Synthesis and Antiinflammatory Activity of 2,3-Bis(*p*-methoxyphenyl)indole and Related Compounds

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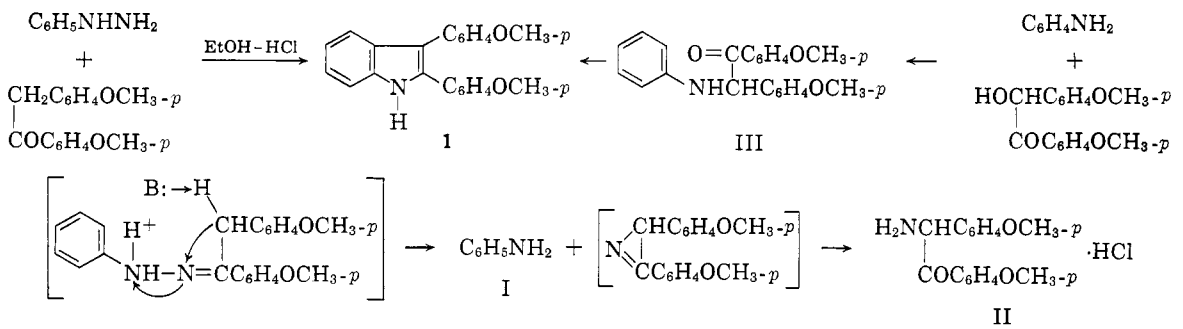
Received January 6, 1966

2,3-Bis(*p*-methoxyphenyl)indole and 48 related compounds are reported. The title compound and several related structures showed pronounced antiinflammatory activity.

The importance of finding a nontoxic nonsteroidal antiinflammatory agent is indicated by the amount of research done in this area during the last few years.[1] Our discovery that 2,3-bis(*p*-methoxyphenyl)indole[2] (**1**)[3] possesses activity in the antiinflammatory area[4] led us to synthesize and test additional indoles and other ring systems in order to determine the scope of this activity. The present paper reports the results of these efforts.

A number of compounds (see Table I) were prepared by the Fischer indole synthesis using either ethanolic hydrogen chloride or polyphosphoric acid (in the case of **30**). The preparation of **1** was accomplished by two routes (see Chart I).

CHART I



When the Fischer indole reaction was used, two by-products[5a] (I and II) were isolated in small yield, and we would like to propose the Neber[6] rearrangement as a possible path for their formation. Compound **1** was also prepared by a second route which involved the condensation of aniline and anisoin[7] with or without isolation of the intermediate amino ketone (III).

The condensation of *m*-methoxyphenylhydrazine with deoxyanisoin led to a mixture of 4- and 6-methoxy-2,3-bis(*p*-methoxyphenyl)indoles (**8** and **10**). These structures are assigned on the basis of relative yields obtained[5b] (3 and 33% yield, respectively) and also spectroscopic evidence. The lower yield would be expected in the case of the 4-methoxy-substituted compound since the 4-methoxy group shows (Dreiding model) considerable steric interaction with the aromatic substituent at position 3 in the final product. The ratio of the yield of **8** and **10** is also in accordance with the indolization mechanism considering the formation of the new C–C bond as being an intramolecular electrophilic attack.[5b] Furthermore, it should be noted (see Table III) that the ultraviolet spectrum of the 6-methoxy compound (**10**) shows a pronounced bathochromic shift of 13 mμ as compared to that of the 4-methoxy compound (**8**) for the maximum in the 300-mμ region. This shift can be explained in terms of considerable steric interaction of the type mentioned above in the case of **8a** and **8b**, but not in the case of **10a** and **10b**.

Several compounds were prepared by N-alkylation or N-acylation (see Chart II) which involved treatment of **1** with 1 equiv of sodium hydride in dimethylformamide (DMF), followed by a dialkylaminoalkyl

