Indole Esters as Heterocyclic Synthons. II [1]. Preparation of 1,3-Oxazino[5,6-*b*]indoles and 3-Substituted-pyrano[3,2-*b*]indoles

Paul C. Unangst* and Richard E. Brown

Warner-Lambert/Parke-Davis Pharmaceutical Research,
Ann Arbor, Michigan 48105

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A number of novel 1,3-oxazino[5,6-*b*]indoles and 2-oxo- or 4-oxopyrano[3,2-*b*]indoles containing # 3-position substituents were prepared. Starting materials were 3-hydroxy-indole-2-carboxylic acid esters in which the # 2-position ester function is converted to carboxamide, β-ketoester, or β-ketosulfone.

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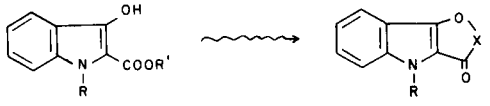
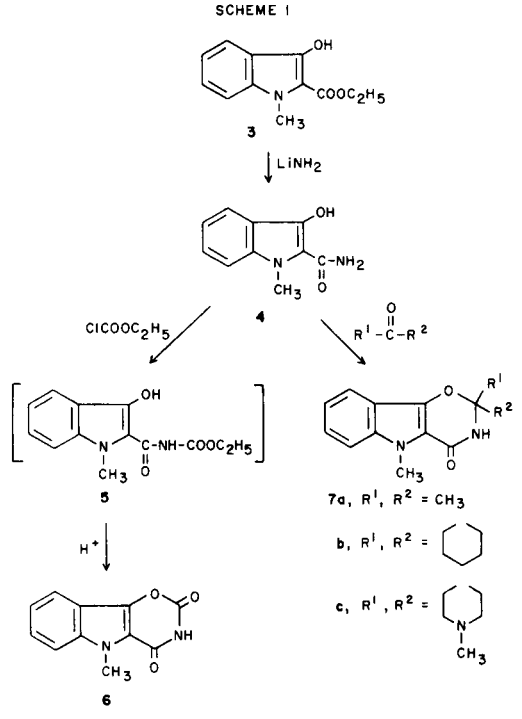
3-Hydroxy-indole-2-carboxylic acid derivatives **1** represent a well-known and readily-prepared chemical class. Surprisingly, only a few examples have been reported where compounds of type **1** serve as synthons for fused heterocycles **2** incorporating the original # 3-position oxygen atom [1-4].



1 2

We have continued to investigate the use of **1** in the preparation of compounds of potential pharmaceutical interest. We describe here the preparation of the novel 1,3-oxazino[5,6-*b*]indole ring system, as well as additional new examples of the pyrano[3,2-*b*]indol-2-one [5] and pyrano-[3,2-*b*]indol-4-one [1] chemical series.

SCHEME I



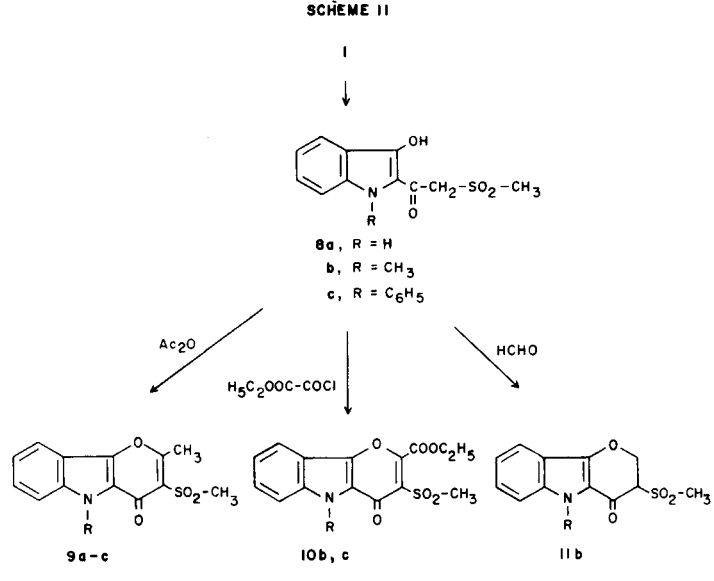
The indole ester **3** [2] was readily converted to the enolic amide **4** by treatment with lithium amide in tetrahydrofuran/liquid ammonia (Scheme I). Amide **4** was a convenient starting material for the preparation of several oxazino-[5,6-*b*]indoles, analogous to the chemistry observed with 2-hydroxybenzamide (salicylamide) [6].

Amide **4** reacted with ethyl chloroformate in pyridine, and the crude intermediate **5** was cyclized in refluxing xylene under a stream of gaseous hydrogen chloride [7] to yield the 1,3-oxazino[5,6-*b*]indole **6**.

