Pyrido[1′,2′:1,2]pyrimido[5,4-*d*]indoles. A New Heterocyclic Ring System

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The preparation of the novel pyrido[1′,2′:1,2]pyrimido[5,4-*b*]indole ring system is described *via* fusion at 180° of ethyl 3-amino-1*H*-indole-2-carboxylate **8a** and several 6-chloronicotinic acid derivatives. Similar fusion of **8a** and thiourea yielded a 2-mercaptopyrimido[5,4-*b*]indole **18**.

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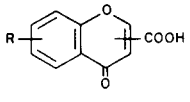
A number of compounds containing an acidic benzopyranone ("chromone") structure **1** have shown antiallergic activity (1). We have previously found that replacement of the benzene ring of acidic chromones with the indole moiety can also lead to antiallergic compounds **2** (2).



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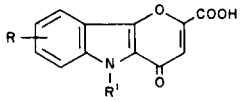
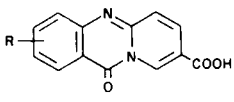


2

In view of the known antiallergic activity of pyrido[2,1-*b*]quinazolines **3** (3,4) and pyrido[1,2-*a*]thieno[3,2-*d*]pyrimidines **4** (5), we, therefore, envisioned the preparation of the hitherto unknown pyrido[1′,2′:1,2]pyrimido[5,4-*b*]indole analogs **5**.



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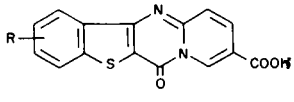

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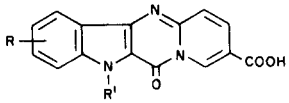
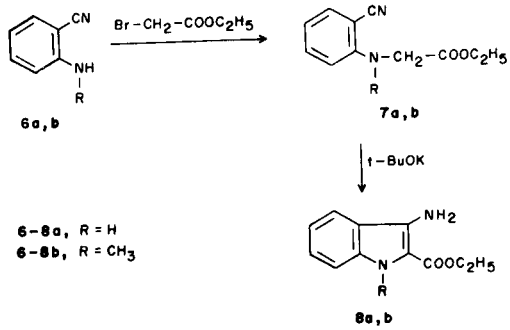


5

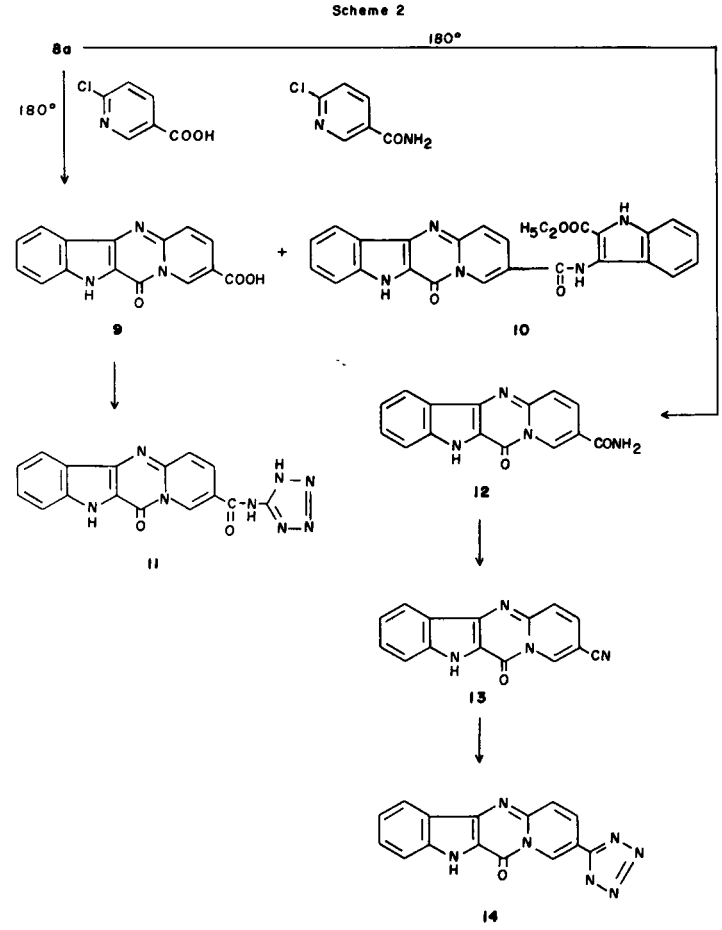
The 3-aminoindole ester **8a** (6) was found to be a convenient precursor to the desired pyridopyrimidoindole ring system. The ester was prepared in moderate yield by Thorpe cyclization of the nitrile ester **7a**, obtained by alkylation of 2-aminobenzonitrile **6a** (Scheme 1).

