Synthetic Studies on Indoles and Related Compounds. XXXI [1]. Chemical Confirmation of the Synthetic Route for the Benz[*f*]indole Skeleton and its Application

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To confirm the structure of ethyl 9-methoxybenz[*f*]indole (**8a**) prepared from ethyl pyrrole-2-carboxylate (**4**) *via* a new synthetic route, the following chemical correlation work was performed. Ethyl 9-methoxybenz[*f*]indole (**8a**) was converted to 1-benzyl-3-methyl-5,6,7,8-tetrahydrobenz[*f*]indole (**25**), which was alternatively and authentically synthesized from ethyl 3-methylpyrrole-2-carboxylate (**11**). On the basis of the established route to the benz[*f*]indole nucleus, two representative benz[*f*]indoles, benz[*f*]indole (**1**) and 4,9-dioxobenz[*f*]indole (**26**) were synthesized.

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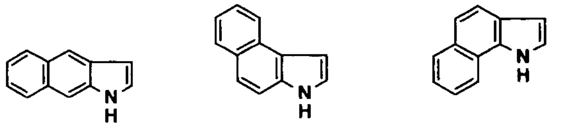
The synthesis of the benz[*f*]indole (**1**) skeleton, one of benz-analogues of indole, is known to be more difficult than those of other benzindoles, benz[*e*]- (**2**) and benz[*g*]- (**3**) indole. Actually only a few syntheses of **1** have been reported [2].



1 benz[f]indole

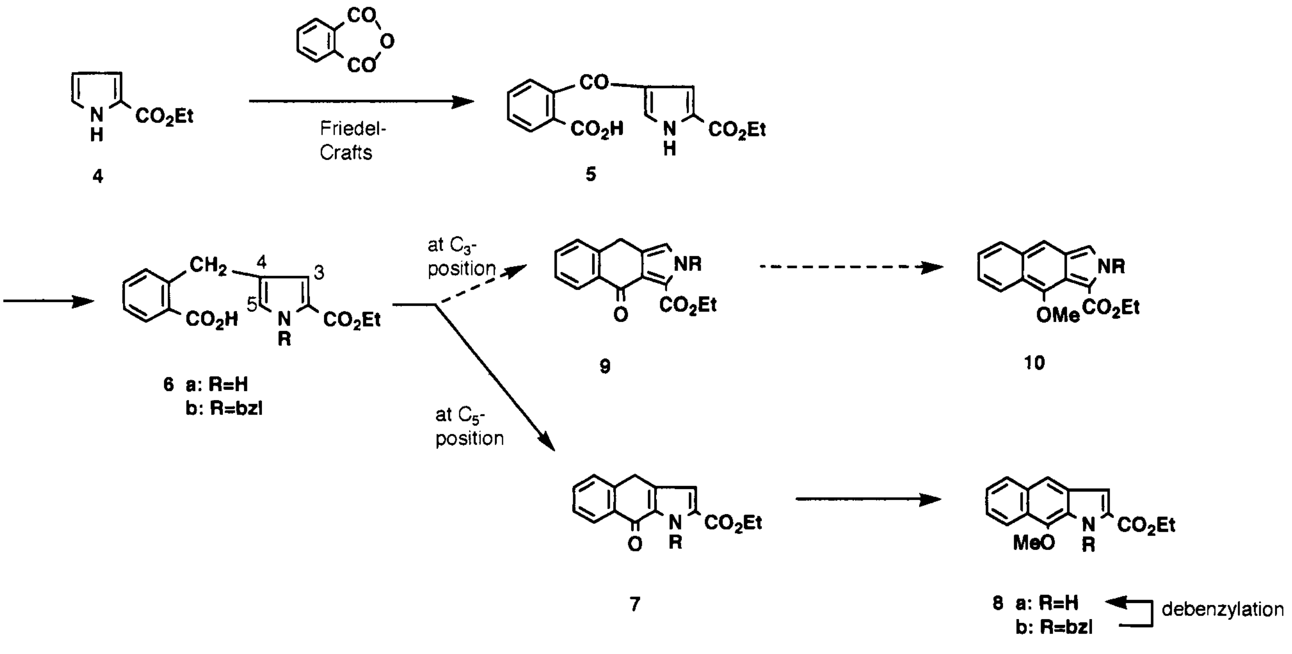
2 benz[e]indole

3 benz[g]indole

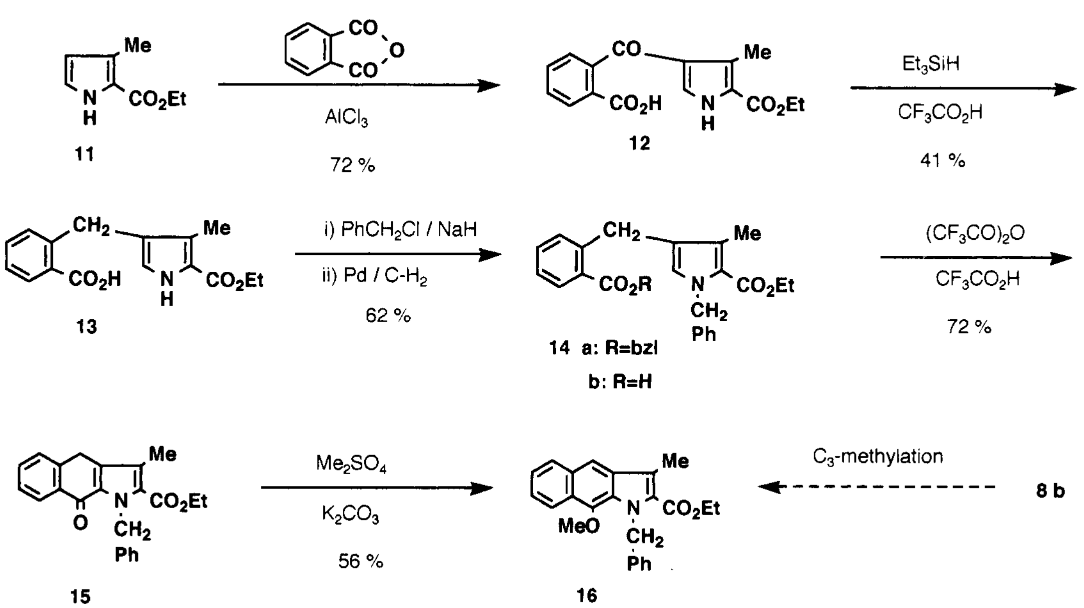
Figure 1

In the previous paper we reported [3] a new synthesis of a benz[*f*]indole, ethyl 9-methoxy-1*H*-benz[*f*]indole-2-carboxylate (**8a**), from ethyl pyrrole-2-carboxylate (**4**) as summarized in Scheme 1. In this sequence, the cyclization of the carboxylic acid **6** cast a slight doubt on the structure of the desired benz[*f*]indole **8**, whose structure was determined by means of ^{1}H-nmr using a shift reagent. The cyclization step might potentially occur in two directions, the C_3- or the C_5-position, although the C_5-position should be more reactive than the C_3-position; that is, in pyrrole derivatives the α-position (the C_5-position in **6**) is generally more reactive to electrophilic reactions than the β-position (the C_3-position in **6**), and the C_3-position of **6** would be deactivated by the C_2-ester group. We decided that the structure of **8** should be determined more firmly because the benz[*f*]indole **8** was a key compound for our subsequent research project [4]. In this paper we report chemical confirmation of the structure of **8**, and the syntheses of several benz[*f*]indoles according to the method described in Scheme 1. The concept of chemical confirmation is shown in Scheme 2.

