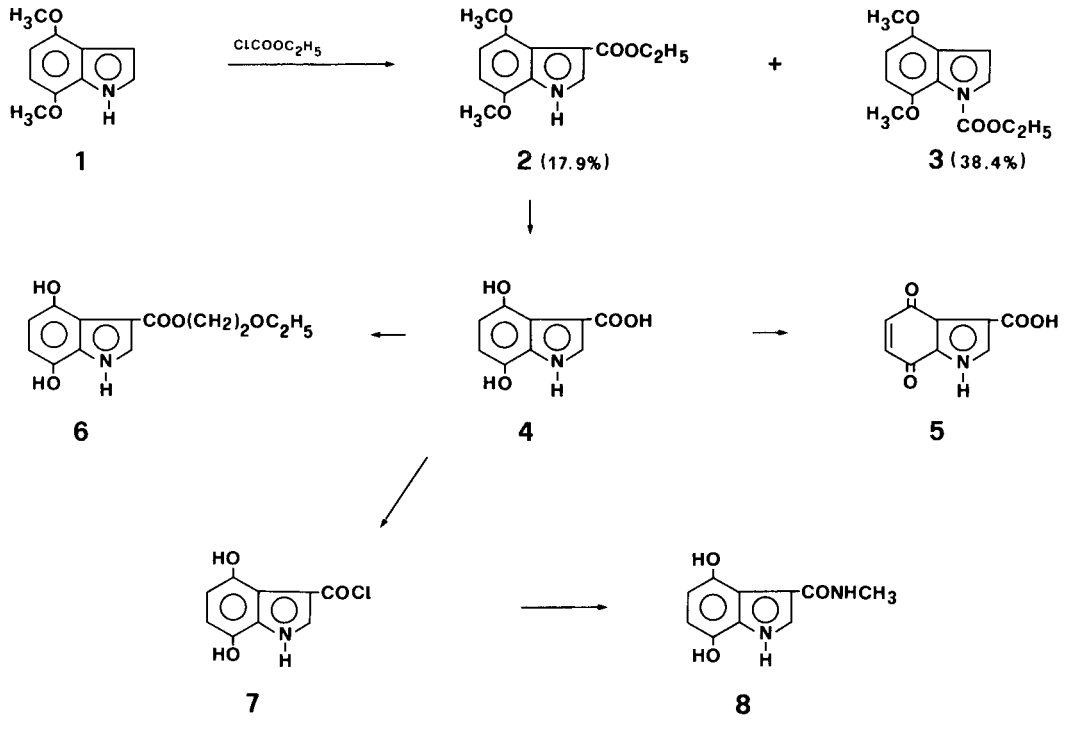
Scheme 1



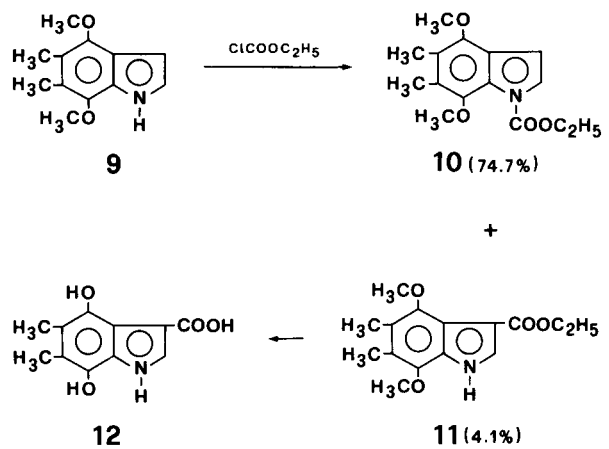
38.4% yield, respectively) which were easily distinguished by nmr and ir spectroscopy. By modifying both the reaction time and the ratio of alkyl halide or alkyl chloroformate in relation to the amount of the starting 4,7-dimethoxyindole, no significative modifications in the proportion of the two at C-3 and N-1 carboylated species were observed.