Scheme 1



Ester **8a** was fused at 180° with 6-chloronicotinic acid in the absence of solvent to afford the desired tetracyclic acid **9**, plus an additional product **10**, probably formed by condensation of **9** with an additional equivalent of the starting ester **8a** (Scheme 2).

Scheme 2



Carboxylic acid **9** was converted to the acidic carboxamidotetrazole **11** by means of 1*H*-tetrazol-5-amine monohydrate and the coupling reagent, 1,1'-carbonyldiimidazole.

The fusion of ester **8a** with 6-chloronicotinamide similarly yielded the tetracyclic-amide **12**. The amide was dehydrated to nitrile **13** with *p*-toluenesulfonyl chloride and pyridine in *N,N*-dimethylformamide. Conversion of nitrile **13** to the acidic tetrazole **14** was accomplished with sodium azide and ammonium chloride in refluxing *N,N*-dimethylformamide.

The preparation of compounds of type **5** containing an alkyl substituent on the indole nitrogen was postulated *via* a fusion reaction with indole ester **8b**. However, 2-(methylamino)benzonitrile **6b** (7) could not be conveniently converted to **8b** under a variety of reaction conditions. In one instance, ester-nitrile **7b** was obtained as an oil which was converted in poor yield to the desired ester **8b**.

As an alternative route to the desired *N*-alkyl derivative, ester **8a** was fused with methyl 6-chloronicotinate to yield the tetracyclic ester **15** (Scheme 3). Methylation of the indole nitrogen of **15** was accomplished with iodomethane and sodium hydride in *N,N*-dimethylformamide. The resulting *N*-methyl ester **16** was hydrolysed under acidic conditions to yield the desired *N*-methyl acid **17**.

Attempted preparation of **17** by alkylation of acid **9** gave a complex mixture, possibly due to concommitant esterification of the carboxylic acid function of **9** in addition to alkylation of the indole nitrogen.

A final fusion reaction of **8a** with thiourea yielded the pyrimido[5,4-*b*]indole **18**, thus offering access to a little-described heterocyclic system of potential pharmaceutical interest.

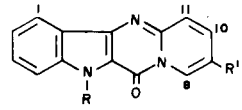
Analytical data for the pyrido[1',2':1,2]pyrimo[5,4-*b*]indoles prepared are summarized in Table I. Specral data are summarized in Table II.

The nmr spectra of all the pyrido[1',2':1,2]pyrimido-[5,4-*b*]indoles prepared exhibit a characteristic peak in the range of δ 9.28-9.70 (DMSO-d_6) or 10.02-10.22 (trifluoroacetic acid). This peak is distinct from the remaining aromatic proton multiplet, and represents the position #8 proton of the pyridine ring. The peak appears as a "split singlet" due to *meta*-splitting by the corresponding position #10 proton (8). In most cases, the #10 proton, appearing as a "split doublet", can also be discerned within the aromatic multiplet.

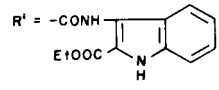
None of the compounds described showed significant activity when tested in the rat Passive Cutaneous Anaphylaxis (PCA) antiallergy assay (9).

Table I

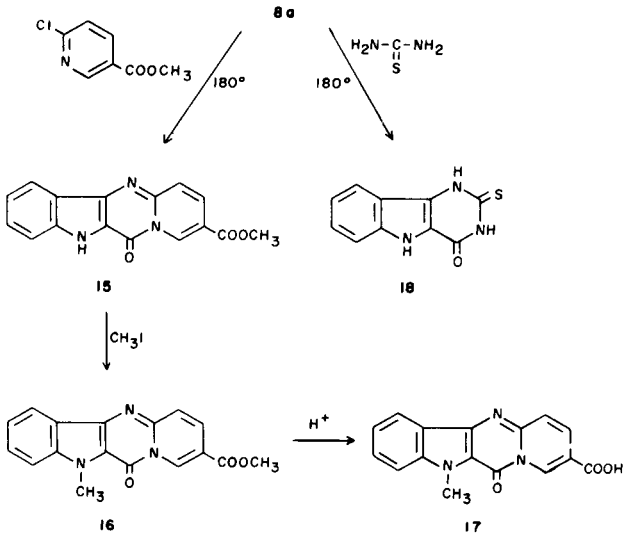
Pyrido[1',2':1,2]pyrimido[5,4-*b*]indoles



