Indole Esters as Heterocyclic Synthons. III [1]. Preparation and Reactions of Furo[3,2-*b*]indoles

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The preparation of furo[3,2-*b*]indoles *via* Dieckmann cyclization is described. The precursor diesters were obtained from 3-hydroxy-1*H*-indole-2-carboxylic acid esters and methyl or ethyl bromoacetate. Reactions of the furo[3,2-*b*]indole enolic esters prepared are discussed.

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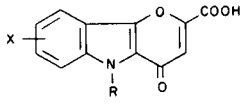
We have been interested for some time in the application of indole-2-carboxylic acid derivatives for the preparation of indole-fused heterocycles [1,2]. This methodology was employed in the preparation of acidic 4-oxopyrano-[3,2-*b*]indoles **1**, a series of compounds possessing anti-allergy activity [3]. The preparation of the related furo-[3,2-*b*]indole ring system **2** thus became of interest as an analog of **1**.



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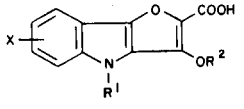


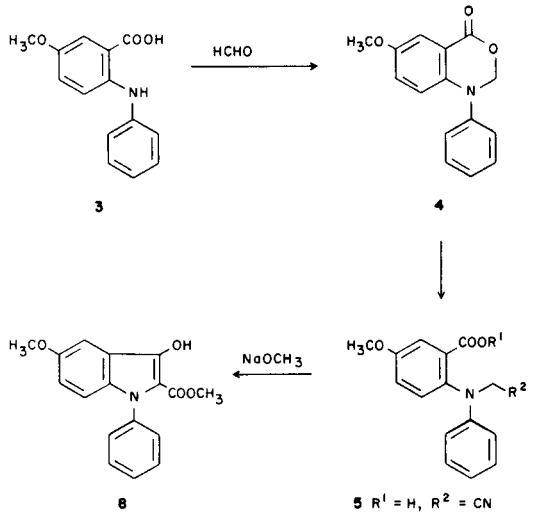
2

Preparation of ring system **2** has been previously described in a series of papers by Tanaka, *et al.* [4], in which a 5-(2′-nitrophenyl)-2-furoic acid ester is converted to the corresponding 2′-azido derivative *via* the 2′-diazonium salt. Thermal cyclization then yields ring system **2** in which R^1 is hydrogen and the OR^2 substituent is replaced by a proton.

We desired an alternate preparative procedure avoiding the diazotization and azide formation steps and permitting R^1 in **2** to be phenyl. This was accomplished by the use of *N*-substituted indole-2-carboxylic acid esters as precursors for a Dieckmann cyclization to form the furan ring of **2**.

Indole ester **8** was prepared (Scheme I) by slight modification of Friedlander's procedure [5] for the preparation of a related indole ester **10b** [6]. Benzoic acid derivative **3** [7] was converted to benzoxazine **4** with aqueous formaldehyde. Ring-opening with cyanide ion, followed by basic hydrolysis, yielded cyano-acid **5** and diacid **6** as crude intermediates. Esterification of **6** yielded diester **7**, which was cyclized with sodium methoxide to yield the desired indole ester **8**. Two additional indole esters **10a,f** were prepared by literature [8,9] procedures.

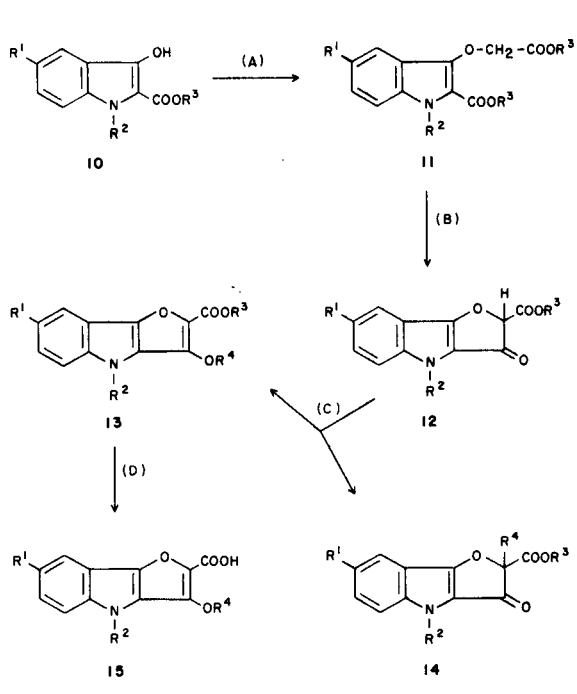
Scheme I



3 **4** **8**

5 $R^1 = H$, $R^2 = CN$
6 $R^1 = H$, $R^2 = COOH$
7 $R^1 = CH_3$, $R^2 = COOCH_3$

Scheme II



10 **11** **13** **12** **15** **14**

Compounds 10–18

Substituent	a	b	c	d	e	f
R^1	H	H	H	CH_3O	CH_3O	H
R^2	CH_3	C_6H_5	C_6H_5	C_6H_5	C_6H_5	H
R^3	C_2H_5	CH_3	CH_3	CH_3	CH_3	C_2H_5
R^4	CH_3	CH_3	C_2H_5	CH_3	C_2H_5	–