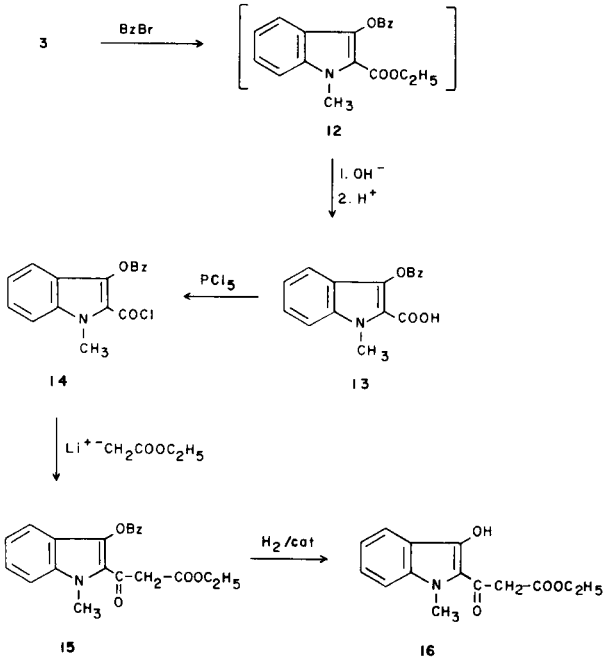
The dimethyl-1,3-oxazino[5,6-*b*]indole **7a** and the spiro-[1,3-oxazino[5,6-*b*]indoles] **7b** and **7c** were obtained, respectively, from the reaction of amide **4** with acetone, cyclohexanone, and 1-methyl-4-piperidone. "Polyphosphate ester" was employed as both catalyst and dehydrating reagent for the reactions [8].

Three indole methylsulfonyl ketones **8a-c** were prepared from esters of type **1** as previously described [9]. Ketones **8a-c** were used to prepare a variety of pyrano[3,2-*b*]-indol-4-ones containing a methylsulfonyl substituent in the # 3-position of the pyran ring (Scheme II).

SCHEME II



SCHEME III



Reaction of **8a-c** with acetic anhydride in pyridine yielded the 2-methyl derivatives **9a-c**, while carbethoxy derivatives **10b,c** were obtained by reaction of **8b,c** with ethyl oxalyl chloride in pyridine. Ester **10b** was unreactive to attempted hydrolysis to the corresponding carboxylic acid under acidic conditions. Attempted base hydrolysis resulted in cleavage of the pyran ring and isolation of precursor **8b** as the principle product.

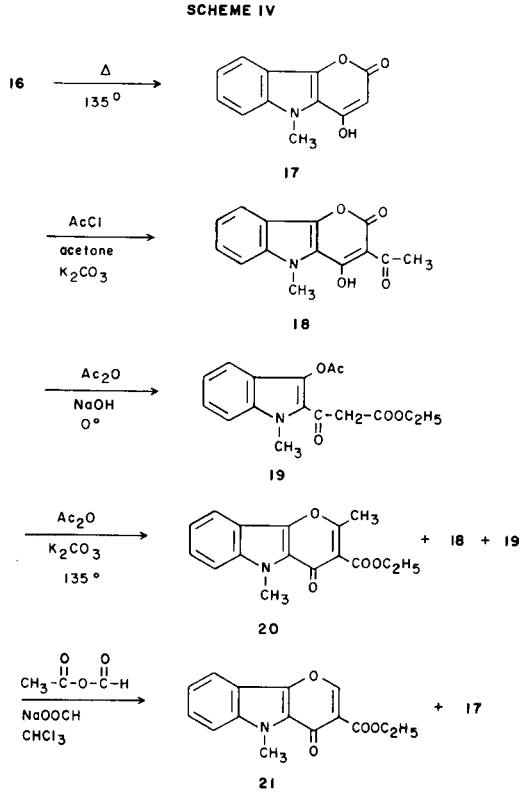
The dihydropyrano[3,2-*b*]indole **11b** was obtained by the reaction of **8b** with one equivalent of aqueous formaldehyde.

A versatile β-keto ester **16** was prepared by a multi-step homologation of enol ester **3** (Scheme III). Treatment of **3** with benzyl bromide in acetone yielded the benzyl ether **12** as an oil. Saponification of **12** and reaction of the resulting acid **13** with phosphorus pentachloride gave the acyl chloride **14** as a solid. Low temperature alkylation of **14** with the lithium salt of ethyl acetate in tetrahydrofuran [10] provided a good yield of the benzyl-protected β-keto ester **15**. Catalytic debenzylation of **15** then yielded the final enolic ester **16**.

A number of 2-oxo- or 4-oxopyrano[3,2-*b*]indoles were prepared by Kostanecki-type reaction [11] from ester **16** (Scheme IV). Cyclization of **16** with acetic anhydride or acetic formic anhydride [12] provided the 3-carbethoxypyranoindoles **20** and **21**, respectively, as well as several by-products.

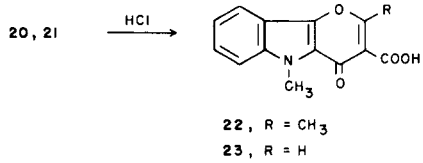
During the conversion of **16** to **21** (obtained in 40% yield), there was also obtained the 2-oxopyranoindole **17** (27% yield), probably resulting from intramolecular cyclization of ester **16**. In fact, **17** was obtained in moderate yield by heating **16** alone in xylene.

SCHEME IV

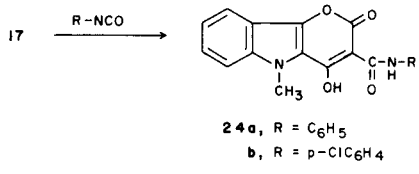


Similarly, in the conversion of **16** to **20** (40% yield), there was also obtained by-product **18** (21% yield) and probable intermediate **19** (10% yield). Compounds **18** and **19** were prepared separate from **20** in high yield *via* acetylation of **16** under alternate conditions (*cf.* Experimental).

The chemistry of the cyclization products of ester **16** was investigated briefly. Esters **20** and **21** were hydrolysed under acidic conditions to the corresponding carboxylic acids **22** and **23**.



The 2-oxopyranoindole **17** reacted with several isocyanates to yield amides **24a** and **24b**, analogous to results observed in the literature with 4-hydroxycoumarin [13].