Compound No.	R	R'	Formula	Analysis Calcd. % (Found %) C	H	N
9	H	COOH	$C_{15}H_9N_3O_3$ (a)	67.03	3.94	15.64
				(67.15	3.98	15.74)
10	H	(b)	$C_{26}H_{19}N_5O_4$	67.09	4.11	15.05
				(66.69	4.42	15.31)
11	H	Tetrazole amide	$C_{16}H_{10}N_8O_2$	55.49	2.91	32.36
				(55.45	3.15	32.24)
12	H	$CONH_2$	$C_{15}H_{10}N_4O_2$	64.74	3.62	20.14
				(64.73	3.66	19.93
13	H	CN	$C_{15}H_8N_4O$ (c)	—	—	—
				—	—	—
14	H	Tetrazole	$C_{15}H_9N_7O$ (d)	56.07	3.45	30.52
				(56.12	3.69	30.80)
15	H	$COOCH_3$	$C_{16}H_{11}N_3O_3$ (e)	64.53	3.89	14.11
				(64.86	3.93	14.26)
16	CH_3	$COOCH_3$	$C_{17}H_{13}N_3O_3$	66.44	4.26	13.68
				(66.45	4.29	13.62)
17	CH_3	COOH	$C_{16}H_{11}N_3O_3$ (f)	62.29	4.95	15.29
				(62.10	4.95	15.24)

(a) Analysis Calcd. as the molecular formula + 1.0 pyridine. (b) R' = -CONH-  (c)No analytical sample was obtained. (d) Analysis Calcd. as the molecular formula + 1.0 water. (e) Analysis Calcd. as the molecular formula + 0.25 water. (f) Analysis Calcd. as the molecular formula + 1.0 *N,N*-dimethylformamide.

Scheme 3



EXPERIMENTAL

Melting points were determined in a Mel-Temp capillary apparatus and are uncorrected. The nmr spectra were recorded at 90 MHz on a Varian EM-390 or a Bruker WH-90 spectrometer, with tetramethylsilane as an internal standard. Infrared spectra were recorded on a Beckman DK-I or a Digilab FTS-14 pulsed Fourier-transform spectrophotometer as potassium bromide discs. Compound **13** was sole exception; its spectrum was determined as a Nujol mull.

Microanalyses and spectra were obtained by the Analytical Chemistry staff of Warner-Lambert Company under the direction of Dr. F. A. MacKellar.

N-(2-Cyanophenyl)glycine Ethyl Ester (**7a**).

A mixture of 400 g (3.39 moles) of 2-aminobenzonitrile (anthranilonitrile), 338 g (4.02 moles) of sodium bicarbonate, and 586 g (3.51 moles) of ethyl bromoacetate in 1200 ml of absolute ethanol was stirred at reflux for 42 hours. After cooling slightly, the clear solution was decanted from the precipitated inorganic material into a pre-warmed flask. Additional cooling yielded the product as large needles. The solid was filtered, stirred in 2.0 ℓ of cold water, and re-filtered, to yield 369 g (53% yield) of ester **7a**. A sample recrystallized from ethanol had mp 91-93°; ir: ν 3388, 2225, 1743, 1610, 1201 cm^{-1}; nmr (DMSO-d_6): δ 1.30 (t, 3H, J = 7.0 Hz, CH_2CH_3), 3.87 (d, 2H, J = 4.5 Hz, $NHCH_2$), 4.25 (q, 2H, J = 7.0 Hz, CH_2CH_3), 5.18 (broad s, 1H, NH), 6.47-6.85 (m, 2H, ArH), 7.22-7.55 (m, 2H, ArH).

Anal. Calcd. for $C_{11}H_{12}N_2O_2$: C, 64.69; H, 5.92; N, 13.72. Found: C, 64.73; H, 5.86; N, 13.82.

Ethyl 3-Amino-1*H*-indole-2-carboxylate (**8a**).