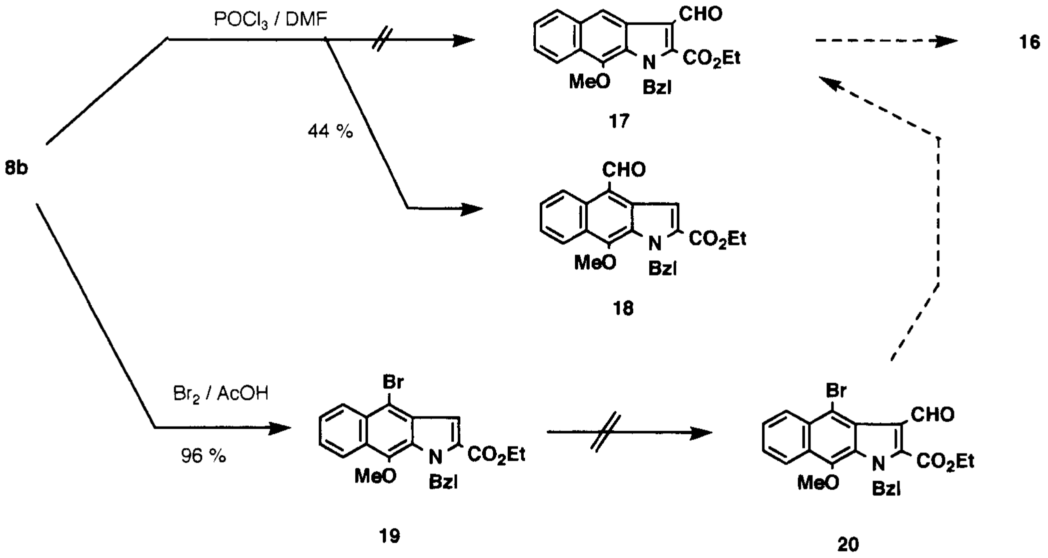
Scheme 1



Scheme 2



Scheme 3



Ethyl 3-methyl-1*H*-pyrrole-2-carboxylate (**11**) in place of 3-unsubstituted pyrrole **4** is converted to the benz[*f*]indole **16** *via* the carboxylic acids **13** and **14** and the cyclic ketone **15** in the same way as described in Scheme 1. In this scheme cyclization of **14** should be restricted at the C$_5$-position and thus yield the cyclic ketone **15**; that is, the structures of **15** and the final product **16** are unquestionable. On the other hand C$_3$-methylation of the 3-unsubstituted benz[*f*]indole **8b** gives the same 3-methylbenz[*f*]indole **16**. The successful correlation gives the final certification to the structure of the benz[*f*]indole **8**. According to the above concept, the synthesis of the 3-methylbenz[*f*]indole **16** from the 3-methylpyrrole **11** was performed.

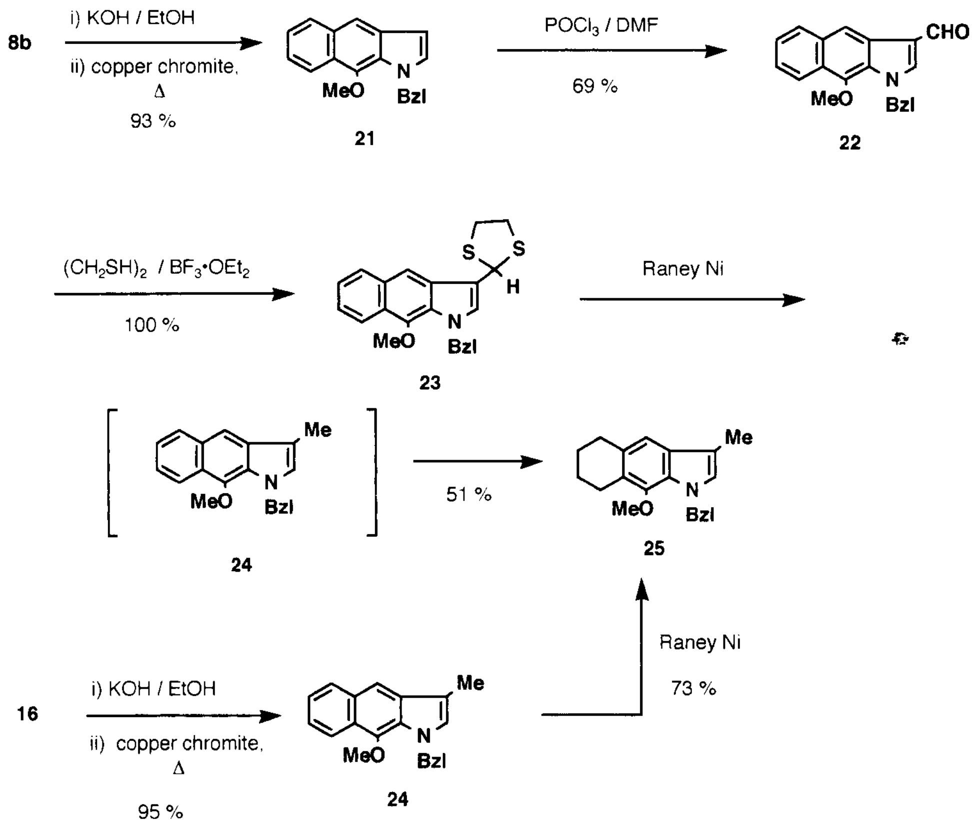
Results and Discussion.

The Friedel-Crafts reaction of ethyl 3-methyl-1*H*-pyrrole-2-carboxylate (**11**) with phthalic anhydride proceeded at the C$_4$-position to give the ketocarboxylic acid **12** as a sole product. As it was already reported [5] since the Friedel-Crafts acylation of ethyl 1*H*-pyrrole-2-carboxylate exclusively occurred at the C_4-position under these conditions, the C_4-substitution in **12** was without doubt. This was further confirmed in terms of the ^{1}H-nmr in as much as chemical shifts of the methyl group at δ 1.32 in the starting material **11** which appeared in a lower region at δ 2.52 in the acyl compound **12** due to the anisotropic effect by the introduced acyl group. Reduction of the keto-acid **12** with triethylsilane/trifluoroacetic acid, followed by benzylation gave the *N*-benzyl compound **14b**. Cyclization of the *N*-benzylcarboxylic acid **14b** with trifluoroacetic anhydride/trifluoroacetic acid, followed by *O*-methylation gave ethyl 1-benzyl-9-methoxy-3-methylbenz[*f*]indole-2-carboxylate (**16**), which served as a tentative relay compound for the correlation. On the other hand, the conversion of the benz[*f*]indole **8b** into the relay compound **16** was performed as shown in Schemes 3 and 4.

First of all, the *N*-benzylbenz[*f*]indole **8b** was allowed to react under Vilsmeier formylation conditions in order to obtain the relay compound **16** *via* the 3-formylindole **17**. However, the reaction gave exclusively the unexpected and undesired 4-formyl compound **18**. The position of the C_4-formyl group was determined in terms of the ^{1}H-nmr of **18** since there still existed the C_3-proton and since the C_3 (δ 8.29) and C_5 (δ 9.08) protons were shifted to lower field in comparison with those of **8b** (C_3-H: δ 7.52 and C_5-H: 7.93 or 8.15 by 400 MHz ^{1}H-nmr). This fact indicated that the most reactive site for an electrophile is not the C_3- but the C_4-position in the benz[*f*]indole **8b**. In order to protect the most reactive C_4-position, **8b** was transformed to the 4-bromobenz[*f*]indole **19** with bromine in acetic acid. However, no formylation occurred on the 4-bromobenz[*f*]indole **19** at all, probably because the reactivity at the C_3-position of benz[*f*]indole **8b** would be potentially lower than the corresponding position of ethyl indole-2-carboxylate.