Dealkylation of 4,7-dimethoxyindole-3-carboxylic acid ethyl ester (**2**) by reflux in dry benzene solution with anhydrous aluminium chloride followed by extraction with ether and concentration in a nitrogen stream, furnished in good yield 4,7-dihydroxy-3-carboxylic acid (**4**) which, by treatment in acetone with a solution of potassium chromate in dilute sulfuric acid, was easily transformed into the corresponding quinonoid derivative (**5**).

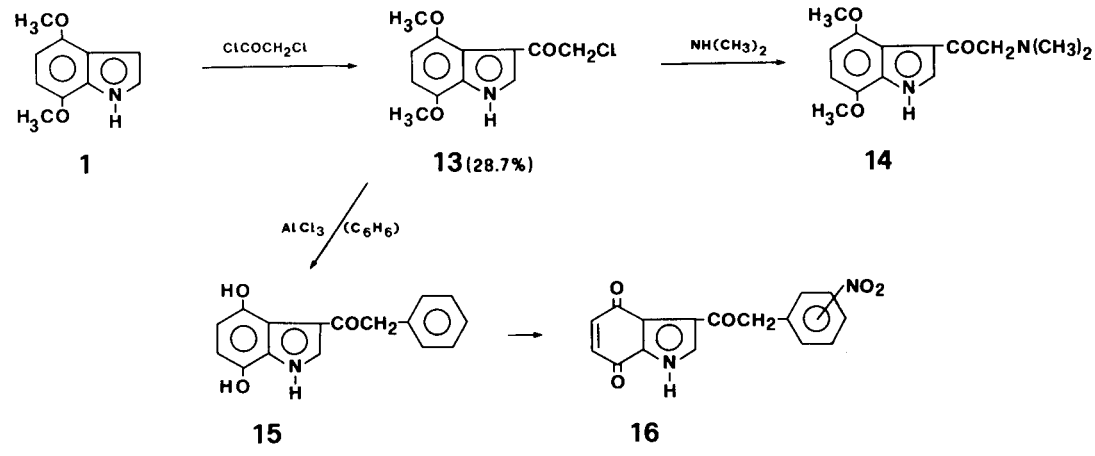
Esterification of indolyl acid **4** with large excess of anhydrous 2-ethoxyethanol under an atmosphere of dry hydrogen chloride gas, gave the corresponding crystalline ethoxyethyl ester **6**. For the preparation of 4,7-dihydroxyindole-3-carboxylic acid methylamide (**8**), acid **4** was previously converted into the corresponding acyl chloride with the classical attack at an acyl carbon performed by thionyl chloride. The reaction of this acyl halide with the excess of methylamine in dry benzene yielded the desired amide **8**. Attempts to transform the same acid **4** into other amides were unsuccessful, probably because of polymerization.

As indicated in the above preparation of esters **2** and **3** at the beginning of the first experimental paragraph, in order to carboxylate 4,7-dimethoxy-5,6-dimethylindole (**9**) (see Scheme 2), the corresponding indolylmagensium bromide in dry ether was treated with ethyl chloroformate at reflux, giving a mixture of 1- and 3-carboxylic acid ethyl esters (compounds **10** and **11**, respectively) in a 79% total yield, much richer in the N-1 derivative. A careful *in vacuo* distillation produced the resolution of the mixture into the two isomers, the structure of which was confirmed by ir and nmr spectroscopy. The same reaction of carboxylation, carried out at lower temperatures, gave ester **11** in a still more moderate yield.

Scheme 2



Scheme 3



In this case also, dealkylation of compound **11** was achieved by refluxing it for several hours with anhydrous aluminium chloride in benzene solution. An attempt to effect a dealkylation on ester **10** under the same reaction conditions led to a complex mixture of dark products.