(1) (a) Abstracts of the 9th National Medicinal Chemistry Symposium of the American Chemical Society, University of Minnesota, June 1964, p 11; (b) M. W. Whitehouse in "Progress in Drug Research," Vol. 8, E. Jucker, Ed., Birkhäuser Verlag, Basel, 1965, p 321; (c) E. W. Boland, *Calif. Med.*, **100**, 145 (1964); (d) C. A. Winter, E. A. Risley, and G. W. Nuss, *J. Pharmacol. Exptl. Therap.*, **141**, 369 (1963); (e) C. V. Winder, J. Wax, L. Scotti, R. A. Scherrer, E. M. Jones, and F. W. Short, *ibid.*, **138**, 405 (1962); (f) C. V. Winder, J. Wax, B. Serrano, E. M. Jones, and M. L. McPhee, *Arthritis Rheumat.*, **6**, 36 (1963); (g) S. Casadio, G. Pala, E. Marazzi-Uberti, and G. Coppi, *Experientia*, **20**, 457 (1964); (h) C. J. E. Niemegeers, F. J. Verbruggen, and P. A. Janssen, *J. Pharm. Pharmacol.*, **16**, 810 (1964); (i) A. M. Katz, C. M. Pearson, and J. M. Kennedy, *Clin. Pharmacol. Therap.*, **6**, 25 (1964); (j) S. S. Adams and E. E. Cliffe, *J. Pharm. Pharmacol.*, **17**, 173 (1965); (k) L. Almirante, L. Polo, A. Mugnaini, E. Provinciali, P. Rugarili, A. Biancotti, A. Gamba, and W. Murmann, *J. Med. Chem.*, **8**, 305 (1965); (l) R. P. Mull, C. Tannenbaum, M. R. Dapero, M. Bernier, W. Yost, and G. deStevens, *ibid.*, **8**, 332 (1965); (m) International Symposium on Non-Steroidal Antiinflammatory Drugs, Milan, Sept 1964, S. Garattini and M. N. Dukes, Ed., Excerpta Medica Foundation, New York, N. Y., 1965.

(2) Generic name: indoxole. This compound is currently undergoing clinical evaluation.

(3) Arabic numerals refer to compounds described also in the tables, while Roman numerals refer to compounds mentioned only in the text.

(4) For more extensive pharmacological studies see (a) E. M. Glenn, *J. Pharmacol. Exptl. Therap.*, submitted for publication; (b) presented at the American Society for Pharmacology and Experimental Therapeutics Meeting, Philadelphia, Pa., Aug 1965.

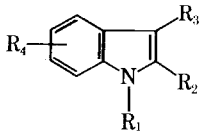
(5) (a) Aniline was encountered previously as a by-product of the Fischer indole reaction: B. Robinson, *Chem. Rev.*, **63**, 296, 373, 382 (1963); (b) *ibid.*, **63**, 389 (1963).

(6) C. O'Brien, *ibid.*, **64**, 81 (1964).

(7) (a) P. L. Julian in "Heterocyclic Compounds," Vol. 3, R. C. Elderfield, Ed., John Wiley, Inc., New York, N. Y., 1952, p 22; (b) "Heterocyclic Compounds with Indole and Carbazole Systems," W. C. Sumpter and F. M. Miller, Ed., Interscience Publishers, Inc., New York, N. Y., 1954, p 12; (c) E. E. Baroni and K. A. Kovyrzina, *J. Gen. Chem. USSR*, **29**, 3815 (1959); *Chem. Abstr.*, **54**, 19643*g* (1960).