Table 1

Prepared Furo[3,2-*b*]indoles **12-15, 17, 18**

Compound No. [a]	Method	Mp, °C	% Yield	Recrystallization Solvent	Formula	Analysis % Calcd./(Found) C	H	N
12a	[b]	121-123	43	Ethanol/Water	$C_{14}H_{13}NO_4$	64.86	5.05	5.40
						(64.60	5.16	5.15)
12b	B	152-154	60	Ethanol	$C_{18}H_{13}NO_4$	70.35	4.26	4.56
						(70.26	4.31	4.52)
12d	B	141-143	74	DMF/Water	$C_{19}H_{15}NO_5$	67.65	4.48	4.15
						(67.36	4.59	4.20)
13a	C	93-95	85	Ethanol/Water	$C_{15}H_{15}NO_4$	65.92	5.53	5.13
						(65.81	5.52	4.94)
13b	C	131-133	81	Ethanol/Water	$C_{19}H_{15}NO_4$	71.02	4.70	4.36
						(70.78	4.83	4.27)
13c	[b]	82-84	71	Ethanol/Water	$C_{20}H_{17}NO_4$	71.63	5.11	4.18
						(71.54	5.12	4.21)
13d	C	121-124	80	Methanol/Water	$C_{20}H_{17}NO_5$	68.37	4.88	3.99
						(68.31	5.01	3.92)
13e	C	119-120.5	36	Methanol/Water	$C_{21}H_{19}NO_5$	69.03	5.24	3.83
						(69.07	5.38	3.90)
14d	[b]	159-161	4	Ethyl Acetate/Hexane	$C_{20}H_{17}NO_5$	68.37	4.88	3.99
						(68.45	5.06	3.88)
15a	D	141-dec	72 [c]	DMF/Water	$C_{13}H_{11}NO_4$	63.67	4.52	5.71
						(63.84	4.63	5.79)
15b	[b]	154-155	45	Methanol	$C_{18}H_{13}NO_4$	70.35	4.26	4.56
						(70.41	4.15	4.53)
15c	[b]	146-147	59	Ethanol	$C_{19}H_{15}NO_4$ [d]	70.03	4.80	4.30
						(69.67	4.93	4.12)
15d	D	148-dec	85 [c]	Acetone/Water	$C_{19}H_{15}NO_5$	67.65	4.48	4.15
						(67.71	4.61	4.06)
15e	D	166-167	85 [c]	2-Methoxyethanol	$C_{20}H_{17}NO_5$	68.37	4.88	3.99
						(68.24	4.87	4.06)
17a	E	225-dec	60	Ethanol	$C_{12}H_{10}N_2O_3$	62.60	4.38	12.17
						(62.32	4.48	11.95)
18a	E	179-182	79	Ethanol/Water	$C_{13}H_{12}N_2O_3$	63.92	4.95	11.47
						(63.88	5.15	11.52)
18b	E	207-208	61	Ethanol	$C_{18}H_{14}N_2O_3$ [e]	69.75	4.68	9.04
						(69.98	4.70	8.85)
18c	E	187-188	92 [c]	Ethanol	$C_{19}H_{16}N_2O_3$	71.24	5.03	8.74
						(71.01	5.18	8.53)
18d	E	210-211	72	Ethanol/Water	$C_{19}H_{16}N_2O_4$	67.85	4.79	8.33
						(67.47	4.72	8.30)

[a] Substituents for specific compounds are given in Scheme II. [b] See Experimental Section. [c] Crude yield before recrystallization. [d] Analysis Calcd. as the molecular formula + 0.25 water. [e] Analysis Calcd. as the molecular formula + 0.20 water.

Indole esters **8** and **10a,b,f** were converted to diesters **11a,b,d,f** by alkylation (Method A) with ethyl or methyl bromoacetate in the presence of potassium carbonate (Scheme II). A Dieckmann cyclization (Method B) employing potassium *t*-butoxide in tetrahydrofuran or benzene converted diesters **11a,b,d** to the enolic furo[3,2-*b*]indole esters **12a,b,d**. (Keto-enol tautomerism is observed in the spectra of these compounds.) A single attempt at conversion of diester **11f** to the corresponding furo[3,2-*b*]indole **12f** under similar conditions was unsuccessful. The failure of the Dieckmann condensation with diester **11f** may be due to the presence of the acidic proton on the indole nitrogen atom [10,11].

The chemistry of the furo[3,2-*b*]indole ring system was investiagated briefly. Esters **12a,b,d** were alkylated (Method C) on the enolic oxygen with methyl and ethyl sulfate in acetone to yield alkoxy esters **13a,b,d,e**. In most cases, an additional reaction product was evident *via* thin-layer chromatography and the nmr spectra of the crude reaction products.