As indicated in Scheme 3, 4,7-dimethoxyindole (**1**), transformed extemporaneously into the corresponding indolyl anion utilizing ethylmagnesium bromide in ether, was acylated by means of chloroacetyl chloride at reflux temperature to give 3-chloroacetyl-4,7-dimethoxyindole (**13**). Attempts to optimize the modest yield (29%) under other carefully defined conditions were unsuccessful.

The reaction of chloroacyl compound **13** with excess of dimethylamine in a warmed sealed tube furnished the corresponding 4,7-dimethoxy-3-(dimethylaminoacetyl)-indole (**14**), which did not undergo convenient demethylation when heated in appropriate dry organic solvents in the presence of the more common dealkylating agents (Lewis acids, pyridinium and magnesium chlorides, *etc.*).

By performing dealkylation of the 3-acyl derivative **13** in refluxing anhydrous benzene solution with aluminium chloride for several hours, besides the expected demethylation, a logical Friedel-Crafts alkylation on the benzene took place, in which the Lewis acid also acted as catalyst. This reaction therefore yielded the interesting new indole derivative **15** [3-(4,7-dihydroxy)indolyl benzyl ketone], identified by its spectral properties and analytical data. Otherwise, by carrying out demethylation on **13** under the same conditions just described, but shortening the reaction times, an unpurifiable mixture of partly demethylated and dechlorinated products was obtained.

It is of interest to point out that similar reaction trials on 3-chloroacetyl-4,7-dimethoxyindole (**13**) worked out with aluminium chloride as demethylating and catalyzing agent in the presence of other aromatic compounds employed as reaction solvents (toluene, methoxybenzene, *etc.*) were of no avail.

Treatment of ketone **15** with cold 65% nitric acid under mild conditions provided a concomitant mononitration on the benzyl group and an oxidation to the quinonoid structure on the indolyl grouping, to give compound **16** in a satisfactory yield.

Repeated attempts to reduce this compound **16**, to the corresponding aminodihdyroxy derivative, although varying the reductive procedures, proved unsuccessful.

EXPERIMENTAL

Melting points were measured with a Büchi-Tottoli SPM-20 apparatus in open capillaries, and are uncorrected. Infrared spectra were recorded with a Perkin-Elmer 437 spectrometer as potassium bromide pressed discs or between sodium chloride plates, calibrated against a polystyrene film; the absorptions are given in cm^{-1}. A Hitachi-Perkin Elmer R-24A or Varian FT-80A spectrometer was used to second the ^1H-nmr spectra using tetramethylsilane as an internal standard; chemical shifts are given in parts per million (δ). Integrals correspond satisfactorily to the chemical formula. Splitting patterns are designated as s, singlet; d, doublet; t, triplet; q, quartet; m, multiplet; addition of br indicates a broadened pattern. In the case of multiplets, chemical shifts quoted were measured from the approximate center.

Elemental analyses were performed by the Microanalytical Laboratory of the Institute of Pharmaceutical Chemistry of the University of Padua.

4,7-Dimethoxyindole (**1**) and its 5,6-dimethyl analogue (**9**) were prepared as previously described (10,8).

Carboxylation of 4,7-Dimethoxyindole.

Into a 250 ml. flask equipped with a condenser with a calcium chloride tube at the top, a magnetic stirring bar and a dropping funnel, 3.6 g. of ethyl bromide (33 mmoles) was added slowly to 0.6. g. of magnesium turnings (25 mmoles) in dry ether (30 ml.). When all the magnesium had reacted, a solution of 3.5 g. of 4,7-dimethoxyindole (**1**) (20 mmoles) in 100 ml. of anhydrous ether was then added slowly and the resulting green-yellow mixture heated for 15 minutes under reflux. To the gummy 4,7-dimethoxyindolylmagnesium bromide a mixture of 2.39 ml. (2.73 g., 25 mmoles) of ethyl chloroformate in 30 ml. of dry ether was added drop by drop; the reaction product was heated for 5 hours under reflux before being poured into ice-water.