Next, removal of the 2-ethoxycarbonyl group was performed in order to enhance the reactivity of the C_3-position of **8b**. Thus, hydrolysis of **8b**, followed by decarboxylation gave the C_2-unsubstituted indole **21**. The formylation of **21** proceeded smoothly to give the 3-formylindole **22**. The position of the formyl group was determined in terms of the ^{1}H-nmr in which there existed C_4-H [δ 8.68 as a singlet, which appeared in lower field than that of **21** (δ 7.92)] and C_2-H [δ 7.80 as a singlet which appeared as doublet (δ 7.22, J = 3.4 Hz) in **21**]. The C_3-formyl compound was converted to the thioketal **23**, which was then treated with Raney Ni in boiling ethanol in order to convert it into the C_3-methyl compound **24**. The resulting product was the excessively hydrogenated product, 3-methyl-5,6,7,8-tetrahydrobenz[*f*]indole **25**. The structure was determined on the basis of ms (M^+, m/z 305) and the ^{1}H-nmr data (δ 1.6-2.1 and 2.6-3.15 due to each aliphatic

Scheme 4



four protons). A characteristic feature of benz[*f*]indole appears to be that mild catalytic reduction gave a tetrahydro compound.

For the correlation of the benz[*f*]indole **16** prepared from the 3-methylpyrrole **11**, it was converted into the tetrahydrobenz[*f*]indole **25**, by hydrolysis of the ester group, decarboxylation, and reduction with Raney Ni (Scheme 4). The product obtained by this series of the reactions was identical with the indole **25** prepared from the thioketal **23**. This fact gave the final evidence to the structure of the ethyl 9-methoxybenz[*f*]indole-2-carboxylate (**8a**).

On the basis of the above result we planned to prepare two kinds of genuine benz[*f*]indoles, **1** and **26** (Scheme 5).

Benz[*f*]indole (**1**) is the parent compound of this group and has been prepared only from 2,3-disubstituted naphthalene derivatives [6,7]. 4,9-Dioxobenz[*f*]indole (**26**) is the skeleton of the antibiotic Kinamycin (**27**) [8] and has been prepared *via* a multi-step route [9]. The carboxylic acid **6a** was reduced to the alcohol **28**, which was converted into the aldehyde by manganese dioxide oxidation. The cyclization of the aldehyde **29** with trifluoroacetic acid gave ethyl benz[*f*]indole-2-carboxylate (**30**). Hydrolysis of the ester (**30**), followed by decarboxylation gave the desired benz[*f*]indole (**1**), mp 194-196° (lit 192° [6], 188-190° [7]). The total yield from the 4-substituted pyrrole **6a** was 51%.

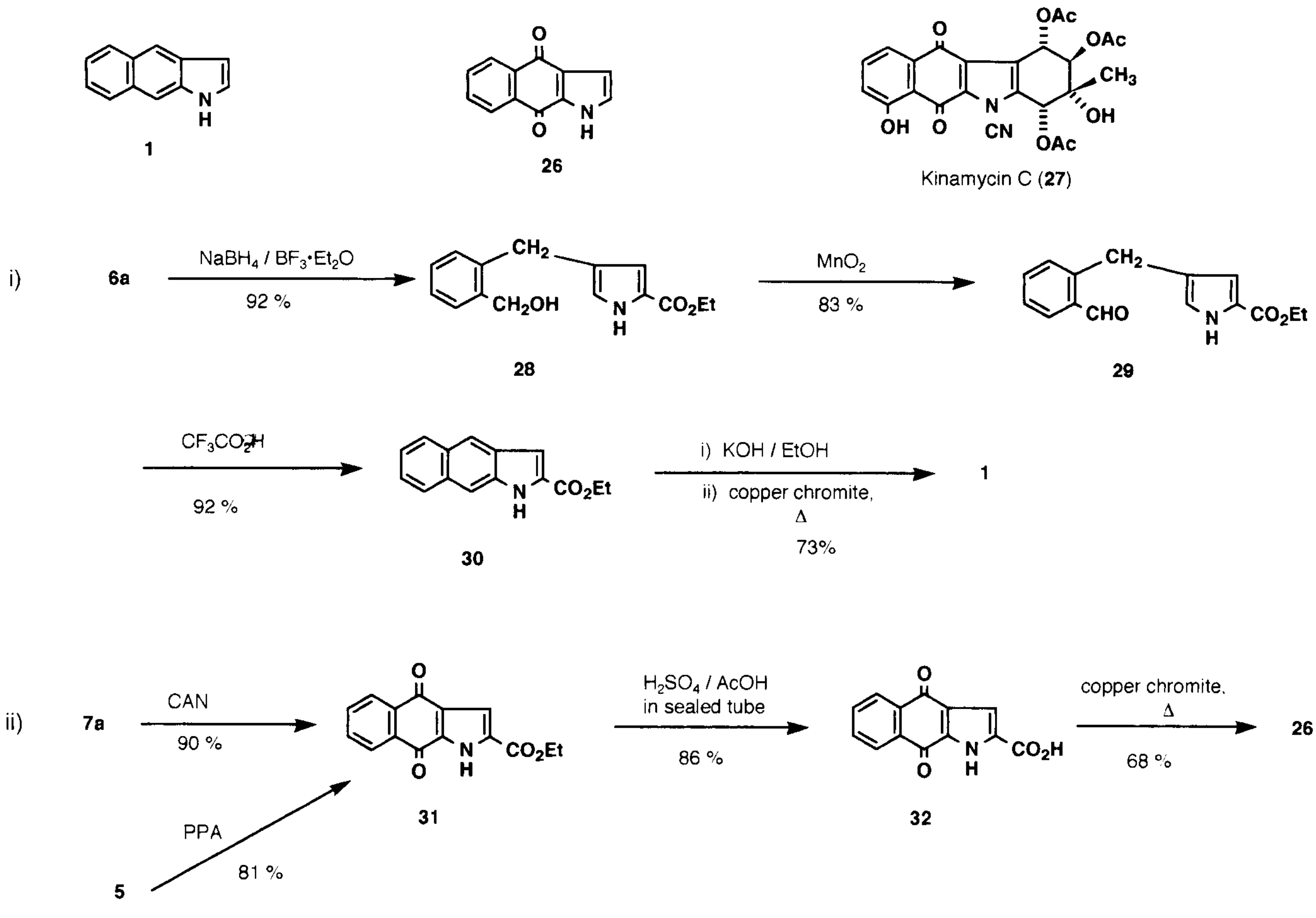
Next, the 9-oxoindole **7a** was oxidized with cerric ammonium nitrate (CAN) to give the 4,9-dioxoindole **31**. The 4,9-dioxoindole **31** was alternatively prepared directly from the 4-acylpyrrole **5** with PPA. Hydrolysis of the ester group of **31** was successful under acidic conditions in a sealed tube, but not under basic conditions. Basic conditions gave only tar. Decarboxylation of the dioxocarboxylic acid **32** thus obtained gave the desired quinone, 4,9-dioxobenz[*f*]indole (**26**), mp 288-291° (lit [9] 282-283°) in the highest yield of 53% from the 9-oxoindole **7a**.