Competitive *O*- and *C*-alkylation of ambident anions generated from β-keto esters has been studied extensively [12]. Ester **14d** was isolated as the minor product in the conversion of enol ester **12d** to alkoxy ester **13d**, demonstrating the occurrence of *C*-alkylation. In the preparation of alkoxy ester **13c**, the reaction conditions were varied in

Table 2

Spectra of Furo[3,2-*b*]indoles **12-15, 17, 18**

Compound No. [a]	Solvent	NMR (δ) NCH_3	OCH_3	Aromatic	Other	Infrared ν (cm^{-1})
12a	$CDCl_3$	3.82		6.95-7.94 (m, 4H)	1.38 (t, 3H, J = 7.5 Hz, CH_2CH_3), 4.37 (q, 2H, J = 7.5 Hz, CH_2CH_3), 5.48 (s, 1H, OCHCO)	1747, 1700, 1393, 1199
12b	DMSO		3.72, 3.82	6.93-7.95 (m, 9H)	6.03 (s, 0.5H, OCHO) [b], 9.89 (broad s, 0.5H, OH)	3318, 1755, 1672, 1456
12d	DMSO		3.75, 3.80	6.77-7.78 (m, 8H)	6.03 (s, 0.5H, OCHO) [b], 9.84 (s, 0.5H, OH)	3325, 1758, 1682, 1202
13a	$CDCl_3$	3.89 or	4.18	6.98-7.99 (m, 4H)	1.47 (t, 3H, J = 7.5 Hz, CH_2CH_3), 4.48 (q, 2H, J = 7.5 Hz, CH_2CH_3)	1698, 1440, 1323, 1145
13b	$CDCl_3$		3.67, 3.94	6.98-8.01 (m, 9H)		1700, 1449, 1332, 1198
13c	$CDCl_3$		3.92	7.02-8.00 (m, 9H)	1.10 (t, 3H, J = 7.5 Hz, CH_2CH_3), 3.81 (q, 2H, J = 7.5 Hz, CH_2CH_3)	1710, 1442, 1329, 1188
13d	$CDCl_3$		3.61, 3.77, 3.90	6.63-6.87 (m, 1H, #6H) 7.03-7.50 (m, 7H)		
13e	$CDCl_3$		3.77, 3.87	6.65-6.92 (m, 1H, #6H) 7.00-7.52 (m, 7H)	1.08 (t, 3H, J = 7.5 Hz, CH_2CH_3), 3.80 (q, 2H, J = 7.5 Hz, CH_2CH_3)	1704, 1501, 1460, 1210
14d	$CDCl_3$		3.80, 3.85	6.92-7.65 (m, 8H)	1.90 (s, 3H, CCH_3)	1750, 1698, 1455, 1251
15a	DMSO	3.96 or	4.18	6.98-8.12 (m, 4H)	12.97 (broad s, 1H, CO_2H	2635, 1685, 1459, 1322
15b	DMSO		3.67	7.04-8.00 (m, 9H)	12.85 (broad s, 1H, CO_2H)	2620, 1668, 1450, 1320
15c	DMSO			7.03-8.03 (m, 9H)	1.07 (t, 3H, J = 7.5 Hz, CH_2CH_3), 3.88 (q, 2H, J = 7.5 Hz, CH_2CH_3), 12.83 (broad s, 1H, CO_2H)	2620, 1671, 1452, 1321
15d	DMSO		3.70, 3.85	6.81-7.12 (m, 1H, #6H), 7.26-7.81 (m, 7H)	12.88 (broad s, 1H, CO_2H)	2620, 1670, 1461, 1221
15e	DMSO		3.85	6.84-7.01 (m, 1H, #6H), 7.22-7.75 (m, 7H)	1.09 (t, 3H, J = 7.5 Hz, CH_2CH_3), 3.90 (q, 2H, J = 7.5 Hz, CH_2CH_3), 12.81 (broad s, 1H, CO_2H)	1670, 1528, 1461, 1220
17a	DMSO			6.90-7.83 (m, 6H) [c]	5.53 (s, 1H, OCHCO)	3497, 1725, 1687, 1398 [d]
18a	$CDCl_3$ + DMSO	3.85 or	4.13	6.97-7.76 (m, 4H)	6.57 (broad s, 2H, NH_2)	3518, 1670, 1588, 1456 [d]
18b	DMSO		3.56	7.00-7.91 (m, 11H) [c]		3470, 1670, 1452, 1162
18c	DMSO			7.00-7.95 (m, 11H) [c]	1.06 (t, 3H, J = 7.5 Hz, CH_2CH_3), 3.82 (q, 2H, J = 7.5 Hz, CH_2CH_3)	3465, 1678, 1452, 1251
18d	DMSO		3.61, 3.81	6.77-6.98 (m, 1H, #6H) 7.08-7.70 (m, 9H) [c]		3449, 1665, 1496, 1273

[a] Substituents for specific compounds are given in Scheme II. [b] Keto-enol tautomers are observed in solution. [c] The NH_2 absorption is apparently overlapped by the aromatic multiplet. [d] Spectrum recorded in chloroform solution.

order to increase the extent of *O*-alkylation.