The organic layer was separated, and the aqueous layer extracted with ether (3 × 600 ml.). The combined extracts were washed with water,

dried over anhydrous sodium sulfate and evaporated to dryness in a rotary evaporator. The crude residue, was rinsed with boiling petroleum ether 30-60° (3 × 30 ml.) and the resulting crystalline mass (2.8 g.) was purified by sublimation *in vacuo*.

a) 4,7-Dimethoxyindole-3-carboxylic Acid Ethyl Ester (**2**).

Sublimation at 115° (0.01 mm) of 2.8 g. of solid product yielded a crystalline sublimate (0.88 g., 17.9% yield) which was suitable for use in the subsequent reactions. An analytical sample was obtained by crystallization from benzene-petroleum ether (3:1 v/v), m.p. 153-154°; ir (potassium bromide): 3308 (NH), 2983-2829 (CH_3 and CH_2), 1688 (C=O) cm^{-1}; nmr (deuterioacetone): δ 1.33 (3H, t, CH_3 of ethyl), 3.81-3.86 (6H, 2s, 2 × OCH_3), 4.13-4.36 (2H, q, CH_2 of ethyl), 6.54-6.58 (2H, 2s, HC_5 and HC_6), 7.81 (1H, s, HC_2).

Anal. Calcd. for $C_{13}H_{15}NO_4$: C, 62.64; H, 6.07; N, 5.62. Found: C, 62.60; H, 6.00; N, 5.60.

b) 4,7-Dimethoxyindole-1-carboxylic Acid Ethyl Ester (**3**).

Removal of the petroleum ether used for rinsing the crude carboxylation products (see above), gave a brown oil which was distilled *in vacuo*. The oily fraction (1.89 g., 38.4% yield) isolated at 85° (0.01 mm) was shown by ir and nmr to be the title compound. By continuing the distillation further at 105° it was possible to recover 34% of the starting material **2**; ir (sodium chloride plates): 3116-2827 (CH_3 and CH_2), 1752-1724 (C=O) cm^{-1}; nmr (deuterioacetone): δ 1.39 (3H, t, CH_3 of ethyl), 3.85 (6H, s, 2 × OCH_3), 4.29-4.54 (2H, q, CH_2 of ethyl), 6.63-7.48 (2H, 2d, HC_3 and HC_2), 6.71-6.78 (2H, 2s, HC_5 and HC_6).

Anal. Calcd. for $C_{13}H_{13}NO_4$: C, 62.64; H, 6.07; N, 5.62. Found: C, 62.54; H, 6.18; N, 5.92.

4,7-Dihydroxyindole-3-carboxylic Acid (**4**).

To a solution of 0.8 g. of ethyl ester **2** in 60 ml. of dry benzene 4 g. of powdered anhydrous aluminium chloride was added and the mixture was refluxed in a water bath for 5 hours. After cooling, the solid mass was broken up and treated with ice-cold water (150 ml.). The organic phase was then separated and the aqueous layer extracted with ether (4 × 400 ml.). The combined ether extracts were washed with water, dried over sodium sulfate and stripped of solvent in a nitrogen stream to give 0.74 g. of yellowish-green solid, which dissolved in boiling ethyl acetate (90 ml.). Filtration and concentration to *ca.* 4 ml. yielded 0.31 g. of crystalline greyish product, m.p. 248-249°; ir (potassium bromide): broad absorption from 3352 to 2888 (NH and OH), 1638 (C=O) cm^{-1}; nmr (DMSO-d_6): δ 6.24-6.50 (2H, 2d, HC_5 and HC_6), 7.83 (1H, d, HC_2), 9.17-10.51 (2H, 2s br, 2 × OH), 11.79 (1H, s, COOH).

Anal. Calcd. for $C_9H_7NO_4$: C, 55.96; H, 3.65; N, 7.25. Found: C, 55.69; H, 3.71; N, 7.09.