We believe that the present methodology serves as a convenient synthetic route to benz[*f*]indoles.

EXPERIMENTAL

All melting points were measured on a micro melting point hot stage (Yanagimoto) and are uncorrected. The ir spectra were recorded in nujol mulls (unless otherwise stated) on a Shimadzu IR-400 spectrometer. The uv spectra were measured with a Hitachi 340 spectrophotometer. The ^{1}H-nmr spectra were recorded in deuteriochloroform (unless otherwise stated) with

Scheme 5



Hitachi R-24B (60 MHz) (unless otherwise stated) and with JEOL EX-400 (400 MHz) spectrometers. In the ^{1}H-nmr spectra, chemical shifts are given in δ-values referred to internal tetramethylsilane, and the assignment of all NH and OH signals was confirmed by the disappearance of their signals after the addition of deuterium oxide. Mass spectra were measured by the direct inlet system on JEOL JMX-DX303 spectrometer. For column chromatography, silica gel (Kiesel gel 60, 70-230 mesh, Merck), and for thin layer chromatography (tlc), Kiesel gel GF_{254}, Merck, were used. The abbreviations used are as follows: s, singlet; d, doublet; dd, double doublet; t, triplet; q, quartet; m, multiplet; br, broad; Ar, aromatic.

2-{[2-(Ethoxycarbonyl)-3-methyl-1*H*-pyrrol-4-yl]carbonyl}benzoic Acid (**12**).

Phthalic anhydride (7.41 g, 50.0 mmoles) was added to an ice-cooled suspension of aluminum chloride (13.33 g, 100 mmoles) in 1,2-dichloroethane (40 ml). After addition of a solution of ethyl 3-methyl-1*H*-pyrrole-2-carboxylate (**11**) [10] (3.83 g, 25.0 mmoles) in 1,2-dichloroethane (30 ml), the mixture was refluxed for 3 hours and poured into a mixture of water and 2*N* sulfuric acid to dissolve any inorganic compounds. The solution was extracted with ethyl acetate. The organic layer was washed with brine, dried over magnesium sulfate, and evaporated to dryness *in vacuo*. Recrystallization of the residue from ethanol-water with decolorizing carbon gave **12** as colorless needles, 5.39 g (72%), mp 171-173°; ir: ν 3250 (NH), 1695 and 1640 (CO) cm^{-1}; ^{1}H-nmr (dimethyl sulfoxide-d$_6$): δ 1.28 (t, J = 7.5 Hz, 3H, CCH_3), 2.52 (s, 3H, $ArCH_3$), 4.26 (q, J = 7.5 Hz, 2H, OCH_2), 6.78 (d, J = 4 Hz, 1H, 5-H), 7.25-8.00 (m, 5H, ArH and COOH), 11.90 (br s, 1H, NH); ms: m/z 301 (M$^+$, 48%), 134 (100%).

Anal. Calcd. for $C_{16}H_{15}NO_5$: C, 63.78; H, 5.02; N, 4.65. Found: C, 63.63; H, 5.03; N, 4.61.

2-{[2-(Ethoxycarbonyl)-3-methyl-1*H*-pyrrol-4-yl]methyl}benzoic Acid (**13**).

Triethylsilane (2.5 ml, 15.7 mmoles) was added to a solution of 2-{[2-(ethoxycarbonyl)-3-methyl-1*H*-pyrrol-4-yl]carbonyl}benzoic acid (**12**) (1.54 g, 5.11 mmoles) in trifluoroacetic acid (12 ml). The reaction mixture was stirred at room temperature for 24 hours and evaporated to dryness *in vacuo* at room temperature. The residue was dissolved in ethyl acetate, and the organic solution was washed with brine, dried over magnesium sulfate, and evaporated to dryness *in vacuo*. The residue (0.923 g) was recrystallized from ethanol to give **13** as colorless prisms, 0.603 g (41%), mp 185-189°; ir; ν 3290 (NH), 1670 (CO) cm^{-1}; ^{1}H-nmr (dimethyl sulfoxide-d$_6$): δ 1.27 (t, J = 7.5 Hz, 3H, CCH_3), 2.15 (s, 3H, $ArCH_3$), 4.08 (s, 2H, $ArCH_2$), 4.22 (q, J = 7.5 Hz, 2H, OCH_2), 6.51 (d, J = 4 Hz, 1H, 5-H), 7.00-7.90 (m, 5H, ArH and COOH), 11.10 (br s, 1H, NH); ms m/z 287 (M$^+$, 66%), 196 (100%).

Anal. Calcd. for $C_{16}H_{17}NO_4$: C, 66.89; H, 5.96; N, 4.87. Found: C, 66.74; H, 5.95; N, 4.88.

2-{[1-Benzyl-2-(ethoxycarbonyl)-3-methyl-1*H*-pyrrol-4-yl]methyl}-benzoic Acid (**14b**).

i) Benzylation.

An ice-cooled solution of 2-{[2-(ethoxycarbonyl)-3-methyl-1*H*-pyrrol-4-yl]methyl}benzoic acid (**13**) (288 mg, 1.0 mmole) in dimethyl sulfoxide (4 ml) was added to 60% sodium hydride in oil (100 mg, 2.5 mmoles) under argon gas and the mixture was stirred at 70° for 20 minutes. Benzyl chloride (0.288 ml, 2.5 mmoles) was added to the stirred solution. The whole mixture was stirred at 70° for 20 minutes, poured into a mixture of ice-water and diluted hydrochloric acid, and extracted with ethyl acetate. The organic layer was washed with saturated sodium bicarbonate and brine, and dried over magnesium sulfate, and evaporated to dryness *in vacuo*. The residue was chromatographed with silica gel using hexane-ethyl acetate (10:1) to give benzyl 2-{[1-benzyl-2-(ethoxycarbonyl)-3-methyl-1*H*-pyrrol-4-yl]methyl}-benzoate (**14a**) as a pale yellow solid, 440 mg (94%); ^{1}H-nmr: δ 1.25 (t, J = 8 Hz, 3H, CCH_3), 2.22 (s, 3H, $ArCH_3$), 4.16 (s, 2H, $ArCH_2$), 4.23 (q, J = 8 Hz, 2H, OCH_2), 5.27 and 5.39 (s, each 2H, NCH_2Ph and OCH_2Ph), 6.43 (s, 1H, 5-H), 6.85-7.60 (m, 13H, ArH), 7.90 (m, 1H, ArH); ms: m/z 467 (M$^+$, 33%), 91 (100%); hrms: Calcd. for $C_{30}H_{29}NO_4$: 467.2097. Found: 467.2106.

ii) Hydrogenolysis.

Without further purification, benzyl 2-{[1-benzyl-2-(ethoxycarbonyl)-3-methyl-1*H*-pyrrol-4-yl]methyl}benzoate (**14a**) was hydrogenated over 10% Pd-C (71 mg) in ethanol (30 ml) at room temperature for 1 hour. The catalyst was filtered off and the filtrate was evaporated to dryness *in vacuo* to give **14b** as fine colorless needles, 250 mg (66%, from **13**), mp 127-129°, which were recrystallized from methylene chloride-hexane; ir: ν 1685 (CO) cm^{-1}; ^{1}H-nmr: δ 1.22 (t, J = 7.5 Hz, 3H, CCH_3), 2.22 (s, 3H, $ArCH_3$), 4.18 (q, J = 7.5 Hz, 2H, OCH_2), 4.25 (s, 2H, $ArCH_2$), 5.40 (s, 2H, NCH_2Ph), 6.50 (s, 1H, 5-H), 6.80-8.15 (m, 9H, ArH), 10.95 (br s, 1H, COOH); ms: m/z 377 (M$^+$, 25%), 91 (100%).