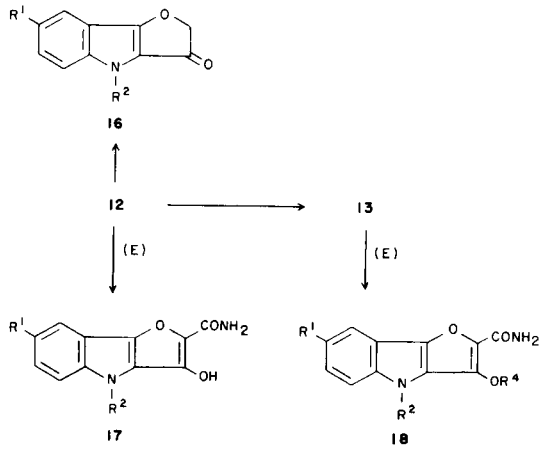
Alkoxy esters **13a-e** were converted (Method D) to alkoxy carboxylic acids **15a-e** by basic hydrolysis. In several cases (**15b,c**) the poor solubility of the ester in the saponification medium necessitated extended reaction time.

Saponification of alkoxy esters **13** generally was also accompanied by formation of furo[3,2-*b*]indole ketones **16** as side-products to carboxylic acid preparation. This is understandable based on the known instability of benzofuran acids and the ready hydrolysis of vinyl ethers [14,15]. Ketones **16a,d** were also prepared in moderate yield by direct saponification-decarboxylation of enol esters **12a,d** (Scheme III).

Enol ester **12a** and alkoxy esters **13a-d** were also converted (Method E) to simple amides **17a** and **18a-d** by reaction with lithium amide in anhydrous ammonia/tetrahydrofuran.

We have described a new procedure for the preparation of furo[3,2-*b*]indoles. Some of the various synthetic procedures employed are summarized as General Methods A-E in the Experimental Section. Tables 1 and 2 represent the analytical data and spectral data for all furo[3,2-*b*]indoles

Scheme III



prepared except **16a,d**.

A number of these compounds have shown significant antiallergy activity. Biological test results will be described elsewhere [16].

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 spectrometer, except for compounds **12a**, **13a**, and **15a**, which were recorded on a Perkin-Elmer R-12B spectrometer at 60 MHz. All nmr spectra were recorded with tetramethylsilane as an internal standard. Infrared spectra were recorded on a Digilab FTS-14 pulsed Fourier-transform spectrophotometer as potassium bromide disks, except for compounds **17a** and **18a**, which were recorded in chloroform solution.

Preparation of Indole Diesters **11** (General Method A).

5-Methoxy-3-(2-methoxy-2-oxoethoxy)-1-phenyl-1*H*-indole-2-carboxylic Acid Methyl Ester (**11d**).

A mixture of 59.5 g (0.20 mole) of indole ester **8**, 32.0 g (0.23 mole) of potassium carbonate (anhydrous), and 19 ml (34.7 g, 0.23 mole) of methyl bromoacetate in 800 ml acetone was stirred at reflux for 24 hours. The mixture was cooled, and the insoluble material was filtered and washed several times with fresh acetone. The combined filtrates were evaporated to yield the crude diester product **11d** as an oil which slowly crystallized. A sample recrystallized several times from methanol was analytically pure, mp 97-100°; ir: ν 1772, 1719, 1499, 1218 cm^{-1} ; nmr (deuteriochloroform): δ 3.72 (s, 3H, OCH_3), 3.85 (s, 3H, OCH_3), 3.92 (s, 3H, OCH_3), 4.88 (s, 2H, CH_2), 6.87-7.02 (m, 1H, #6H), 7.13-7.70 (m, 7H, ArH).

Anal. Calcd. for $C_{20}H_{19}NO_6$: C, 65.03; H, 5.18; N, 3.79. Found: C, 64.64; H, 5.14; N, 3.66.

3-(2-Methoxy-2-oxoethoxy)-1-phenyl-1*H*-indole-2-carboxylic Acid Methyl Ester (**11b**).

Prepared by the procedure described in General Method A from 120 g (0.45 mole) of indole ester **10b**. Recrystallization of the crude product from ethyl acetate/hexane yielded 102 g (67% yield) of the diester **11b**, mp 76-80°. An additional recrystallization yielded an analytically pure sample, mp 76-77°; ir: ν 1762, 1700, 1528, 1218 cm^{-1}; nmr (deuteriochloroform): δ 3.71 (s, 3H, OCH_3), 3.82 (s, 3H, OCH_3), 4.86 (s, 2H, CH_2), 6.85-7.61 (m, 8H, ArH), 7.71-7.96 (m, 1H, #4H).

Anal. Calcd. for $C_{19}H_{17}NO_5$: C, 67.25; H, 5.05; N, 4.13. Found: C, 67.01; H, 5.24; N, 4.10.

3-(2-Ethoxy-2-oxoethoxy)-1*H*-indole-2-carboxylic Acid Ethyl Ester (**11f**).