We have described a number of examples in which 3-hydroxyindole-2-carboxylic acid derivatives **1** function as starting materials for the preparation of novel indole-fused heterocycles.

EXPERIMENTAL

Melting points were determined on a Thomas-Hoover capillary apparatus and are uncorrected. Infrared spectra were recorded on a Beckman DK-I spectrophotometer as Nujol mulls, except for compounds **7a** and **24a**, which were recorded on a Digilab FTS-14 spectrophotometer as potassium bromide disks. The nmr spectra were recorded on a Perkin-Elmer R-12B spectrometer at 60 MHz, except for compounds **7b, 18**, and **24a**, which were recorded on a Varian EM-390 spectrometer at 90 MHz, and compounds **7c** and **24b**, recorded on a Varian XL-200 spectrometer at 200 MHz.

Microanalyses and spectra were obtained by the Analytical Chemistry staff of Warner-Lambert Company under the direction of Mrs. U. Zeek and Dr. C. Greenough.

3-Hydroxy-1-methyl-1*H*-indole-2-carboxamide (**4**).

A flask fitted with a Dewar condenser containing dry ice/acetone was cooled in a dry ice/acetone bath and charged with 200 ml of anhydrous ammonia. A few crystals of hydrated ferric nitrate catalyst were added, and the cooling bath was removed. Lithium amide was then generated by the addition, over one hour, of 3.3 g (0.48 mole) of freshly cut lithium metal ribbon. After the addition of 80 ml of cold tetrahydrofuran, a solution of 32.9 g (0.15 mole) of ester **3** [2] in 250 ml of tetrahydrofuran was added over 45 minutes. The mixture was cooled and stirred for an additional 90 minutes and then for 16 hours with the Dewer condenser replaced with a water condenser, allowing excess ammonia to evaporate. After addition to 1.3 kg ice/water and filtration to remove a small amount of insoluble material, the filtrate was acidified with 3.0 *N* hydrochloric acid to precipitate the amide product (22.4 g, 79% crude yield). Recrystallization from aqueous ethanol yielded analytically pure amide **4** (19.5 g, 69% yield) containing 1.0 equivalent of water, mp 100° dec; ir: ν 3462, 3350, 1653, 1508, 728 cm^{-1}; nmr (DMSO-d_6): δ 3.38 (s, 2H, NH_2), 3.93 (s, 3H, NCH_3), 6.77-7.60 (m, 3H, Ar*H*), 7.60-8.00 (m, 1H, #4 Ar*H*), 10.33 (broad s, 1H, O*H*).

Anal. Calcd. for $C_{10}H_{10}N_2O_2 \cdot H_2O$: C, 57.68; H, 5.81; N, 13.46. Found: C, 57.94; H, 5.89; N, 13.41.

5-Methyl-1,3-oxazino[5,6-*b*]indole-2,4(3*H*,5*H*)-dione (**6**).

A solution of 7.0 g (0.034 mole) of amide **4** in 70 ml of pyridine was cooled in ice and treated with 8.4 g (7.4 ml, 0.078 mole) of ethyl oxalyl chloride over 15 minutes. The mixture was then warmed on the steam bath for 2 hours, cooled, and added to 300 g ice/water. After filtration, the insoluble material (5.2 g) was shown by thin-layer chromatography to be a two-component mixture composed of the cyclized oxazine product **6** and presumed intermediate **5**. The cyclization was completed by suspending the total crude product mixture in 150 ml of xylene, heating to reflux, adding excess gaseous hydrogen chloride, and distilling off the solvent and the ethanol formed on cyclization. The flask residue after distillation was recrystallized from 2-propanol/*N,N*-dimethylformamide to yield the oxazine product **6** (3.6 g, 87% crude yield). A sample recrystallized as above several additional times yielded analytically pure **6**, mp 280° dec; ir: ν 3170, 3080, 1791, 1768, 1313 cm^{-1}; nmr (trifluoroacetic acid): δ 4.14 (s, 3H, CH_3), 7.08-8.12 (m, 4H, Ar*H*).

Anal. Calcd. for $C_{11}H_8N_2O_3$: C, 61.12; H, 3.73; N, 12.96. Found: C, 60.87; H, 3.72; N, 13.05.

5′-Methylspiro[cyclohexane-1,2′(3′*H*)[1,3]oxazino[5,6-*b*]indol]-4′(5′*H*)-one (**7b**).

A suspension of 2.0 g (0.0096 mole) of amide **4** and 1.1 g (0.011 mole) of cyclohexanone in 20 ml of chloroform was treated with a solution of 8.7 g (0.020 mole) of "polyphosphate ester" [8] in 10 ml of chloroform. The mixture was stirred at reflux under a nitrogen atmosphere for 21 hours. After evaporation of the solvent, the residue was extracted with cold 10% aqueous sodium hydroxide. The insoluble material was filtered, washed with cold water, and recrystallized from aqueous 2-propanol to yield the spiro-oxazine product **7b** in analytical purity (1.5 g, 57% yield), mp 220-222°; ir: ν 3208, 3090, 1667, 1318, 733 cm^{-1}; nmr (trifluoroacetic acid): δ 1.29-2.23 (m, 8H, CH_2), 2.23-2.70 (m, 2H, CH_2), 3.90 (s, 3H, NCH_3), 6.96-7.90 (m, 4H, Ar*H*).

Anal. Calcd. for $C_{16}H_{18}N_2O_2$: C, 71.09; H, 6.71; N, 10.36. Found: C, 70.82; H, 6.77; N, 10.16.

1′,5′-Dimethylspiro[1,3-oxazino[5,6-*b*]indole-2,4′-piperidine]-4(3*H*)-one (**7c**).