Anal. Calcd. for $C_{23}H_{23}NO_4$: C, 73.19; H, 6.14; N, 3.71. Found: C, 72.90; H, 6.11; N, 3.73.

Ethyl 1-Benzyl-3-methyl-9-oxo-4,9-dihydro-1*H*-benz[*f*]indole-2-carboxylate (**15**).

Trifluoroacetic anhydride (0.089 ml, 0.630 mmole) was added to an ice-cooled solution of 2-{[1-benzyl-2-(ethoxycarbonyl)-3-methyl-1*H*-pyrrol-4-yl]methyl}benzoic acid (**14b**) (160 mg, 0.423 mmole) in trifluoroacetic acid (1.2 ml). The mixture was stirred at room temperature for 1 hour and then evaporated to dryness *in vacuo*. The residue was dissolved in ethyl acetate and washed with saturated sodium bicarbonate and brine, dried over magnesium sulfate, and evaporated to dryness *in vacuo*. The residue was chromatographed with silica gel using chloroform-hexane (1:1) to give **15** as pale yellow plates, 110 mg (72%), mp 196-200.5°, which were recrystallized from ethyl acetate-ethanol; ir: ν 1690 and 1635 (CO) cm^{-1}; ^{1}H-nmr: δ 1.30 (t, J = 7.5 Hz, 3H, CCH_3), 2.35 (s, 3H, ArH), 4.02 (s, 2H, $ArCH_2$), 4.32 (q, J = 7.5 Hz, 2H, OCH_2), 6.33 (s, 2H, NCH_2Ph), 6.80-8.45 (m, 9H, ArH); ms: m/z 359 (M$^+$, 57%), 91 (100%).

Anal. Calcd. for $C_{23}H_{21}NO_3$: C, 76.86; H, 5.89; N, 3.90. Found: C, 76.69; H, 5.88; N, 3.74.

Ethyl 1-Benzyl-9-methoxy-3-methyl-1*H*-benz[*f*]indole-2-carboxylate (**16**).

A solution of ethyl 1-benzyl-3-methyl-9-oxo-4,9-dihydro-1*H*-benz[*f*]indole-2-carboxylate (**15**) (402 mg, 1.12 mmoles) in DMF (17 ml) was added to ice-cooled anhydrous potassium carbonate (467 mg, 3.38 mmoles). After addition of dimethyl sulfate (0.159 ml, 1.68 mmoles), the reaction mixture was stirred at 0° for 20 minutes poured into ice water, and extracted with ether. The organic layer was washed with 10% hydrochloric acid and brine, dried over magnesium sulfate, and evaporated to dryness *in* *vacuo.* The residue was chromatographed on silica gel using hexane-ethyl acetate (10:1) as an eluant to give **16** as pale yellow prisms (unstable), 235 mg (56%), mp 89-92°, which were recrystallized from hexane; ir: ν 1700 (CO) cm^{-1}; ^{1}H-nmr: δ 1.30 (t, J = 7.5 Hz, 3H, CCH_3), 2.65 (s, 3H, $ArCH_3$), 3.82 (s, 3H, OCH_3), 4.33 (q, J = 7.5 Hz, 2H, OCH_2), 6.11 (s, 2H, NCH_2Ph), 6.80-8.30 (m, 10H, ArH); ms: m/z 373 (M$^+$, 100%); hrms: Calcd. for $C_{24}H_{23}NO_3$: 373.1678. Found: 373.1676.

1-Benzyl-9-methoxy-3-methyl-1*H*-benz[*f*]indole (**24**).

A solution of ethyl 1-benzyl-9-methoxy-3-methyl-1*H*-benz[*f*]indole-2-carboxylate (**16**) (100 mg, 0.268 mmole) in ethanol (2 ml) containing potassium hydroxide (93 mg, 1.41 mmoles) was refluxed for 45 minutes. The reaction mixture was poured into ice-water, acidified with 10% hydrochloric acid, and the resulting precipitates were filtered with suction. The solid was washed with water and dried to give 1-benzyl-9-methoxy-3-methyl-1*H*-benz[*f*]indole-2-carboxylic acid as a yellow solid, 88 mg, mp 230-236°.

A mixture of the crude carboxylic acid and copper chromite (10 mg) in quinoline (1 ml) was heated at 200° for 15 minutes. The reaction mixture was poured into ice-water and extracted with ethyl acetate. The extract was washed with 10% hydrochloric acid, saturated sodium bicarbonate and brine, dried over magnesium sulfate, and evaporated to dryness *in vacuo.* The residue was chromatographed on silica gel using hexane-ethyl acetate (10:1) as an eluant to give **24** as a brown oil, 76.9 mg (95%); ir: no characteristic absorption; ^{1}H-nmr: δ 2.36 (d, J = 1.5 Hz, 3H, $ArCH_3$), 3.83 (s, 3H, OCH_3), 5.59 (s, 2H, NCH_2Ph), 6.90 (d, J = 1.5 Hz, 1H, 2-H), 7.03-8.23 (m, 10H, ArH); ms: m/z 301 (M$^+$, 100%). This compound was characterized as the picrate, black needles, mp 135-136°, which were recrystallized from ethanol.

Anal. Calcd. for $C_{21}H_{19}NO \cdot C_6H_3N_3O_7$: C, 61.13; H, 4.18; N, 10.56. Found: C, 61.14; H, 4.28; N, 10.52.

Ethyl 1-Benzyl-4-formyl-9-methoxy-1*H*-benz[*f*]indole-2-carboxylate (**18**).

A mixture of phosphoryl chloride (0.035 ml, 0.375 mmole) and dimethylformamide (DMF) (0.5 ml) was stirred at 0° for 30 minutes and to this solution ethyl 1-benzyl-9-methoxy-1*H*-benz[*f*]indole-2-carboxylate (**8b**) [3] (91 mg, 0.253 mmole) in DMF (1.5 ml) was added. The reaction mixture was heated at 60° for 4 hours, poured into ice-water, basified with 10% sodium carbonate, and extracted with ethyl acetate. The organic layer was washed with 10% hydrochloric acid and brine, dried over magnesium sulfate, and evaporated to dryness *in vacuo.* The residue was chromatographed on silica gel using hexane-ethyl acetate (20:1) as an eluant to give **18**, as a yellow solid, 43 mg (44%), mp 146.5-148°, which were recrystallized from ethanol; ir: ν 1720 and 1660 (CO) cm^{-1}; ^{1}H-nmr (400 MHz): δ 1.37 (t, J = 7.1 Hz, 3H, CCH_3), 3.86 (s, 3H, OCH_3), 4.36 (q, J = 7.1 Hz, 2H, OCH_2), 6.27 (s, 2H, NCH_2Ph), 6.97 (d, J = 7.3 Hz, 2H, ArH), 7.13-7.30 (m, 3H, ArH), 7.48-7.65 (m, 2H, 6- and 7-H), 8.23 (d, J = 8.8 Hz, 1H, 8-H), 8.29 (s, 1H, 3-H), 9.08 (d, J = 8.8 Hz, 1H, 5-H), 11.19 (s, 1H, CHO); ms: m/z 387 (M$^+$, 89%), 91 (100%).

Anal. Calcd. for $C_{24}H_{21}NO_4$: C, 74.40; H, 5.46; N, 3.62. Found: C, 74.44; H, 5.57; N, 3.67.