Prepared by the procedure described in General Method A from 20.5 g (0.10 mole) of indole ester **10f** [9] and ethyl bromoacetate. Recrystallization of the crude product from isopropyl ether yielded 19.7 g (68% yield) of diester **11f**, mp 87-91°; literature [17,18] mp 88-90°, 75°; ir: ν 3320, 1759, 1675, 1203 cm^{-1}; nmr (deuteriochloroform): δ 1.10-1.57 (m, 6H, two CH_2CH_3), 4.00-4.52 (m, 4H, two CH_2CH_3), 4.80 (s, 2H, OCH_2), 6.84-7.36 (m, 3H, ArH), 7.62-7.83 (m, 1H, #4H), 8.41 (broad s, 1H, NH).

Anal. Calcd. for $C_{15}H_{17}NO_5$: C, 61.85; H, 5.88; N, 4.81. Found: C, 61.62; H, 5.81; N, 4.71.

3-(2-Ethoxy-2-oxoethoxy)-1-methyl-1*H*-indole-2-carboxylic Acid Ethyl Ester (**11a**).

Prepared by the procedure described in General Method A from indole ester **10a** and ethyl bromoacetate. The product diester **11a** was obtained as an oil, which was converted to enol ester **12a** without additional purification.

Preparation of Enol Esters **12** (General Method B).

3-Hydroxy-7-methoxy-4-phenyl-4*H*-furo[3,2-*b*]indole-2-carboxylic Acid Methyl Ester (**12d**).

A suspension of 30 g (0.27 mole) of potassium *t*-butoxide in 400 ml of tetrahydrofuran was stirred and cooled in ice while a solution of 67.0 g (0.18 mole) of indole diester **11d** was added over 45 minutes. The rate of addition was adjusted to maintain the temperature of the reaction mixture at $\leq 15°$. The cooling bath was removed, and the reaction mixture was stirred for an additional 18 hours. The mixture was again cooled in ice, treated with 25 ml of glacial acetic acid, and added to 2.75 kg ice/water. After stirring for several hours, the solid was filtered, stirred on 1.0 ℓ of fresh water, and refiltered. Recrystallization from *N,N*-dimethylformamide/water yielded the furoindole product **12d**. Also prepared by General Method B was:

3-Hydroxy-4-phenyl-4*H*-furo[3,2-*b*]indole-2-carboxylic Acid Methyl Ester (**12b**).

This compound was prepared from 29.0 g (0.085 mole) of **11b**.

Enol ester **12a** was prepared by the following variation of General Method B.

3-Hydroxy-4-methyl-4*H*-furo[3,2-*b*]indole-2-carboxylic Acid Ethyl Ester (**12a**).

A suspension of 10.8 g (0.096 mole) of potassium *t*-butoxide in 200 ml of benzene was treated over 15 minutes with a solution of 22.4 g (0.074 mole) of indole diester oil **11a** in 100 ml of benzene. The mixture was then stirred at reflux under a nitrogen atmosphere for 18 hours. The solvent was removed under vacuum, and the residue was cooled in ice and treated with 300 ml of ice water and 200 ml of chloroform. After acidification with acetic acid, the layers were separated, and the aqueous layer was washed with additional chloroform. The combined organic layers were washed with water, 5% aqueous sodium bicarbonate (twice), and again with water. After drying over anhydrous sodium sulfate, the organic layer was evaporated, and the residue was recrystallized to yield enol ester **12a**.

Preparation of Alkoxy Esters **13** (General Method C).

3-Methoxy-4-phenyl-4*H*-furo[3,2-*b*]indole-2-carboxylic Acid Methyl Ester (**13b**).

A mixture of 16.0 g (0.052 mole) of enol ester **12b**, 7.9 g (0.057 mole) of anhydrous potassium carbonate, and 5.3 ml (7.0 g, 0.056 mole) of dimethyl sulfate in 300 ml of acetone was stirred at reflux for 42 hours. The mixture was cooled and filtered and the insoluble material was washed several times with fresh acetone. The combined filtrates were evaporated, and the residue was recrystallized from ethanol/water to yield the methoxy ester product **13b**.

Also prepared by General Method C were the following:

3-Methoxy-4-methyl-4*H*-furo[3,2-*b*]indole-2-carboxylic Acid Ethyl Ester (**13a**).

This compound was prepared from 47.0 g (0.18 mole) of **12a**.

3-Ethoxy-7-methoxy-4-phenyl-4*H*-furo[3,2-*b*]indole-2-carboxylic Acid Methyl Ester (**13e**).

This compound was prepared from 12.9 g (0.038 mole) of **12b** and diethyl sulfate.

3,7-Dimethoxy-4-phenyl-4*H*-furo[3,2-*b*]indole-2-carboxylic Acid Methyl Ester (**13d**).

This compound was prepared from 30.0 g (0.089 mole) of **12d**.

During subsequent large-scale preparations of **13d**, the recrystallization mother liquors were combined and condensed to precipitate a solid consisting of **13d** plus an additional product (by thin-layer chromatography). The solid was chromatographed (E. Merck Lichroprep Si 60, methylene chloride elution) to isolate the keto-ester side product, 3,4-dihydro-7-methoxy-2-methyl-3-oxo-4-phenyl-2*H*-furo[3,2-*b*]indole-2-carboxylic acid methyl ester (**14d**).