A stirred suspension of 98.8 g (0.88 mole) of potassium *t*-butoxide in 475 ml of tetrahydrofuran was maintained at ≤30° while a solution of the ester **7a** (180 g, 0.88 mole) in 700 ml of tetrahydrofuran was added over 45 minutes. The mixture was stirred for an additional two hours, and then added to 3.0 kg of ice/water. The crude product was filtered, stirred in 1500 ml cold water, and re-filtered. Recrystallization from methanol/water yielded the indole **8a** as large orange crystals of mp 150-152° (90.0 g, 50% yield); ir: ν 3448, 3345, 1650, 1620, 1255 cm^{-1}; nmr (deuteriochloroform): δ 1.41 (t, 3H, J = 7.0 Hz, CH_2CH_3), 4.40 (d, 2H, J = 7.0 Hz, CH_2CH_3), 4.73 (broad s, 2H, NH_2), 6.90-7.63 (m, 4H, ArH), 7.89 (broad s, 1H, NH).

Anal. Calcd. for $C_{11}H_{12}N_2O_2$: C, 64.69; H, 5.92; N, 13.72. Found: C, 64.85; H, 5.89; N, 13.75.

N-(2-Cyanophenyl)-*N*-methylglycine Ethyl Ester (**7b**) and Ethyl 3-Amino-1-methylindole-2-carboxylate (**8b**).

To a solution of 1.0 g (0.0072 mole) of potassium carbonate in 10 ml of water was added 0.90 g (0.0068 mole) of 2-(methylamino)benzonitrile (7) and 10 ml of ethanol. The mixture was treated with 3.9 g (2.6 ml, 0.023 mole) of ethyl bromoacetate and stirred at reflux for 96 hours. The reaction mixture was cooled, added to 100 g ice/water, and extracted with chloroform (3 × 50 ml). The combined extracts were washed with water (1 × 50 ml), dried (sodium sulfate), and evaporated to yield the crude ester **7b** as an orange oil.

Oil **7b** was dissolved in 15 ml of benzene and the solution was added over 15 minutes to a suspension of 1.0 g (0.0089 mole) of potassium *t*-butoxide in 15 ml of benzene. The reaction mixture was stirred for an additional 21 hours, then decomposed with ice and saturated aqueous ammonium chloride solution. The layers were separated, and the aqueous layer was extracted with chloroform (3 × 40 ml). The combined organic layers were back washed with water, dried (sodium sulfate), and evaporated to yield the crude indole **8b** as an oil which slowly crystallized. Recrystallization from aqueous ethanol followed by chloroform/hexane yielded 0.33 g (22% yield) of indole **8b**, mp 99-101°; ir: ν 3438, 3342, 1662, 1543, 1286 cm^{-1}; nmr (deuteriochloroform): δ 1.36 (t, 3H, J = 7.0 Hz, CH_2CH_3), 3.76 (s, 3H, NCH_3), 4.28 (q, 2H, J = 7.0 Hz, CH_2CH_3), 4.72 broad s, 2H, NH_2), 6.67-7.40 (m, 4H, ArH).

Anal. Calcd. for $C_{12}H_{14}N_2O_2$: C, 66.03; H, 6.47; N, 12.84. Found: C, 66.07; H, 6.74; N, 12.69.

5,6-Dihydro-6-oxopyrido[1′,2′:1,2]pyrimido[5,4-*b*]indole-9-carboxylic Acid (**9**).

A mixture of 7.0 g (0.034 mole) of the aminoindole **8a** and 5.6 g (0.036 mole) of 6-chloronicotinic acid was placed in a round-bottom flask connected to a water aspirator. The flask was heated in an oil bath at 180-190° (bath temperature) for 15 minutes under aspirator vacuum. After cooling, the solid mixture was recrystallized from pyridine and washed on the funnel with hexane, to yield the fused indole acid **9** as a 1:1 complex with pyridine (3.1 g, 25% yield). A second recrystallization from pyridine yielded an analytical sample of **9**, mp >330°, also containing one equivalent of pyridine.

3-[[[5,6-Dihydro-6-oxopyrido[1′,2′:1,2]pyrimido[5,4-*b*]indol-9-yl]carbonyl]-amino]-1*H*-indole-2-carboxylic Acid Ethyl Ester (**10**).

The pyridine recrystallization filtrate from the preparation of acid **9** was treated with warm and allowed to stand. Cooling yielded a precipitate of amide **10** (1.4 g, 9% yield). Filtration and recrystallization from *N,N*-dimethylformamide/water yielded an analytical sample of **10**, mp 345° dec.

5,6-Dihydro-6-oxopyrido[1′,2′:1,2]pyrimido[5,4-*b*]indole-9-carboxamide (**12**).