Ethyl 1-Benzyl-4-bromo-9-methoxy-1*H*-benz[*f*]indole-2-carboxylate (**19**).

To a solution of 1-benzyl-9-methoxy-1*H*-benz[*f*]indole-2-carboxylate (**8b**) (288 mg, 0.801 mmole) in acetic acid (7.5 ml) was added bromine (0.045 ml, 0.873 mmole), and the whole mixture was stirred at room temperature for 5 minutes. The reaction mixture was poured into ice-water. The resulting precipitates were collected, washed with 10% sodium carbonate and water, and dried. The crude solid was chromatographed on silica gel using hexane-ethyl acetate (10:1) as an eluant to give **19** as yellow prisms, 338 mg (96%), mp 130-132°, which were recrystallized from ethanol; ir: ν 1710 (CO) cm^{-1}; ^{1}H-nmr: δ 1.38 (t, J = 8 Hz, 3H, CCH_3), 3.83 (s, 3H, OCH_3), 4.35 (q, J = 8 Hz, 2H, OCH_2), 6.22 (s, 2H, NCH_2Ph), 6.8-7.7 (m, 8H, ArH), 7.9-8.5 (m, 2H, ArH); ms: m/z 439 (M$^+$+2, 75%), 437 (M$^+$, 74%), 91 (100%).

Anal. Calcd. for $C_{23}H_{20}BrNO_3$: C, 63.03; H, 4.60; N, 3.20. Found: C, 62.86; H, 4.58; N, 3.27.

1-Benzyl-9-methoxy-1*H*-benz[*f*]indole (**21**).

A solution of ethyl 1-benzyl-9-methoxy-1*H*-benz[*f*]indole-2-carboxylate (**8b**) (99.2 mg, 0.276 mmole) in ethanol (1.5 ml) containing potassium hydroxide (96 mg, 1.45 mmoles) was refluxed for 30 minutes. The reaction mixture was poured into ice-water, acidified with 10% hydrochloric acid, and extracted with ethyl acetate. The organic layer was washed with water, dried over magnesium sulfate, and evaporated to dryness *in vacuo* to give 1-benzyl-9-methoxy-1*H*-benz[*f*]indole-2-carboxylic acid as a yellow solid, 84 mg.

A mixture of the crude carboxylic acid and copper chromite (15 mg) in quinoline (1.5 ml) was heated at 200° for 15 minutes. The reaction mixture was poured into ice-water and extracted with ethyl acetate. The extract was washed with 10% hydrochloric acid, saturated sodium bicarbonate and brine, dried over magnesium sulfate, and evaporated to dryness *in vacuo.* The residue was chromatographed on silica gel using hexane-ethyl acetate (10:1) as an eluant to give **21** as pale brown oil (unstable), 73.8 mg (93%); ir: no characteristic absorption; ^{1}H-nmr (400 MHz): δ 3.87 (s, 3H, OCH_3), 5.72 (s, 2H, NCH_2Ph), 6.67 (d, J = 3.4 Hz, 1H, 3-H), 7.11 (d, J = 6.8 Hz, 2H, ArH), 7.18-7.40 (m, 5H, ArH), 7.22 (d, J = 3.4 Hz, 1H, 2-H), 7.92 (s, 1H, 4-H), 7.93 and 8.13 (d, J = 8.8 Hz, each 1H, 5- and 8-H); ms: m/z 287 (M$^+$, 80%), 91 (100%); hrms: Calcd. for $C_{20}H_{17}NO$: 287.1310. Found: 287.1322.

1-Benzyl-3-formyl-9-methoxy-1*H*-benz[*f*]indole (**22**).

A mixture of phosphoryl chloride (0.068 ml, 0.730 mmole) and dimethylformamide (DMF) (0.5 ml) was stirred at 0° for 30 minutes and to this solution 1-benzyl-9-methoxy-1*H*-benz[*f*]indole (**21**) (70.0 mg, 0.244 mmole) in DMF (0.5 ml) was added. The reaction mixture was heated at 0° after 30 minutes, poured into ice-water, basified with 5% sodium hydroxide, and extracted with ethyl acetate. The organic layer was washed with brine, dried over magnesium sulfate, and evaporated to dryness *in vacuo.* The residue was chromatographed on silica gel using hexane-ethyl acetate (10:1) as an eluant to give **22**, as colorless solid, 52.9 mg (69%), mp 131-134°, which were recrystallized from ethanol; ir: ν 1650 (CO) cm^{-1}; ^{1}H-nmr (400 MHz): δ 3.89 (s, 3H, OCH_3), 5.77 (s, 2H, NCH_2Ph), 7.21 (d, J = 6.8 Hz, 2H, ArH), 7.27-7.50 (m, 5H, ArH), 7.80 (s, 1H, 2-H), 8.03 and 8.15 (d, J = 8.3 Hz, each 1H, 5- and 8-H), 8.68 (s, 1H, 4-H), 9.97 (s, 1H, CHO); ms: m/z 315 (M$^+$, 70%), 91 (100%).

Anal. Calcd. for $C_{21}H_{17}NO_2$: C, 79.98; H, 5.43; N, 4.44. Found: C, 79.92; H, 5.46; N, 4.54.

1-Benzyl-3-[2-(1,3-dithiolanyl)]-9-methoxy-1*H*-benz[*f*]indole (**23**).

To a solution of 1-benzyl-3-formyl-9-methoxy-1*H*-benz[*f*]indole

(**22**) (52.9 mg, 0.168 mmole) in acetic acid (1.5 ml) was added ethanedithiol (0.035 ml, 0.417 mmole) and boron trifluoride-etherate (0.031 ml, 0.252 mmole). The whole mixture was stirred at room temperature for 45 minutes. The reaction mixture was poured into ice-water, basified with 5% sodium hydroxide, and extracted with ethyl acetate. The extract was washed with 5% sodium hydroxide and brine, dried over magnesium sulfate, and evaporated to dryness *in vacuo* to give **23** as pink oil, 66.0 mg, (100%); ir: no characteristic absorption; ^{1}H-nmr: δ 3.41 (s, 4H, SCH_2), 3.82 (s, 3H, OCH_3), 5.62 (s, 2H, NCH_2Ph), 6.08 (s, 1H, 2-H or ArCH-S), 6.95-7.55 (m, 8H, ArH), 7.8-8.2 (m, 3H, ArH); ms: m/z 391 (M^+, 60%), 105 (100%); hrms: Calcd. for $C_{23}H_{21}NOS_2$: 391.1065. Found: 391.1053.

1-Benzyl-9-methoxy-3-methyl-5,6,7,8-tetrahydro-1*H*-benz[*f*]indole (**25**).

a) From 1-Benzyl-3-[2-(1,3-dithiolanyl)]-9-methoxy-1*H*-benz[*f*]indole (**23**).