3-Ethoxy-4-phenyl-4*H*-furo[3,2-*b*]indole-2-carboxylic Acid Methyl Ester (**13c**).

A mixture of 24.3 g (0.079 mole) of **12b** and 10.7 g (0.095 mole) of potassium *t*-butoxide in 240 ml of dimethyl sulfoxide was stirred and treated over 45 minutes with 64.4 g (54.7 ml, 0.42 mole) of diethyl sulfate. After stirring for 24 hours, the mixture was added to 1.5 kg of ice/water. The clear liquid was decanted from the resulting gummy product. Recrystallization of the residual gum from aqueous ethanol yielded ethoxy ester **13c**.

Preparation of Alkoxy Acids **15** (General Method D).

3,7-Dimethoxy-4-phenyl-4*H*-furo[3,2-*b*]indole-2-carboxylic Acid (**15d**).

A suspension of 11.5 g (0.033 mole) of alkoxy ester **13d** in 200 ml of 50% aqueous ethanol was treated with 25 ml of 10% aqueous sodium hydroxide solution. After stirring at reflux for 90 minutes, the reaction mixture was cooled and distributed between 750 ml of water and 250 ml of dichloromethane. The insoluble material (primarily the sodium salt of the product) was removed by filtration. The filtrate layers were separated, and the organic layer was discarded. The aqueous layer was washed several times with fresh dichloromethane, cooled in ice, and acidified with 4*N* hydrochloric acid. The precipitated crude product was filtered and washed with water. The original insoluble sodium salt was stirred for several hours in 400 ml of cold 1*N* hydrochloric acid, and the product acid was filtered, washed with water, and combined with the material obtained from acidification of the original aqueous layer. A sample was recrystallized from acetone/water to yield alkoxy acid **15d**.

Also prepared by General Method D were the following:

3-Methoxy-4-methyl-4*H*-furo[3,2-*b*]indole-2-carboxylic Acid (**15a**).

This compound was prepared from 35.8 g (0.13 mole) of **13a**.

3-Ethoxy-7-methoxy-4-phenyl-4*H*-furo[3,2-*b*]indole-2-carboxylic Acid (**15e**).

This compound was prepared from 4.9 g (0.013 mole) of **13e**.

Alkoxy acids **15b,c** were prepared by the following variations of General Method D.

3-Methoxy-4-phenyl-4*H*-furo[3,2-*b*]indole-2-carboxylic Acid (**15b**).

A suspension of 13.5 g (0.042 mole) of alkoxy ester **13b** in 75 ml of methanol was treated with 70.6 ml of 1.0*N* aqueous sodium hydroxide. The mixture was stirred at reflux for 17 hours, then added to 1.4 ℓ of water. The insoluble material was filtered, added to 1.0 ℓ of water, and acidified with acetic acid while cooling in an ice bath. The crude acid product was recovered by filtration. The original filtrate from the reaction mixture and 1.4 ℓ of water was also cooled in ice and acidified with acetic acid. The crude product obtained was filtered and combined with the earlier crop. The combined crude products were stirred in 400 ml of water, filtered, and recrystallized to yield alkoxy acid **15b**.

3-Ethoxy-4-phenyl-4*H*-furo[3,2-*b*]indole-2-carboxylic Acid (**15c**).

A suspension of 12.0 g (0.036 mole) of alkoxy ester **13c** in 100 ml of methanol was treated with 60 ml of 1.0*N* aqueous sodium hydroxide. After stirring at reflux for 20 hours, the cooled reaction mixture was added to 1.2 kg ice/water, and the mixture was acidified with acetic acid. The crude product was filtered, washed with water, and recrystallized to yield alkoxy acid **15c**.

Preparation of Amides **17**, **18** (General Method E).

3-Methoxy-4-methyl-4*H*-furo[3,2-*b*]indole-2-carboxamide (**18a**).

A flask fitted with a Dewar condenser containing dry ice/acetone was cooled in a dry ice/acetone bath and charged with 350 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 1.78 g (0.26 mole) of freshly cut lithium metal ribbon. After the addition of 65 ml of cold tetrahydrofuran, a solution of 16.5 g (0.060 mole) of alkoxy ester **13a** in 75 ml of tetrahydrofuran was added over 30 minutes. The Dewar condenser was removed, and the mixture was stirred for 16 hours as the excess ammonia evaporated. The total reaction mixture was added to 600 g of ice/water, and the crude amide product was filtered, washed with water, and recrystallized to yield alkoxy amide **18a**.

Also prepared by General Method E were the following:

3-Methoxy-4-phenyl-4*H*-furo[3,2-*b*]indole-2-carboxamide (**18b**).

This compound was prepared from 23.3 g (0.073 mole) of **13b**.

3-Ethoxy-4-phenyl-4*H*-furo[3,2-*b*]indole-2-carboxamide (**18c**).

This compound was prepared from 8.5 g (0.025 mole) of **13c**.

3,7-Dimethoxy-4-phenyl-4*H*-furo[3,2-*b*]indole-2-carboxamide (**18d**).

This compound was prepared from 19.5 g (0.056 mole) of **13d**.