4,7-Dioxoindole-3-carboxylic Acid (**5**).

A 10% aqueous solution of potassium chromate (2.8 ml.) was added dropwise with stirring to a solution of 0.27 g. of acid **4** dissolved in 30 ml. of acetone in the presence of 10 ml. of 10% sulfuric acid. After the mixture had been stirred at 0° for 30 minutes, the brown solution was allowed to warm at 20° for 1 hour. The reaction mixture was poured into 15 ml. of water and extracted with 500 ml. of chloroform. The chloroform solution was dried (sodium sulfate) and concentrated *in vacuo* to give 0.22 g. of crude product. This solid was dissolved in 200 ml. of boiling toluene, and, after filtration, the solution was concentrated to 25 ml., leaving 0.097 g. of a crystalline red product, infusible up to 320°.

Anal. Calcd. for $C_9N_5NO_4$: C, 56.55; H, 2.64; N, 7.33. Found: C, 56.25; H, 2.75; N, 7.10.

4,7-Dihydroxyindole-3-carboxylic Acid Ethoxyethyl Ester (**6**).

Into a solution of 0.50 g. of acid **4** in 30 ml. (27.8 g.) of 2-ethoxyethanol, cooled in an ice-bath, a stream of dry hydrogen chloride gas was passed for 3 hours. The mixture was then refluxed (135°) and, after suitable cooling at room temperature, the solvents were removed by rotary evaporation, leaving a brown resinous residue which was dissolved in 100 ml. of boiling toluene. Concentration of this solution to *ca.* 10 ml. yielded 0.21 g. of powdered solid, m.p. 190°.

An analytical sample was obtained by vacuum sublimation at 150° (0.01 mm) to give colorless prisms, m.p. 196-197° dec.; ir (potassium bromide): broad band at 3290 (NH and OH), 3060-2863 (CH_3 and CH_2) and 1618 (C=O) cm^{-1}; nmr (deuterioacetone): δ 1.17 (3H, t, CH_3 of ethyl), 3.55 (2H, q, CH_2 of ethyl), 3.74 (2H, q, CH_2), 4.15 (2H, q, CH_2), 6.34-6.64 (2H, 2d, HC_3, HC_6), 7.90 (1H, d, HC_2).

Anal. Calcd. for $C_{13}H_{15}NO_5$: C, 58.86; H, 5.70; N, 5.28. Found: C, 59.18; H, 5.52; N, 5.53.

4,7-Dihydroxyindole-3-carbonyl Chloride (**7**).

To a suspension of 0.56 g. (2.9 mmoles) of acid **6** in 50 ml. of dry benzene in a 100 ml. round-bottomed flask fitted with a reflux water-condenser, 3 ml. (4.91 g., 41.3 mmoles) of thionyl chloride was added. The mixture was heated under reflux for 12 hours and then filtered. The yellowish filtrate was evaporated *in vacuo* to yield the crude carbonyl chloride as a brown crystalline solid (0.25 g.). Recrystallization from ethyl acetate/petroleum ether (1:1 v/v) gave brown needles, infusible up to 300°.

Anal. Calcd. for $C_9H_6ClNO_3$: C, 51.08; H, 2.86; Cl, 16.75. Found: C, 51.16; H, 2.85; Cl, 16.43.

4,7-Dihydroxyindole-3-carboxylic Acid Methylamide (**8**).

To a solution of 0.42 g. (2 mmoles) of compound **7** in 60 ml. of dry benzene in a flask immersed in a brine-bath equipped with a reflux condenser protected with a calcium chloride drying tube, a cold mixture of 2.8 ml. (1.95 g., 62.9 mmoles) of methylamine in 30 ml. of dry benzene was added dropwise with stirring. The addition was done at such a rate that the temperature remained below −5°. After 4 hours, the mixture was stirred under reflux for 1 hour and cooled to room temperature. The resulting solid was collected, washed repeatedly with boiling water and dried, giving 0.22 g. of a black solid, which was dissolved by adding 200 ml. of absolute ethanol and heating to boiling point. The hot solution was filtered and concentrated *in vacuo* yielding nearly black crystals, infusible up to 300°, the structure of which was confirmed by ir and elemental analysis; ir (potassium bromide): 3360-3228-3112 [NH (iminic and amidic), OH], 1698-1639 (C=O) cm^{-1}.