The title compound was prepared by the procedure employed in the preparation of **7b**. From 6.7 g (0.032 mole) of amide **4** and 4.2 g (0.040 mole) of 1-methyl-4-piperidone there was obtained 5.6 g (61% yield) of analytically pure **7c**, mp 205° dec; ir: ν 3178, 3055, 1670, 1308, 737 cm^{-1}; nmr (trifluoroacetic acid): δ 2.33-2.67 (m, 2H, CH_2), 2.93-3.13 (m, 2H, CH_2), 3.19 (s, 3H, NCH_3), 3.43-3.90 (m, 4H, CH_2), 4.00 (s, 3H, indole NCH_3), 7.13-7.90 (m, 4H, Ar*H*).

Anal. Calcd. for $C_{16}H_{19}N_3O_2$: C, 67.34; H, 6.71; N, 14.73. Found: C, 67.18; H, 6.67; N, 14.58.

2,3-Dihydro-2,2,5-trimethyl-1,3-oxazolo[5,6-*b*]indol-4(5*H*)-one (**7a**).

The title compound was prepared by the procedure employed in the preparation of **7b**, except that the ketone (acetone) reagent was employed in 4-fold excess and heating time was increased to 45 hours. From 10.0 g (0.048 mole) of amide **4** there was obtained 6.7 g (61% yield) of crude product **7a**. A sample recrystallized several times from aqueous 2-propanol yielded analytically pure oxazine **7a**, mp 188-191°; ir: ν 3195, 1668, 1511, 1378, 745 cm^{-1}; nmr (deuteriochloroform): δ 1.82 (s, 6H, CCH_3), 4.07 (s, 3H, NCH_3), 6.67-7.93 (m, 4H, Ar*H*).

Anal. Calcd. for $C_{13}H_{14}N_2O_2$: C, 67.81; H, 6.13; N, 12.17. Found: C, 67.79; H, 6.20; N, 12.05.

2,5-Dimethyl-3-(methylsulfonyl)pyrano[3,2-*b*]indol-4(5*H*)-one (**9b**).

A suspension of 8.0 g (0.030 mole) of indole sulfone **8b** [9] in 80 ml of pyridine was treated with 8.6 g (8.0 ml, 0.084 mole) of acetic anhydride. The mixture was stirred at reflux under a nitrogen atmosphere for 6 hours, cooled, and added to 500 g ice/water. The aqueous mixture was filtered, and the filtrate was acidified with 4.0 *N* hydrochloric acid. The precipitated crude pyrone **9b** was filtered, washed with water, and recrystallized twice form acetonitrile to yield the analytically pure product **9b** (5.2 g, 60% yield), mp 253.5-256°; ir: ν 1638, 1315, 1147, 967, 745 cm^{-1}; nmr (deuteriochloroform): δ 2.98 (s, 3H, CCH_3), 3.46 (s, 3H, SCH_3), 4.18 (s, 3H, NCH_3), 7.08-7.62 (m, 3H, Ar*H*), 7.71-8.05 (m, 1H, #9 Ar*H*).

Anal. Calcd. for $C_{14}H_{13}NO_4S$: C, 57.72; H, 4.50; N, 4.81; S, 11.01. Found: C, 58.01; H, 4.61; N, 4.82; S, 11.26.

2-Methyl-3-(methylsulfonyl)-5-phenylpyrano[3,2-*b*]indol-4(5*H*)-one (**9c**).

The title compound was prepared by the procedure employed in the preparation of **9b**. From 3.1 g (0.0094 mole) of indole sulfone **8c** [9] and 3.2 g (3.0 ml, 0.032 mole) of acetic anhydride there was obtained 1.6 g (49% yield) of analytically pure **9c**, mp 257-259°; ir: ν 1640, 1441, 1313, 1139, 742 cm^{-1}; nmr (DMSO-d_6): δ 2.96 (s, 3H, CCH_3), 3.34 (s, 3H, SCH_3), 7.09-7.88 (m, 8H, Ar*H*), 7.88-8.22 (m, 1H, #9 Ar*H*).

Anal. Calcd. for $C_{19}H_{15}NO_4S$: C, 64.58; H, 4.28; N, 3.96; S, 9.07. Found: C, 64.56; H, 4.35; N, 4.03; S, 9.13.

2-Methyl-3-(methylsulfonyl)pyrano[3,2-*b*]indol-4(5*H*)-one (**9a**).

The title compound was prepared by the procedure employed in the preparation of **9b**, except that the heating time was increased to 37 hours. From 5.0 g (0.020 mole) of indole sulfone **8a** [9] and 5.4 g (5.0 ml, 0.053 mole) of acetic anhydride there was obtained, after one recrystallization from acetonitrile, 1.3 g (24% purified yield) of partially purified pyrone **9a**. A sample recrystallized a second time as above yielded **9a** in analytical purity, mp >300°; ir: ν 3183, 1627, 1307, 1140, 751 cm^{-1}; nmr (DMSO-d_6): δ 2.90 (s, 3H, CCH_3), 3.42 (s, 3H, SCH_3), 7.18-7.72 (m, 3H, Ar*H*), 7.75-8.15 (m, 1H, #9 Ar*H*), 12.25 (broad s, 1H, N*H*).

Anal. Calcd. for $C_{13}H_{11}NO_4S$: C, 56.31; H, 4.00; N, 5.05; S, 11.56.

Found: C, 56.10; H, 4.11; N, 5.24; S, 11.38.

Ethyl 4,5-Dihydro-5-methyl-3-(methylsulfonyl)-4-oxopyrano[3,2-*b*]indole-2-carboxylate (**10b**).