3,4-Dihydro-4-methyl-3-oxo-2*H*-furo[3,2-*b*]indole-2-carboxamide (**17a**).

This compound was prepared from 3.9 g (0.015 mole) of **12a**.

Yields, physical properties, and spectra for the compounds prepared by General Method B-E are given in Tables 1 and 2.

4-Methyl-2*H*-furo[3,2-*b*]indole-3(4*H*)-one (**16a**).

A mixture of 47.0 g (0.18 mole) of enol ester **12a** in 450 ml of 95% ethanol was treated with 450 ml of 30% aqueous sodium hydroxide. The mixture was stirred at reflux for two hours, cooled, added to 3 kg ice/water, and acidified with 6.0*N* hydrochloric acid. The product was filtered, washed with water, and recrystallized from aqueous ethanol to yield 17.9 g (53% yield) of ketone **16a**, mp 113-116°. An additional recrystallization yielded an analytically pure sample, mp 115.8-118°; ir: ν 1681, 1512, 1486, 1218 cm^{-1}; nmr (deuteriochloroform): δ 3.73 (s, 3H, NCH_3), 4.95 (s, 2H, CH_2), 6.91-7.75 (m, 4H, Ar*H*).

Anal. Calcd. for $C_{11}H_9NO_2$: C, 70.58; H, 4.85; N, 7.48. Found: C, 70.28; H, 4.97; N, 7.35.

7-Methoxy-4-phenyl-2*H*-furo[3,2-*b*]indole-3(4*H*)-one (**16d**).

A mixture of 39.0 g (0.12 mole) of enol ester **12d** in 195 ml of *N,N*-dimethylformamide and 80 ml of water was treated with 40 ml of 50% aqueous sodium hydroxide. The mixture was heated on the steam bath for two hours. The product was isolated by the procedure described in the preparation of **16a**. Recrystallization from 2-methoxyethanol/*N,N*-dimethylformamide gave 15.8 g (49% yield) of ketone **16d**, mp 175° dec. An additional recrystallization yielded an analytically pure sample, mp 185-187°; ir: ν 1679, 1502, 1459, 1203 cm^{-1}; nmr (deuteriochloroform): δ 3.87 (s, 3H, OCH_3), 5.08 (s, 2H, CH_2), 6.92-7.71 (m, 8H, Ar*H*).

Anal. Calcd. for $C_{17}H_{13}NO_3$: C, 73.10; H, 4.69; N, 5.02. Found: C, 72.86; H, 4.66; N, 4.94.

1,2-Dihydro-6-methoxy-1-phenyl-4*H*-3,1-benzoxazine-4-one (**4**).

A mixture of 15.0 g (0.062 mole) of 5-methoxy-2-(phenylamino)benzoic acid [7] and 75 ml of 37% aqueous formaldehyde solution in 75 ml of ethanol was heated on a steam bath for 75 minutes. The mixture was cooled and added to 400 g ice/water. The crude oxazine product was filtered, stirred in 75 ml of 5% aqueous sodium bicarbonate, and refiltered to yield 13.0 g (83% yield) of the product **4**, mp 99.5-101°. A sample recrystallized from hexane was analytically pure, mp 100-102°; ir: ν 1723, 1498,

1249, 1027 cm^{-1}; nmr (deuteriochloroform): δ 3.87 (s, 3H, OCH_3), 5.58 (s, 2H, CH_2), 6.86-7.70 (m, 8H, ArH).

Anal. Calcd. for $C_{15}H_{13}NO_3$: C, 70.58; H, 5.13; N, 5.49. Found: C, 70.47; H, 5.19; N, 5.52.

2-[(Cyanomethyl)phenylamino]-5-methoxybenzoic Acid (**5**).

To a solution of 268 g (4.1 moles) of potassium cyanide in 1.6 ℓ of water was added 1021 g (4.0 moles) of benzoxazine **4** at a rate such that the reaction mixture temperature was 35-40°. The resulting soution was stirred and maintained at 35-40° for two hours, and then added dropwise to a solution of 8.0 ℓ of ice water and 800 ml of acetic acid. The resulting suspended solid was filtered and washed with water to yield 1084 g (96% yield) of the crude nitrile, mp 122-130°. This material was converted to diacid **6** without additional purification.

2-[(Carboxymethyl)phenylamino]-5-methoxybenzoic Acid (**6**).

To a solution of 3.4 ℓ of 25% aqueous sodium hydroxide being stirred at reflux, was added 1936 g (6.86 moles) of nitrile **5** in portions over one hour. After the addition to 1.0 ℓ of water, the resulting solution was stirred at reflux for an additional hour. The solution was cooled, added to 18 kg of ice/water, and treated with acetic acid until *p*H 7. The mixture was filtered, and the filtrate was cooled in ice and made strongly acidic with concentrated hydrochloric acid. The resulting solid was filtered and washed with water to yield 1612 g (78% yield) of the crude diacid product **6**, mp 158-161°. This material was converted to diester **7** without additional purification.

5-Methoxy-2-[(2-methoxy-2-oxoethyl)phenylamino]benzoic Acid Methyl Ester (**7**).