A mixture of 1-benzyl-3-[2-(1,3-dithiolanyl)]-9-methoxy-1*H*-benz[*f*]indole (**23**) (66.0 mg, 0.169 mmole), Raney Ni-W4 (wet volume 0.8 ml) in ethanol (12 ml) and ethyl acetate (2 ml) was refluxed for 30 minutes. After addition of more Raney Ni (wet volume 1 ml) and ethanol (5 ml), the reaction mixture was refluxed for 30 minutes and the catalyst was filtered off. The filtrate was evaporated to dryness *in vacuo*. The residue was chromatographed on silica gel using benzene as an eluant to give **25** as a colorless oil, 26.0 mg (51%); ir: no characteristic absorption; uv (ethanol): λ max (log ϵ) 228 (4.38), 267 (3.57), 280 (3.61), 292 (3.60), 303 (3.48) nm; ^{1}H-nmr: δ 1.6-2.1 (m, 4H, 6- and 7-H), 2.25 (s, 3H, $ArCH_3$), 2.6-3.15 (m, 4H, 5- and 8-H), 3.61 (s, 3H, OCH_3), 5.48 (s, 2H, NCH_2Ph), 6.67 (s, 1H, 2-H), 6.85-7.4 (m, 6H, ArH); ms: m/z 305 (M^+, 83%), 91 (100%); hrms: Calcd. for $C_{21}H_{23}NO$: 305.1780. Found: 305.1778.

b) From 1-Benzyl-9-methoxy-3-methyl-1*H*-benz[*f*]indole (**24**).

A mixture of the 1-benzyl-9-methoxy-3-methyl-1*H*-benz[*f*]indole (**24**) (36.4 mg, 0.121 mmole), Raney Ni-W4 (wet volume 1 ml) in ethanol (1 ml) was refluxed for 1 hour. After addition of more Raney Ni (wet volume 1 ml), the reaction mixture was refluxed for 30 minutes and the catalyst was filtered off. The filtrate was evaporated to dryness *in vacuo*. The residue was chromatographed on silica gel using hexane-ethyl acetate (10:1) as an eluant to give **25** as colorless oil, 26.8 mg (73%).

This compound was identical with the sample **25** from 1-benzyl-3-[2-(1,3-dithiolanyl)]-9-methoxy-1*H*-benz[*f*]indole (**23**).

Ethyl 4-{[(2-Hydroxymethyl)phenyl]methyl}-1*H*-pyrrole-2-carboxylate (**28**).

To a suspension of sodium borohydride (492 mg, 13.0 mmoles) in tetrahydrofuran (THF) (11 ml) was added 2-{[2-(ethoxycarbonyl)-1*H*-pyrrol-4-yl]methyl}benzoic acid (**6a**) [3] (2.74 g, 10.0 mmoles) and boron trifluoride-etherate (1.85 ml, 15.0 mmoles) in THF (35 ml) under ice-cooling and argon atmosphere. The whole mixture was stirred at room temperature for 4.5 hours. The reaction mixture was poured into ice-water and extracted with ethyl acetate. The extract was washed with saturated sodium bicarbonate and brine, dried over magnesium sulfate, and evaporated to dryness *in vacuo*. The residue was chromatographed on silica gel using hexane-ethyl acetate as an eluant to give **28** as colorless prisms, 2.39 g (92%), mp 84-85° which were recrystallized from hexane-ethyl acetate; ir: ν 3270 (NH), 1660 (CO) cm^{-1}; ^{1}H-nmr: δ 1.24 (t, J = 7 Hz, 3H, CCH_3), 2.61 (s, 1H, OH), 3.79 (s, 2H, $ArCH_2O$), 4.17 (q, J = 7 Hz, 2H, OCH_2), 4.59 (s, 2H, $ArCH_2Ar'$), 6.40-6.73 (m, 2H, ArH), 7.02-7.43 (m, 4H, ArH), 9.52 (br s, 1H, NH); ms: m/z 259 (M^+, 43%), 140 (100%).

Anal. Calcd. for $C_{15}H_{17}NO_3$: C, 69.48; H, 6.61; N, 5.40. Found: C, 69.30; H, 6.64; N, 5.44.

Ethyl 4-[(2-Formylphenyl)methyl]-1*H*-pyrrole-2-carboxylate (**29**).

A mixture of ethyl 4-{[(2-hydroxymethyl)phenyl]methyl}-1*H*-pyrrole-2-carboxylate (**28**) (1.00 g, 3.86 mmoles) and active manganese dioxide (6.20 g, 71.3 mmoles) in methylene chloride (20 ml) was refluxed for 2 hours. The inorganic compound was filtered off and the filtrate was evaporated to dryness *in vacuo*. The residue was chromatographed on silica gel using hexane-ethyl acetate to give **29** as colorless prisms, 0.82 g (83%), mp 77-80°, which were recrystallized from hexane-ethyl acetate; ir: ν 3230 (NH), 1680 (CO) cm^{-1}; ^{1}H-nmr: δ 1.28 (t, J = 7 Hz, 3H, CCH_3), 4.20 (s, 2H, $ArCH_2Ar'$), 4.23 (q, J = 7 Hz, 2H, OCH_2), 6.62 (d, J = 3 Hz, 2H, ArH), 7.1-7.9 (m, 4H, ArH), 8.75-9.3 (br s, 1H, NH), 10.20 (s, 1H, CHO); ms: m/z 257 (M^+, 100%).

Anal. Calcd. for $C_{15}H_{15}NO_3$: C, 70.02; H, 5.88; N, 5.44. Found: C, 69.97; H, 5.86; N, 5.54.

Ethyl 1*H*-Benz[*f*]indole-2-carboxylate (**30**).

To a solution of ethyl 4-[(2-formylphenyl)methyl]-1*H*-pyrrole-2-carboxylate (**29**) (669 mg, 2.60 mmoles) in methylene chloride (10 ml) was added trifluoroacetic acid (0.600 ml, 7.79 mmoles) and the whole mixture was stirred at 0° for 40 minutes. The reaction mixture was evaporated to dryness *in vacuo*. The residue was chromatographed on silica gel using benzene as an eluant to give **30** as pale yellow prisms, 574 mg (92%), mp 188-190°, which were recrystallized from benzene; ir: ν 3300 (NH), 1680 (CO) cm^{-1}; ^{1}H-nmr: δ 1.44 (t, J = 7 Hz, 3H, CCH_3), 4.43 (q, J = 7 Hz, 2H, OCH_2), 7.2-7.5 (m, 3H, ArH), 7.7-8.0 (m, 3H, ArH), 8.15 (s, 1H, 4- or 9-H), 8.80 (br s, 1H, NH); ms: m/z 239 (M^+, 67%), 193 (100%).

Anal. Calcd. for $C_{15}H_{13}NO_2$: C, 75.30; H, 5.48; N, 5.85. Found; C, 75.29; H, 5.44; N, 5.72.

1*H*-Benz[*f*]indole (**1**).

A solution of ethyl 1*H*-benz[*f*]indole-2-carboxylate (**30**) (112 mg, 0.468 mmole) in ethanol (1.5 ml) containing potassium hydroxide (140 mg, 2.12 mmoles) was refluxed for 30 minutes. The reaction mixture was poured into ice-water, acidified with 10% hydrochloric acid, and extracted with ethyl acetate. The organic layer was washed with water, dried over magnesium sulfate, and evaporated to dyrness *in vacuo* to give 1*H*-benz[*f*]indole-2-carboxylic acid as yellow solid, 90 mg.

A mixture of the crude carboxylic acid and copper chromite (15 mg) in quinoline (0.8 ml) was heated at 200° for 15 minutes. The reaction mixture was poured into ice-water and extracted with ethyl acetate. The extract was washed with 10% hydrochloric acid, saturated sodium bicarbonate and brine, dried over magnesium sulfate, and evaporated to dryness *in vacuo*. The residue was chromatographed on silica gel using hexane-ethyl acetate (10:1) as an eluant to give **1** as pale yellow prisms, 56.8 mg (73%), mp 194-196° (lit 192° [6] and 188-190° [7]), which were recrystallized from benzene-hexane; ir: ν 3410 (NH); ^{1}H-nmr: δ 6.65 (m, 1H, 3-H), 7.15-8.20 (m, 8H, NH and ArH); ms: m/z 167 (M^+, 100%).