A solution of 10.0 g (0.038 mole) of indole sulfone **8b** [9] in 100 ml of pyridine was cooled in an ice bath and treated with 10.8 g (9.0 ml, 0.079 mole) of ethyl oxalyl chloride over 1 hour. The mixture was stirred at room temperature for 16 hours, warmed on the steam bath for 30 minutes, cooled, and added to 400 g ice/water. The insoluble material was filtered and washed well with water to yield 9.3 g (71% crude yield) of ester **10b**. A sample recrystallized several times from acetonitrile/hexane yielded analytically pure **10b**, mp 219-220°; ir: ν 1753, 1657, 1322, 1155, 970 cm^{-1}; nmr (trifluoroacetic acid): δ 1.60 (t, 3H, J = 7.5 Hz, CH_2CH_3), 3.67 (s, 3H, SCH_3), 4.28 (s, 3H, NCH_3), 4.73 (q, 2H, J = 7.5 Hz, CH_2CH_3), 7.22-7.83 (m, 3H, Ar*H*), 7.83-8.18 (m, 1H, #9 Ar*H*).

Anal. Calcd. for $C_{16}H_{15}NO_6S$: C, 55.01; H, 4.33; N, 4.01; S, 9.18. Found: C, 55.18; H, 4.44; N, 3.93; S, 9.07.

Ethyl 4,5-Dihydro-3-(methylsulfonyl)-4-oxo-5-phenylpyrano[3,2-*b*]indole-2-carboxylate (**10c**).

The title compound was prepared by the procedure employed in the preparation of **10b**. From 3.5 g (0.011 mole) of indole sulfone **8c** [9] and 3.1 g (2.5 ml, 0.022 mole) of ethyl oxalyl chloride there was obtained 2.6 g (59% crude yield) of ester **10c**. A sample recrystallized twice from aqueous acetone yielded analytically pure **10c**, mp 221-223°; ir: ν 1749, 1657, 1325, 1251, 742 cm^{-1}; nmr (deuteriochloroform): δ 1.46 (t, 3H, J = 7.5 Hz, CH_2CH_3), 3.36 (s, 3H, SCH_3), 4.55 (t, 2H, J = 7.5 Hz, CH_2CH_3), 7.12-7.72 (m, 8H, Ar*H*), 7.82-8.13 (m, 1H, #9 Ar*H*).

Anal. Calcd. for $C_{21}H_{17}NO_6S$: C, 61.31; H, 4.17; N, 3.40; S, 7.79. Found; C, 61.35; H, 4.22; N, 3.36; S, 7.89.

2,3-Dihydro-5-methyl-3-(methylsulfonyl)pyrano[3,2-*b*]indol-4(5*H*)-one (**11b**).

A suspension of 1.4 g (0.0052 mole) of indole sulfone **8b** [9] and 0.45 g (0.0054 mole) of 36% aqueous formaldehyde solution in 35 ml of methanol was treated with 3 drops of triethylamine. The mixture was stirred at reflux for 17 hours, cooled in ice, and the precipitated product was filtered and washed with cold ether. Pyrone **11b** thus obtained (0.88 g, 44% crude yield) was recrystallized from ethanol to yield analytically pure **11b** (0.51 g, 25% yield), mp 205-207°; ir: ν 1653, 1509, 1307, 1132, 752 cm^{-1}; nmr (DMSO-d_6): δ 3.26 (s, 3H, SCH_3), 4.02 (s, 3H, NCH_3), 4.78-5.50 (m, 2H, CH_2), 6.93-7.43 (m, 1H, C*H*), 7.43-7.92 (m, 4H, Ar*H*).

Anal. Calcd. for $C_{13}H_{13}NO_4S$: C, 55.90; H, 4.69; N, 5.02; S, 11.48. Found: C, 55.91; H, 4.82; N, 4.90; S, 11.48.

Ethyl 1-Methyl-3-(phenylmethoxy)-1*H*-indole-2-carboxylate (**12**).

A mixture of 45.5 g (0.21 mole) of indole ester **3** [2], 33.1 g (0.24 mole) of anhydrous potassium carbonate, and 38.4 g (26.7 ml, 0.22 mole) of benzyl bromide in 900 ml of acetone was stirred at reflux for 18 hours. The mixture was cooled and filtered, and the inorganic filter cake was washed several times with fresh acetone. The combined acetone filtrates were evaporated (vacuum) to yield the crude benzyl ester **12** as an oil. The crude product was converted to acid **13** without additional purification.

1-Methyl-3-(phenylmethoxy)-1*H*-indole-2-carboxylic Acid (**13**).

The total crude ester **12** obtained as described above, was treated with 450 ml of 50% aqueous ethanol followed by 70 g (0.63 mole OH^-) of 50% aqueous potassium hydroxide solution. The mixture was stirred at reflux for 4 hours, cooled, and added to 600 g ice/water. After washing with ether (3 × 300 ml, washed discarded), the aqueous layer was filtered, cooled in ice, and acidified to *p*H 3 with 4.0 *N* hydrochloric acid. The precipitated product was filtered and washed with cold water to yield 37.3 g (64% crude yield) of acid **13**, mp 110-113°. A sample recrystallized from carbon tetrachloride yielded analytically pure **13**, mp 117-118°; ir: ν 1670, 1520, 1335, 1278, 744 cm^{-1}; nmr (deuteriochloroform): δ 4.00 (s, 3H, NCH_3), 5.43 (s, 2H, CH_2), 6.81-8.02 (m, 9H, Ar*H*), 8.78 (broad s, 1H, COO*H*).