Anal. Calcd. for $C_{10}H_{10}N_2O_3 \cdot 2H_2O$: C, 49.58; H, 5.83; N, 11.57. Found: C, 49.87; H, 5.72; N, 11.54.

Carboxylation of 4,7-Dimethoxy-5,6-dimethylindole.

The 4,7-dimethoxy-5,6-dimethylindole (**9**) was carboxylated in a manner identical to that used for compound **1** described above. Treatment of 4,7-dimethoxy-5,6-dimethylindolylmagnesium bromide [prepared from the reaction of 2.04 g. (9.9 mmoles) of 4,7-dimethoxy-5,6-dimethylindole in anhydrous ether with 1.35 ml. (1.96 g., 18 mmoles) of ethyl bromide and 0.312 g. (12.8 mmoles) of magnesium turnings] with 1.5 ml. (1.71 g., 15.7 mmoles) of ethyl chloroformate in dry ether at reflux for 2 hours, yielded 2.51 g. of a residual violet oil after dilution with cold water, ethereal extraction and removal of organic solvents in a rotary evaporator.

a) 4,7-Dimethoxy-5,6-dimethylindole-1-carboxylic Acid Ethyl Ester (**10**).

The crude oily residue of carboxylation was fractionally distilled under vacuum. The fractions collected at 90-95° (bath temperature) (0.05 mm), all of the same title compound **10**, were combined (2.06 g., 74.7% yield). A sample of this material was redistilled to give an analytical specimen; ir (sodium chloride plates): 2978-2927-2826 (CH_3 and CH_2) 1728-1710 (C=O) cm^{-1}; nmr (deuterioacetone): δ 1.45 (3H, t, CH_3 of ethyl), 2.25-2.29 (6H, 2s, 2 × CH_3), 3.67-3.80 (6H, 2s, 2 × OCH_3), 4.31-4.54 (2H, q, CH_2 of ethyl), 6.61-7.49 (2H, 2d, HC_3 and HC_2).

Anal. Calcd. for $C_{15}H_{19}NO_4$: C, 64.96; H, 6.91; N, 5.05. Found: C, 65.10; H, 6.77; N, 5.01.

b) 4,7-Dimethoxy-5,6-dimethylindole-3-carboxylic Acid Ethyl Ester (**11**).

After complete distillation of the oily N-carboxylated isomer **10**, the

residual solid crude product was subjected to *in vacuo* sublimation at 130° (bath-temperature) and 0.05 mm giving white crystalline solid consisting of **12** (0.112 g., 4.1% yield) which, when recrystallized from toluene, afforded the pure title compound, m.p. 177-178°; ir (potassium bromide): 3263 (NH), 2972-2918-2822 (CH_3 and CH_2), 1652-1604 (C=O) cm^{-1}; nmr (deuterioacetone): δ 1.34 (3H, t, CH_3 of ethyl), 2.25 (6H, s, 2 × CH_3), 3.74-3.79 (6H, 2s, 2 × OCH_3), 4.19-4.37 (2H, q, CH_2 of ethyl), 7.87-7.91 (1H, d, HC_2).

Anal. Calcd. for $C_{15}H_{19}NO_4$: C, 64.96; H, 6.91; N, 5.05. Found: C, 64.82; H, 6.91; N, 4.91.

4,7-Dihydroxy-5,6-dimethylindole-3-carboxylic Acid (**12**).