Anal. Calcd. for $C_{12}H_9N$: C, 86.20; H, 5.42; N, 8.38. Found: C, 86.51; H, 5.34; N, 8.33.

Ethyl 4,9-Dioxo-4,9-dihydro-1*H*-benz[*f*]indole-2-carboxylate (**31**).

a) Oxidation of Ethyl 9-Oxo-4,9-dihydro-1*H*-benz[*f*]indole-2-carboxylate (**7a**).

To a solution of ethyl 9-oxo-4,9-dihydro-1*H*-benz[*f*]indole-2-carboxylate (**7a**) [3] (145 mg, 0.568 mmole) in acetonitrile (2.5 ml) was added a solution of ceric ammonium nitrate (1.566 g, 2.86 mmoles) in water (7.5 ml), and the whole mixture was stirred at room temperature for 24 hours. The reaction mixture was poured into water. The resulting precipitates were collected, washed with water and dried to give **31**, 137 mg (90%), mp 234-236°, as yellow needles which were recrystallized from chloroform-ethanol; ir: ν 3220 (NH), 1720 and 1660 (CO) cm^{-1}; ^{1}H-nmr: δ 1.42 (t, J = 8 Hz, 3H, CCH_3), 4.44 (q, J = 8 Hz, 2H, OCH_2), 7.36 (d, J = 3 Hz, 1H, 3-H), 7.5-7.9 (m, 2H, ArH), 8.0-8.35 (m, 3H, ArH and NH); ms: m/z 269 (M$^+$, 100%).

Anal. Calcd. for $C_{15}H_{11}NO_4$: C, 66.91; H, 4.12; N, 5.20. Found: C, 66.92; H, 4.05; N, 5.28.

b) Cyclization of 2-{[2-(Ethoxycarbonyl)-1*H*-pyrrol-4-yl]carbonyl}-benzoic Acid (**5**) with Polyphosphoric Acid (PPA).

A mixture of 2-{[2-(ethoxycarbonyl)-1*H*-pyrrol-4-yl]carbonyl}-benzoic acid (**5**) (288 mg, 1.00 mmole) and PPA (2.42 g) was heated at 100° for 3 hours. The reaction mixture was poured into ice-water. The resulting precipitates were collected, washed with water and dried to give **31** , 219 mg (81%), mp 232-234.5°, as yellow needles which were recrystallized from ethyl acetate-ethanol.

This compound was identified with the quinone **31** prepared from ethyl 9-oxo-4,9-dihydro-1*H*-benz[*f*]indole-2-carboxylate (**7a**) by oxidation.

4,9-Dioxo-4,9-dihydro-1*H*-benz[*f*]indole-2-carboxylic Acid (**32**).

A suspension of ethyl 4,9-dioxo-4,9-dihydro-1*H*-benz[*f*]indole-2-carboxylate (**31**) (271 mg, 1.01 mmoles) in concentrated sulfuric acid (2 ml), acetic acid (20 ml), and water (10 ml) was heated at 130° for 16 hours in a sealed tube. The reaction mixture was poured into ice-water. The resulting precipitates were collected, washed with water, and dried to give **32**, 209 mg (86%), mp over 300° dec, as yellow needles which were recrystallized from ethanol-water; ir: ν 3300-2550 (OH), 3220 (NH), 1700 and 1660 (CO) cm^{-1}; ^{1}H-nmr (400 MHz) (dimethyl sulfoxide-d$_6$): δ 7.17 (d, J = 1 Hz, 1H, 3-H), 7.84 (m, 2H, 6- and 7-H), 8.09 (m, 2H, 5- and 8-H), 13.38 and 13.62 (br s, each 1H, NH and OH); ms: m/z 241 (M$^+$, 100%); hrms: Calcd. for $C_{13}H_7NO_4$: 241.0375. Found: 241.0344.

1*H*-benz[*f*]indole-4,9-dione (**26**).

A mixture of 4,9-dioxo-4,9-dihydro-1*H*-benz[*f*]indole-2-carboxylic acid (**32**) (106 mg, 0.439 mmole) and copper chromite (11 mg) in quinoline (1 ml) was heated at 200° for 3 hours. The reaction mixture was poured into ice-water and extracted with ethyl acetate. The extract was washed with 10% hydrochloric acid, saturated sodium bicarbonate and brine, dried over magnesium sulfate, and evaporated to dryness *in vacuo*. The residue was chromatographed on silica gel using benzene-ethyl acetate (20:1) as an eluant to give the quinone (**26**) as yellow needles, 58.8 mg (68%), mp 288-291° dec (lit [9] 282-283°), which were recrystallized from ethyl acetate-ethanol; ir: ν 3230 (NH), 1650 (CO) cm^{-1}; ^{1}H-nmr (dimethyl sulfoxide-d$_6$): δ 6.71 and 7.38 (m, each 1H, 2- and 3-H), 7.80 (m, 2H, 6- and 7-H), 8.08 (m, 2H, 5- and 8-H), 12.96 (br s, 1H, NH); ms: m/z 197 (M$^+$, 100%).

Anal. Calcd. for $C_{12}H_7NO_2$: C, 73.09; H, 3.58; N, 7.10. Found: C, 73.03; H, 3.53; N, 7.13.

REFERENCES AND NOTES

[1] Part **XXIX**: T. Watanabe, H. Takahashi, H. Kamakura, S. Sakaguchi, M. Osaki, S. Toyama, Y. Mizuma, I. Ueda and Y. Murakami, *Chem. Pharm. Bull.*, **39**, 3145 (1991); Part **XXX**: M. Tani, H. Ikegami, M. Tashiro, T. Hiura, H. Tsukioka, C. Kaneko, T. Notoya, M. Shimizu, M. Uchida, Y. Aida, Y. Yokoyama and Y. Murakakami, *Heterocycles*, **34**, 2349 (1992).

[2] R. Livingstone, in Rodd's Chemistry of Carbon Compounds, Vol. **IV**, Part **A**, Heterocyclic Compounds, S. Coffey, ed, Elsevier, Amsterdam, 2nd Ed, 1973, p 492.

[3] Y. Murakami, T. Watanabe and H. Ishii, *J. Chem. Soc., Perkin Trans. I*, 3005 (1988).

[4] Y. Murakami, T. Watanabe, M. Sakai and Y. Yokoyama, *Chem. Pharm. Bull.*, **36**, 3732 (1988).

[5] Y. Murakami, M. Tani, T. Ariyasu, C. Nishiyama, T. Watanabe and Y. Yokoyama, *Heterocycles*, **27**, 1855 (1988).

[6] O. Süs, M. Glos, K. Möller and H.-D. Eberhardt, *Liebigs Ann. Chem.*, **583**, 150 (1953).

[7] T. Sakamoto, Y. Kondo and H. Yamanaka, *Heterocycles*, **24**, 1845 (1986).

[8] S. Omura, A. Nakagawa, H. Yamada, T. Hata, A. Furusaki and T. Watanabe, *Chem. Pharm. Bull.*, **21**, 931 (1973).

[9] G. Malesani, M. G. Ferlin and S. Masiero, *J. Heterocyclic Chem.*, **19**, 633 (1982).

[10] W. C. Terry, A. H. Jackson, G. W. Kenner and G. Kornis, *J. Chem. Soc.*, 4389 (1965).