Anal. Calcd. for $C_{17}H_{15}NO_3$: C, 72.58; H, 5.37; N, 4.98. Found: C, 72.47; H, 5.48; N, 5.16.

1-Methyl-3-(phenylmethoxy)-1*H*-indole-2-carbonyl Chloride (**14**).

A solution of 29.0 g (0.14 mole) of phosphorus pentachloride in 550 ml of benzene was treated over 15 minutes with 39.0 g (0.14 mole) of acid **13**. The mixture was stirred at room temperature for two hours, and the solvent was removed under reduced pressure. The residue was treated twice with 200 ml of fresh benzene and reevaporated. Recrystallization of the final residue from hexane yielded acid chloride **14** (27.3 g, 66% purified yield), mp 93-96°. An additional recrystallization yielded an analytically pure sample of **14**, mp 99-100°; ir: ν 1715, 1507, 1410, 1251, 922 cm^{-1}; nmr (deuteriochloroform): δ 3.88 (s, 3H, NCH_3), 5.30 (s, 2H, CH_2), 6.57-8.07 (m, 9H, Ar*H*).

Anal. Calcd. for $C_{17}H_{14}ClNO_2$: C, 68.12; H, 4.71; N, 4.67; Cl, 11.83. Found: C, 68.25; H, 4.76; N, 4.61; Cl, 11.82.

Ethyl 1-Methyl-β-oxo-3-(phenylmethoxy)-1*H*-indole-2-propanoate (**15**).

A solution of 48.0 g (0.34 mole) of *N*-isopropylcyclohexylamine in 350 ml of dry tetrahydrofuran was treated under nitrogen atmosphere with 144 ml (0.35 mole) of 2.4 *N* *n*-butyllithium in hexane, added over 45 minutes. The reaction mixture was cooled to −78°, and 14.6 g (0.17 mole) of freshly distilled ethyl acetate in 45 ml of tetrahydrofuran was added over 15 minutes, followed by a solution of 49.6 g (0.17 mole) of acyl chloride **14** in 350 ml of tetrahydrofuran, added over 45 minutes (reaction temperature rose to −65°).

After stirring an additional 15 minutes, 350 ml of 6.0 *N* hydrochloric acid was added over 1 hour to quench remaining organo-lithium compounds (temperature rose to ≤ −50°). The cooling bath was removed, and stirring was continued while the mixture warmed gradually to 0°. Water (500 ml) was added, and the two-phase mixture was separated. The aqueous layer was washed with ether (2 × 300 ml), and the combined ether washes were added to the original organic layer. The new organic layer was washed with 5% sodium bicarbonate (3 × 300 ml), water (1 × 300 ml), dried (magnesium sulfate), and evaporated to an oil. Several days standing in the cold yielded yellow cubes of benzylated β-keto ester **15**, removed with the aid of a small amount of cold hexane (50.2 g, 87% crude yield). A sample recrystallized from aqueous methanol yielded analytically pure **15**, mp 48-50°; ir: ν 1738, 1650, 1323, 1188, 743 cm^{-1}; nmr (deuteriochloroform): δ 1.21 (t, 3H, J = 7.5 Hz, CH_2CH_3), 4.00 (s, 5H, NCH_3 and $COCH_2CO$), 4.12 (q, 2H, J = 7.5 Hz, CH_2CH_3), 5.4 (s, 2H, benzyl CH_2), 6.87-7.60 (m, 8H, Ar*H*), 7.60-7.93 (m, 1H, #4 Ar*H*).

Anal. Calcd. for $C_{21}H_{21}NO_4$: C, 71.78; H, 6.02; N, 3.99. Found: C, 71.77; H, 6.10; N, 3.96.

Ethyl 3-Hydroxy-1-methyl-β-oxo-1*H*-indole-2-propanoate (**16**).

A solution of 18.0 g (0.051 mole) of the benzyl ether **15** in 220 ml of methanol was hydrogenated for 2.5 hours (1.0 g of 10% Pd/C catalyst; initial hydrogen pressure 40 psig). Removal of the catalyst by filtration and evaporation of the filtrate left an oil which quickly crystallized. Recrystallization from aqueous ethanol followed by an additional recrystallization from chloroform/hexane yielded analytically pure enol ester **16** containing 0.50 equivalent of water (8.0 g, 60% yield), mp 107-110°; ir: ν 3290, 1730, 1613, 1327, 732 cm^{-1}; nmr (deuteriochloroform): δ 1.32 (t, 3H, J = 7.5 Hz, CH_2CH_3), 3.84 (s, 3H, NCH_3), 4.03 (s, 2H, $COCH_2CO$), 4.29 (q, 2H, J = 7.5 Hz, CH_2CH_3), 6.85-7.57 (m, 3H, Ar*H*), 7.57-8.00 (m, 1H, #4 Ar*H*), 10.20 (broad s, 1H, O*H*).

Anal. Calcd. for $C_{14}H_{15}NO_4 \cdot 0.5H_2O$: C, 62.21; H, 5.97; N, 5.18. Found: C, 62.42; H, 6.09; N, 5.12.

4-Hydroxy-5-methylpyrano[3,2-*b*]indol-2(5*H*)-one (**17**).

A suspension of 12.7 g (0.048 mole) of enol ester **16** in 200 ml of xylene was stirred at reflux for two hours. The mixture initially became one phase, and then a precipitate began to appear after ~30 minutes heating time. The mixture was cooled, and the crude product was filtered and recrystallized from aqueous methanol to yield analytically pure pyrone **17** (5.6 g, 54% yield), mp 250° dec; ir: ν 3090, 1662, 1637, 1395, 834 cm^{-1}; nmr (trifluoroacetic acid): δ 4.12 (s, 3H, NCH_3), 6.47 (s, 1H, C*H*=),

7.12-8.12 (m, 4H, Ar*H*).