A mixture of 0.21 g. of ester **11** and 1 g. of powdered aluminium chloride in 25 ml. of anhydrous benzene was heated for 6 hours in a water bath in a flask fitted with a reflux condenser eqipped with a calcium chloride tube. After the mixture had cooled, the solid residue was broken up and treated with crushed ice. Extraction with ether (3 × 200 ml.), washing with water, drying (sodium sulfate) and removal of the solvents under a nitrogen atmosphere afforded a greyish crude product (0.19 g.) which was crystallized from ethyl acetate, m.p. 189° dec.; ir (potassium bromide): 3318, 3168, 3120 (OH and NH); 2927 (CH_3); 1655 (C=O) cm^{-1}; nmr (DMSO-d_6): δ 1.99-2.08 (6H, 2s, 2 × CH_3), 7.31 (1H, s, br, OH), 7.70-7.74 (1H, d, HC_2), 11.18 (1H, s, br, NH), 11.57 (1H, s, COOH), 13.54 (1H, s, br, OH).

Anal. Calcd. for $C_{11}H_{11}NO_4$: C, 59.72; H, 5.01; N, 6.33. Found: C, 59.72; H, 5.07; N, 6.14.

3-Chloroacetyl-4,7-dimethoxyindole (**13**).

In a three-necked flask equipped with a magnetic stirrer and a reflux condenser protected from moisture, 2.48 ml. (3.6 g., 33 mmoles) of ethyl bromide in 15 ml. of ether was added from a dropping funnel to 0.6 g. (25 mmoles) of magnesium turnings in 20 ml. of dry ether. When all the metal had reacted, a solution of 3.54 g. (20 mmoles) of 4,7-dimethoxyindole (**1**) in 100 ml. of dry ether was added slowly and to the resulting suspension, heated for 20 minutes under reflux, 1.96 ml. (2.85 g., 25 mmoles) of chloracetyl chloride in 20 ml. of dry ether was introduced. The mixture was then heated for 3 hours at reflux with stirring, before being poured into ice-cold water (200 ml.). The organic layer was separated, and the aqueous layer extracted with ether (3 × 500 ml.). The combined extracts were washed with water, dried (sodium sulfate) and evaporated to dryness to give a grey-green crude residue, which was crystallized from 30 ml. of absolute ethanol to provide 1.44 g. (28.7% yield) of **13**, m.p. 151°. An analytical sample was prepared by recrystallization from ethanol, m.p. 154°; ir (potassium bromide): 3240 (NH), 3017-2836 (CH_3 and CH_2) and 1640 (C = O) cm^{-1}; nmr (deuterioacetone): δ 3.90 (6H, s, 2 × OCH_3), 4.93 (3H, s, CH_2), 6.64 (2H, s, HC_5 and HC_6), 7.93 (1H, d, HC_2), 11.03 (1H, s, br, NH).

Anal. Calcd. for $C_{12}H_{12}ClNO_3$: C, 56.81; H, 4.77; OCH_3, 24.47; Cl, 13.98. Found: C, 57.07; H, 4.56; OCH_3; 24.70; Cl, 13.92.

4,7-Dimethoxy-3-(dimethylaminoacetyl)indole (**14**).

To a cooled (0°) solution of 1 g. (3.9 mmoles) of 3-chloroacetyl-4,7-dimethoxyindole (**13**) in 80 ml. of absolute ethanol in a Carius tubing, 4 ml. (2.72 g., 61 mmoles) of cold methylamine was added, and the sealed tube, placed in heavy iron tubing, was heated for 5 hours at 100-110° After being allowed to stand for 30 minutes at room temperature, the Carius tube was cut and the reaction mixture evaporated *in vacuo* to give 1.2 g. of a crude residue, which was dissolved in 20 ml. of 2*N* hydrochloric acid. The filtered solution was adjusted to *ca.* *p*H 8 with an aqueous 20% solution of sodium bicarbonate and then extracted with ether. The combined extracts (3 × 400 ml.) were washed with water, dried over anhydrous sodium sulfate and concentrated in a rotary evaporator to yield 0.76 g. of a viscous brown residue, which was subjected to distillation *in vacuo* at 110-115° (0.01 mm). On standing at room temperature, the distilled oil solidified into a vitreous yellowish mass (m.p. 127-128°), consisting of a practically pure **14**; ir (potassium bromide): 3120-3104 (NH and NR_2), 2992-2766 (CH_3 and CH_2), 1666 (C=O) cm^{-1}; nmr (DMSO-d_6): δ 2.59-2.73 (4H, 2s, 2 × CH_3), 3.69 (2H, s, CH_2), 3.72 (6H, s, 2 × OCH_3), 6.46 (2H, s, HC_5 and HC_6), 7.63 (1H, s, HC_2).