A mixture of 113 g (0.40 mole) of diacid **6** in 800 ml of *N,N*-dimethylformamide was treated with 128 g (0.80 mole) of 25% aqueous sodium hydroxide. After stirring at ambient temperature for 30 minutes, there was added 156 g (1.10 moles) of iodomethane. The mixture was stirred without external heating for three hours, then warmed to 50-55° for 30 minutes. The reaction mixture was added to 1 kg of ice/water and the product was extracted by washing several times with dichloromethane. The combined organic layers were back-washed with saturated sodium bicarbonate solution then water, and dried over anhydrous sodium sulfate. Evaporation of the organic layer left the crude diester **7** as an oil, 106 g (80% yield), which was used for conversion to indole ester **8**. A sample of the oil crystallized from methanol yielded the final product **7** as a solid in analytical purity, mp 85-87°; ir: ν 1750, 1728, 1501, 1209 cm^{-1}; nmr (deuteriochloroform): δ 3.64 (s, 3H, OCH_3), 3.70 (s, 3H, OCH_3), 3.82 (s, 3H, OCH_3), 4.30 (s, 2H, CH_2), 6.26-7.59 (m, 8H, ArH).

Anal. Calcd. for $C_{18}H_{19}NO_5$: C, 65.64; H, 5.81; N, 4.25. Found: C, 65.69; H, 5.80; N, 4.23.

2-[(2-Methoxy-2-oxoethyl)phenylamino]benzoic Acid Methyl Ester (**9**).

A mixture of 258 g (0.95 mole) of 2-[(carboxymethyl)phenylamino]benzoic acid [5,6] in 4.0 ℓ of methanol was treated cautiously with 90 ml of concentrated sulfuric acid. The mixture was stirred at reflux through a Soxhlet condenser containing 3A° Molecular Sieve for 20 hours. The cooled reaction mixture was condensed (vacuum) to 1.5 ℓ and added to 6.0 ℓ of water. The new mixture was extracted with methylene chloride (4 × 1.6 ℓ), and the combined extracts were washed with 1.0*N* aqueous sodium carbonate (4 × 4.0 ℓ), water (1 × 4.0 ℓ), dried (sodium sulfate), and evaporated to a syrup which slowly crystallized. The crude yield of diester **9** was 263 g (92%). A sample of the crude solid was stirred in 0.5*N* aqueous sodium carbonate, filtered, and dissolved in a minimum of hexane. The hexane solution was filtered and evaporated, resulting in an oil which slowly crystallized to yield diester **9** as a solid in analytical purity, mp 43-46°; ir: ν 1749, 1729, 1501, 1200 cm^{-1}; nmr (deuteriochloroform): δ 3.71 (s, 3H, OCH_3), 3.81 (s, 3H, OCH_3), 4.45 (s, 2H, CH_2), 6.43-7.77 (m, 8H, ArH), 7.87-8.08 (m, 1H, #6H).

Anal. Calcd. for $C_{17}H_{17}NO_4$: C, 68.21; H, 5.73; N, 4.68. Found: C, 68.39; H, 5.62; N, 4.82.

3-Hydroxy-5-methoxy-1-phenyl-1*H*-indole-2-carboxylic Acid Methyl Ester (**8**).

A mixture of 1.7 kg (5.2 moles) of diester **7** and 303 g (5.6 moles) of sodium methoxide in 10.0 ℓ of anhydrous methanol was stirred at reflux for 90 minutes. The mixture was cooled to 20°, filtered, and treated with 336 g (320 ml, 5.6 moles) of glacial acetic acid. The mixture was cooled in ice, and the precipitated crude product was filtered and washed with cold methanol followed by hexane. There was obtained 1267 g (82% yield) of the indole ester product **7** in analytical purity, mp 114-116°; ir: ν 3348, 1670, 1463, 1220 cm^{-1}; nmr (deuteriochloroform): δ 3.72 (s, 3H, OCH_3), 3.90 (s, 3H, OCH_3), 6.89-7.08 (m, 1H, #6H), 7.11-7.62 (m, 7H, ArH).

Anal. Calcd. for $C_{17}H_{15}NO_4$: C, 68.67; H, 5.09; N, 4.71. Found: C, 68.33; H, 5.02; N, 4.47.

3-Hydroxy-1-phenyl-1*H*-indole-2-carboxylic Acid Methyl Ester (**10b**).

The title compound was prepared by the procedure employed in the preparation of indole ester **8**. From 874 g (2.92 moles) of diester **9** there was obtained 557 g (71% yield) of indole ester **10b**, mp 144.5-146° [6]; ir: ν 3290, 1651, 1548, 1232 cm^{-1}; nmr (deuteriochloroform): δ 3.64 (s, 3H, OCH_3), 6.83-7.58 (m, 8H, ArH), 7.64-7.89 (m, 1H, #4H), 8.70 (broad s, 1H, OH).

Anal. Calcd. for $C_{16}H_{13}NO_3$: C, 71.90; H, 4.90; N, 5.24. Found: C, 71.93; H, 5.04; N, 5.24.

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