Anal. Calcd. for $C_{12}H_9NO_3$: C, 66.97; H, 4.22; N, 6.51. Found: C, 66.78; H, 4.23; N, 6.42.

3-Acetyl-4-hydroxy-5-methylpyrano[3,2-*b*]indol-2(5*H*)-one (**18**).

A mixture of 6.4 g (0.024 mole) of enol ester **16** and 3.5 g (0.025 mole) of potassium carbonate in 125 ml of acetone was treated in one portion with 2.0 g (1.8 ml, 0.025 mole) of acetyl chloride. The mixture was stirred at reflux for 19 hours, cooled, and filtered. The insoluble material was washed several times with fresh acetone, then dissolved in 550 ml of water. After acidification of the aqueous solution with 3.0 *N* hydrochloric acid, the precipitated crude pyrone **18** was filtered and washed with cold water. There was obtained 5.0 g (82% crude yield) of **18**, mp 200-204°. A sample recrystallized from chloroform/hexane yielded analytically pure **18**, mp 214-216°; ir: ν 1715, 1593, 1253, 908, 757 cm^{-1}; nmr (deuteriochloroform): δ 2.73 (s, 3H, CCH_3), 4.03 (s, 3H, NCH_3), 6.95-7.58 (m, 3H, Ar*H*), 7.60-7.91 (m, 1H, #9 Ar*H*), 18.36 (s, 1H, O*H*).

Anal. Calcd. for $C_{14}H_{11}NO_4$: C, 65.36; H, 4.31; N, 5.45. Found: C, 65.36; H, 4.47; N, 5.43.

Ethyl 3-(Acetyloxy)-1-methyl-β-oxo-1*H*-indole-2-propanoate (**19**).

A solution of 7.2 g (0.028 mole) of enol ester **16** in a minimum of ice-cold 0.5% aqueous sodium hydroxide (~400 ml) was stirred and treated dropwise with acetic anhydride until a *p*H of 3-4 persisted. The mixture was then stirred in ice for an additional three hours, and the crude product **19** was filtered and washed with cold water. Recrystallization from chloroform/hexane yielded 4.7 g (56% purified yield) of purified product of mp 88-91°. An additional recrystallization as above yielded analytically pure acetate **19**, mp 93-95°; ir: ν 1768, 1741, 1663, 1317, 1203 cm^{-1}; nmr (deuteriochloroform): δ 1.28 (t, 3H, J = 7.5 Hz, CH_2CH_3), 3.90 (s, 2H, $COCH_2CO$), 4.03 (s, 3H, NCH_3), 4.22 (q, 2H, J = 7.5 Hz, CH_2CH_3), 6.89-7.63 (m, 4H, Ar*H*).

Anal. Calcd. for $C_{16}H_{17}NO_5$: C, 63.36; H, 5.65; N, 4.62. Found: C, 63.31; H, 5.71; N, 4.54.

Ethyl 4,5-Dihydro-2,5-dimethyl-4-oxopyrano[3,2-*b*]indole-3-carboxylate (**20**).

A mixture of 9.0 g (0.035 mole) of enol ester **16**, 18.5 g (0.13 mole) of potassium carbonate, and 20.0 g (0.20 mole) of acetic anhydride in 170 ml of xylene was heated at 80° until no further gas evolution was evident (~15 minutes). The mixture was then stirred at reflux (~135°) for 90 minutes, cooled, and the insoluble material (1.9 g, identified as **18**) was filtered and washed with fresh xylene. The combined xylene solutions were washed several times with water, then dried (magnesium sulfate) and concentrated to 40 ml. The concentrated xylene solution was treated with an equal volume of warm hexane. Cooling yielded the crude pyrone ester **20**, mp 118-122°. Several recrystallizations from chloroform/hexane yielded analytically pure **20** (4.0 g, 40% yield), mp 125-127°; ir: ν 1742, 1637, 1341, 1089, 739 cm^{-1}; nmr (deuteriochloroform): δ 1.46 (t, 3H, J = 7.5 Hz, CH_2CH_3), 2.58 (s, 3H, CCH_3), 4.19 (s, 3H, NCH_3), 4.48 (q, 2H, J = 7.5 Hz, CH_2CH_3), 7.00-7.62 (m, 3H, Ar*H*), 7.72-8.08 (m, 1H, #9 Ar*H*).

Anal. Calcd. for $C_{16}H_{15}NO_4$: C, 67.36; H, 5.30; N, 4.91. Found: C, 67.25; H, 5.32; N, 4.90.

Further condensation of the chloroform/hexane filtrate from **20** yielded an additional product, shown by thin layer chromatography to be primarily the acetylated ester **19** (~1.0 g).

Ethyl 4,5-Dihydro-5-methyl-4-oxopyrano[3,2-*b*]indole-3-carboxylate (**21**).