A mixture of 5.0 g (0.025 mole) of the aminoindole **8a** and 4.0 g (0.026 mole) of 6-chloronicotinamide was fused at 180-190° by the method described in the preparation of **9**. The total reaction mixture was then digested for two hours in 200 ml of pyridine on the steam bath, and then filtered while still warm. The insoluble material was digested for 45 minutes in 100 ml of methanol and again filtered warm, to yield the insoluble amide **12** in analytical purity (4.6 g, 68% yield), mp >350°.

5,6-Dihydro-6-oxopyrido[1′,2′:1,2]pyrimido[5,4-*b*]indole-9-carboxylic Acid Methyl Ester (**15**).

A mixture of 1.2 g (0.0059 mole) of the aminoindole **8a** and 1.0 g (0.0058 mole) of methyl 6-chloronicotinate was fused at 180-190° by the method described in the preparation of **9**. The total reaction mixture was digested (steam) in 60 ml of 2-propanol, and then filtered while still warm. The insoluble material was recrystallized twice from *N,N*-dimethylformamide/water, and the crystals were washed on the funnel with a little cold methanol. The product ester **15** was obtained as yellow crystals (0.5 g, 29% yield) containing 0.25 equivalent of water, mp 325° dec.

Table II

Spectra of Pyrido[1′,2′:1,2]pyrimido[5,4-*b*]indoles

Compound No.	Infrared ν, cm^{-1}	Solvent	NMR (δ) Indole NH	Pyrido # 10H	Pyrido # 8H	Remaining Aromatic H
9	3220, 2500, 1705, 1622, 1420	DMSO-d_6	12.17 (s)	7.80 (m)	9.43 (m)	7.05-7.68 (m, 5H) 7.92-8.18 (m, 1H)
10	3328, 3235, 1687, 1595, 1257	DMSO-d_6	11.84 (s) 12.35 (s)	—	9.81 (m)	6.98-8.31 (m, 10H) (m, 10H)
11	3220, 1693, 1593, 1424, 1300	DMSO-d_6	12.29 (s)	—	9.90 (m)	7.08-8.29 (m, 6H)
12	3328, 3180, 1678, 1529, 1415	trifluoroacetic acid	—	8.87 (m)	10.22 (m)	7.34-8.48 (m, 5H)
13	2240, 1722, 1695 (a)	trifluoroacetic acid	—	8.82 (m)	10.02 (m)	7.67-8.72 (m, 5H)
14	3225, 2750, 1692, 1622, 1440	DMSO-d_6	12.25 (s)	—	9.70 (m)	7.11-8.24 (m, 6H)
15	3220, 1725, 1695, 1532, 1305	DMSO-d_6	12.28 (s)	7.78 (m)	9.46 (m)	7.11-7.70 (m, 4H) 7.95-8.20 (m, 1H)
16	1730, 1697, 1470, 1300, 1131	trifluoroacetic acid	—	8.78 (m)	10.17 (m)	7.37-8.35 (m, 5H)
17	2500, 1718, 1613, 1472, 1253	DMSO-d_6	—	7.74 (m)	9.28 (m)	7.03-7.59 (m, 4H) 7.86-8.10 (m, 1H)

(a) Spectrum recorded as a Nujol mull.

3,5-Dihydro-2-mercapto-4*H*-pyrimido[5,4-*b*]indol-4-one (**18**).

A mixture of 8.2 g (0.040 mole) of the aminoindole **8a** and 6.0 g (0.079 mole) of thiourea was fused at 175-185° by the method described in the preparation of **9**. The total reaction mixture was digested (steam) in 200 ml of methanol and filtered while still warm. The insoluble material was recrystallized form *N,N*-dimethylformamide/water, and the crystals were washed on the funnel with methanol to yield the thiourea product **18**, (2.6 g, 30% yield). Several additional recrystallizations as above yielded an analytical sample of **18** containing one equivalent of *N,N*-dimethylformamide, yellow flakes of mp 350° dec; ir: ν 3200, 1670, 1560, 1230, 1143 cm^{-1}; nmr (DMSO-d_6): δ 6.97-7.56 (m, 3H, ArH), 8.00-8.23 (m, 1H, ArH), 12.0 (s, 1H, Indole NH), 12.30 (broad s, 1H, pyrimido NH), 13.25 (broad s, 1H, pyrimido NH).