Anal. Calcd. for $C_{14}H_{18}N_2O_3$: C, 64.10; H, 6.92; N, 10.68. Found: C, 63.82; H, 6.86; N, 10.44.

3-(4,7-Dihydroxy)indolyl Benzyl Ketone (**15**).

The procedure described above for dealkylation of various 4,7-dimethoxyindole derivatives was used to transform the 3-chloroacetyl-4,7-dimethoxyindole (**13**).

Freshly powdered anhydrous aluminium chloride (7 g.) and 0.7 g. of **13** were placed in a reaction vessel, protected from moisture and fitted with a condenser. Dry benzene (70 ml.) was added and the mixture heated for 15 hours in a boiling water bath. The suspension was allowed to come to room temperature, then 150 g. of minced ice was added and the mixture was extracted repeatedly with ether (3 × 400 ml.). The combined extracts were dried over anhydrous sodium sulfate, washed with water, filtered and evaporated to dryness by passing a slow stream of nitrogen, affording 0.68 g. of a yellow crusty residue, which was dissolved thoroughly with 30 ml. of acetone. Addition of an equal amount of petroleum ether to the solution reduced in a volume of 10 ml. by evaporation *in vacuo*, afforded 0.413 g. of fine gold-yellow flakes, m.p. 272° dec.; ir (potassium bromide): 3320-3100 (broad band; OH and NH), 2720-2640 (CH_2), 1640 (C=O) cm^{-1}; nmr (DMSO-d_6): δ 4.23 (2H, s, CH_2), 6.26-6.52 (2H, 2d, HC_5 and HC_6), 7.41 (5H, s, aromatic protons of benzyl), 8.50 (1H, d, HC_2), 9.21 (1H, s, OHl), 10.27 (1H, s, OH).

Anal. Calcd. for $C_{16}H_{13}NO_3$: C, 71.90; H, 4.90; N, 5.24; O, 17.96. Found: C, 71.70; H, 4.96; N, 5.35; O, 18.22.

3-(4,7-Dioxo)indolyl Nitrobenzyl Ketone (**16**).

Nitration and concomitant oxidation was carried out with 65% nitric acid at 0° on slightly stirred aliquots of compound **15**. Each reaction flask containing 0.6 g. of 3-(4,7-dihydroxy)indolyl benzyl ketone was cooled in an ice water bath while 1.5 ml. of cold nitric acid was added dropwise under stirring. After 20 minutes at this temperature, the reaction mixture was warmed to room temperature for 30 minutes and then 6 g. of crushed ice was added to the suspension. The reaction product was filtered, thoroughly washed with water, dried by suction (0.18 g.) and crystallized from boiling toluene (200 ml.). Concentration to *ca.* 6 ml. afforded the title compound as yellow microcrystals with a poorly identifiable m.p.; ir (potassium bromide): 3130 (NH), 1653-1620 (broad band of C=O), 1530-1398 (NO_2 vibrations).

Anal. Calcd. for $C_{16}H_{10}N_2O_5$: C, 61.94; H, 3.25; N, 9.03. Found: C, 61.92; H, 3.12; N, 8.89.

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