A mixture of 9.1 g (0.035 mole) of enol ester **16** and 23.8 g (0.035 mole) of sodium formate in 200 ml of chloroform was cooled briefly in ice while a solution of 30.8 g (0.35 mole) of acetic formic anhydride [12] in 100 ml of chloroform was added slowly. The mixture was stirred at room temperature for 16 hours, then heated at reflux for four hours. After cooling and the addition of 200 g ice/water, the insoluble material (2.0 g, identified as **17**) was filtered and the filtrate layers were separated. The aqueous layer was washed with fresh chloroform (2 × 75 ml), and the combined organic layers were back-washed with water (2 × 150 ml), dried (magnesium sulfate), and evaporated. The residue was recrystallized twice from ethyl acetate/hexane to yield analytically pure pyrone ester **21** (3.7 g, 40% yield), mp 134-136°; ir: ν 1738, 1638, 1300, 1109, 755 cm^{-1}; nmr (deueriochloroform): δ 1.44 (t, 3H, J = 7.5 Hz, CH_2CH_3), 4.21 (s, 3H, NCH_3), 4.43 (t, 2H, J = 7.5 Hz, CH_2CH_3), 4.21 (s, 3H, NCH_3), 4.43 (t, 2H, J = 7.5 Hz), CH_2CH_3), 7.0-7.62 (m, 3H, Ar*H*), 7.73-8.05 (m, 1H, #9 Ar*H*), 8.58 (s, 1H, =C*H*).

Anal. Calcd. for $C_{15}H_{13}NO_4$: C, 66.41; H, 4.83; N, 5.18. Found; C, 66.46; H, 4.81; N, 5.06.

4,5-Dihydro-2,5-dimethyl-4-oxopyrano[3,2-*b*]indole-3-carboxylic Acid (**22**).

A mixture of 3.6 g (0.013 mole) of ester **20** in 50 ml of concentrated hydrochloric acid was stirred at 100° for 45 minutes. The mixture was cooled, poured over 200 g of ice, and the insoluble material was filtered and washed with cold water. The crude yield of acid **22** was 2.9 g (89%). A sample recrystallized several times from ethanol yielded analytically pure **22**, mp 258-259°; ir: ν 1732, 1630, 1597, 1335, 750 cm^{-1}; nmr (trifluoroacetic acid): δ 3.46 (s, 3H, CCH_3), 4.42 (s, 3H, NCH_3), 7.37-8.09 (m, 3H, Ar*H*), 8.09-8.42 (m, 1H, #9 Ar*H*).

Anal. Calcd. for $C_{14}H_{11}NO_4$: C, 65.37; H, 4.31; N, 5.44. Found: C, 65.22; H, 4.28; N, 5.31.

4,5-Dihydro-5-methyl-4-oxopyrano[3,2-*b*]indole-3-carboxylic Acid (**23**).

The title compound was prepared by the procedure employed in the preparation of **22**. From 4.3 g (0.016 mole) of ester **21** there was obtained 3.7 g of crude acid **23** (94% yield). A sample recrystallized several times from ethyl acetate yielded analytically pure **23**, mp 251° dec; ir: ν 1709, 1613, 1292, 943, 759 cm^{-1}; nmr (trifluoroacetic acid): δ 4.48 (s, 3H, NCH_3), 7.46-8.14 (m, 3H, Ar*H*), 8.14-8.50 (m, 1H, #9 Ar*H*), 9.62 (s, 1H, =C*H*).

Anal. Calcd. for $C_{13}H_9NO_4$: C, 64.20; H, 3.73; N, 5.76. Found: C, 64.03; H, 3.73; N, 5.71.

N-(4-Chlorophenyl)-2,5-dihydro-4-hydroxy-5-methyl-2-oxopyrano[3,2-*b*]-indole-3-carboxamide (**24b**).

A mixture of 1.0 g (0.0047 mole) of pyrone **17** in 10 ml of dimethyl sulfoxide was treated with 0.49 g (0.67 ml, 0.0048 mole) of triethylamine followed by 0.73 g (0.0048 mole) of 4-chlorophenyl isocyanate. The mixture was stirred at room temperature for 24 hours, then added to 30 ml of ice-cold 4.0 *N* hydrochloric acid. The precipitated crude product **24a** was filtered, washed with cold water, and recrystallized from 2-propanol/*N*,*N*-dimethylformamide to yield 0.74 g (43% yield) of purified product. A sample recrystallized again as above yielded analytically pure amide **24b**, mp 256-258°; ir: ν 3130, 1680, 1558, 1343, 828 cm^{-1}; nmr (DMSO-d_6): δ 4.06 (s, 3H, NCH_3), 7.20-7.81 (m, 3H, Ar*H*), 7.81-7.97 (m, 1H, #9 Ar*H*), 11.37 (s, 1H, N*H*).

Anal. Calcd. for $C_{19}H_{13}ClN_2O_4$: C, 61.88; H, 3.55; N, 7.60; Cl, 9.61. Found: C, 61.81; H, 3.52; N, 7.52; Cl, 9.62.

2,5-Dihydro-4-hydroxy-5-methyl-2-oxo-*N*-phenylpyrano[3,2-*b*]indole-3-carboxamide (**24a**).

The title compound was prepared by the procedure employed in the preparation of **24b**. From 1.0 g (0.0047 mole) of pyrone **17** and 0.56 g (0.51 ml, 0.0047 mole) of phenyl isocyanate there was obtained 1.3 g (84% crude yield) of **24a**. A sample recrystallized several times from 2-propanol/*N*,*N*-dimethylformamide yielded purified amide **24a** of mp 240-242°; ir: ν 1682, 1606, 1559, 1346, 745 cm^{-1}; nmr (trifluoroacetic acid): δ 4.02 (s, 3H, NCH_3), 7.00-7.60 (m, 8H, Ar*H*), 7.60-7.86 (m, 1H, #9 Ar*H*).

Anal. Calcd. for $C_{19}H_{14}N_2O_4$: C, 68.25; H, 4.22; N, 8.38. Found: C, 67.97; H, 4.33; N, 8.60.

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