Anal. Calcd. for $C_{10}H_7N_3OS{\cdot}C_3H_7NO$: C, 53.77; H, 4.86; N, 19.30, S, 11.04. Found: C, 53.70; H, 4.82; N, 18.99; S, 11.12.

5,6-Dihydro-6-oxo-*N*-(1*H*-tetrazol-5-yl)pyrido[1′,2′:1,2]pyrimido[5,4-*b*]-indole-9-carboxamide (**11**).

A mixture of 5.0 g (0.014 mole) of the acid **9** and 5.0 g (0.031 mole) of 1,1′-carbonyldiimidazole in 100 ml of *N,N*-dimethylformamide was heated on the steam bath with occasional shaking for 30 minutes. The mixture was cooled, and 1.6 g (0.016 mole) of 5-aminotetrazole monohydrate was added. After heating an additional 30 minutes, cooling yielded a precipitate of the crude carboxamidotetrazole **11**. The crude product was 2.4 g (50% yield). A sample was purified by digesting (steam bath) in glacial acetic acid followed by a second digestion in *N,N*-dimethylformamide. The yellow solid recovered by filtration was stirred briefly in 50% aqueous ethanol and again recovered by filtering, to yield the final product **11** in analytical purity, mp 335° dec.

5,6-Dihydro-6-oxopyrido[1′,2′:1,2]pyrimido[5,4-*b*]indole-9-carbonitrile (**13**).

A mixture of 2.0 g (0.0072 mole) of amide **12**, 3.5 ml (3.4 g, 0.043 mole) of pyridine, and 4.2 g (0.022 mole) of *p*-toluenesulfonyl chloride in 25 ml of *N,N*-dimethylformamide was heated on the steam bath for four hours. The cooled reaction mixture was added to 300 g ice/water, and the crude product was filtered and washed with water. Recrystallization from aqueous *N,N*-dimethylformamide yielded the nitrile **13** (1.4 g, 75% yield), mp >350°, in sufficient purity for conversion to the tetrazole.

9-(1*H*-Tetrazol-5-yl)pyrido[1′,2′:1,2]pyrimido[5,4-*b*]indole-6-(5*H*)-one (**14**).

A mixture of 2.3 g (0.088 mole) of the nitrile **13**, 1.5 g (0.023 mole) of sodium azide, and 1.25 g (0.023 mole) of ammonium chloride in 50 ml of *N,N*-dimethylformamide was stirred at reflux under nitrogen for 21 hours. The cooled reaction mixture was added to 350 g ice/water and acidified at ≤5° with 4*N* hydrochloric acid (Caution: hydrazoic acid is evolved). The crude tetrazole product was filtered and washed with water (crude yield = 2.1 g, 79%). Recrystallization from aqueous *N,N*-dimethylformamide followed by washing with methanol yielded the tetrazole **14** in analytical purity as a monohydrate (1.1 g, 41% yield), mp 320° dec.

5,6-Dihydro-5-methyl-6-oxopyrido[1′,2′:1,2]pyrimido[5,4-*b*]indole-9-carboxylic Acid Methyl Ester (**16**).

A suspension of 1.0 g (0.021 mole) of 50% sodium hydride in 25 ml of *N,N*-dimethylformamide was cooled in an ice bath and treated, under nitrogen, with 5.0 g (0.017 mole) of powdered ester **15**. The ester was added in small portions over 30 minutes. After stirring for an additional 30 minutes, a solution of 1.5 ml (3.4 g, 0.024 mole) of iodomethane in 10 ml of *N,N*-dimethylformamide was added over 20 minutes. The ice bath was removed, and the mixture was stirred for 17 hours, added to 250 g ice/water, and acidified with acetic acid. The precipitated solid was filtered and washed with water to yield 4.8 g (94% crude yield) of the crude ester. A sample recrystallized from ethyl acetate/*N,N*-dimethylformamide yielded analytically pure **16**, mp 268-271°.

5,6-Dihydro-5-methyl-6-oxopyrido[1′,2′:1,2]pyrimido[5,4-*b*]indole-9-carboxylic Acid (**17**).

A mixture of 0.50 g (0.0016 mole) of ester **16** in 25 ml of 6.0 *N* hydrochloric acid was stirred at reflux for 17 hours. The cooled mixture was filtered, and the insoluble material was washed with water. Two recrystallizations of the crude product from aqueous *N,N*-dimethylformamide yielded 0.25 g (52% yield) of the analytically pure acid **17**, containing one equivalent of *N,N*-dimethylformamide, mp 335° dec.

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