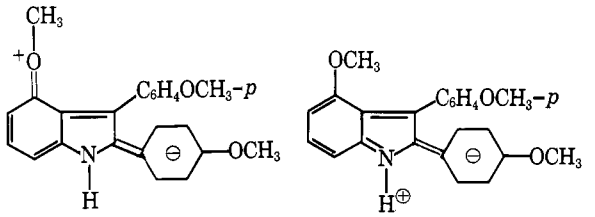
TABLE I

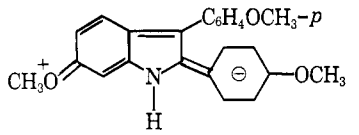
SUBSTITUTED INDOLES

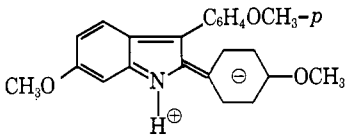


No.	R_1	R_2	R_3	R_4	Mp, °C	Method of prepn	Yield, %	Recrystn solvents[a]	Formula	Calcd, % C	Calcd, % H	Calcd, % N	Found, % C	Found, % H	Found, % N	Anti-inflammatory act.[b]
1	H	$C_6H_4OCH_3$-*p*	$C_6H_4OCH_3$-*p*	H	150–151	*c*	41	Et	$C_{22}H_{19}NO_2$	80.22	5.81	4.25	79.90	5.85	4.15	1
2	CH_3	$C_6H_4OCH_3$-*p*	$C_6H_4OCH_3$-*p*	H	127–129.5	*d*	23	Et	$C_{23}H_{21}NO_2$	80.44	6.16	4.08	80.83	5.84	4.23	0.5–1
3	C_2H_5	$C_6H_4OCH_3$-*p*	$C_6H_4OCH_3$-*p*	H	107–108	*d*	23	Et	$C_{24}H_{23}NO_2 \cdot 0.25EtOH$	79.75	6.69	3.80	79.81	6.54	3.86	0
4	$CH_2CH_2N(C_2H_5)_2$	$C_6H_4OCH_3$-*p*	$C_6H_4OCH_3$-*p*	H	109–111	*c*	96	M	$C_{28}H_{32}N_2O_2$	78.47	7.53	6.54	78.58	7.85	6.88	0.3
5	$(CH_2)_3N(C_2H_5)_2$	$C_6H_4OCH_3$-*p*	$C_6H_4OCH_3$-*p*	H	59–60.5	*e*	43	P	$C_{29}H_{34}N_2O_2$	78.70	7.74	6.33	79.04	7.75	6.16	0.5
6	COC_6H_4Cl-*p*	$C_6H_4OCH_3$-*p*	$C_6H_4OCH_3$-*p*	H	151–152	*c*	43	E–P	$C_{29}H_{22}ClNO_3$	74.43	4.74	2.99[f]	74.61	4.96	3.06	0.2
7	$COCH_3$	$C_6H_4OCH_3$-*p*	$C_6H_4OCH_3$-*p*	H	146.5–148	*cc, g*	54	E	$C_{24}H_{21}NO_3$	77.60	5.70	3.77	77.32	5.96	3.74	0.5–1
8	H	$C_6H_4OCH_3$-*p*	$C_6H_4OCH_3$-*p*	4-OCH_3	164.5–165.5	*c*	3	Me–Et	$C_{23}H_{21}NO_3$	76.86	5.89	3.90	77.00	5.98	3.96	0.3
9	H	$C_6H_4OCH_3$-*p*	$C_6H_4OCH_3$-*p*	5-OCH_3	170–171	*d*	34	Et	$C_{23}H_{21}NO_3$	76.86	5.89	3.90	76.49	5.94	3.70	0.75
10	H	$C_6H_4OCH_3$-*p*	$C_6H_4OCH_3$-*p*	6-OCH_3	183.5–184.5	*c*	33	Me–Et	$C_{23}H_{21}NO_3$	76.86	5.89	3.90	76.40	5.99	3.97	0.5
11	H	$C_6H_4OCH_3$-*p*	$C_6H_4OCH_3$-*p*	7-OCH_3	169–170	*d*	16	Me–Et	$C_{23}H_{21}NO_3$	76.86	5.89	3.90	76.62	6.32	3.40	0.2
12	H	$C_6H_4OCH_3$-*p*	$C_6H_4OCH_3$-*p*	5-CH_3	161–162	*d*	20	Et	$C_{23}H_{21}NO_2$	80.44	6.16	4.08	80.58	6.11	4.27	1.5
13	H	$C_6H_4OCH_3$-*p*	$C_6H_4OCH_3$-*p*	7-CH_3	124–125	*d*	10	Me–Et	$C_{23}H_{21}NO_2$	80.44	6.16	4.08	80.55	6.21	4.23	0.5
14	H	$C_6H_4OCH_3$-*p*	$C_6H_4OCH_3$-*p*	5-F	129–130	*d*	13	Me–Et	$C_{23}H_{18}FNO_2$	76.06	5.22	4.03[f]	75.86	5.17	4.07	1.0
15	H	$C_6H_4OCH_3$-*p*	$C_6H_4OCH_3$-*p*	7-F	159–159.5	*d, h*	6	Me–Et	$C_{23}H_{18}FNO_2$	76.06	5.22	4.03[f]	76.25	5.31	4.04	1.0
16	H	$C_6H_4OCH_3$-*p*	$C_6H_4OCH_3$-*p*	5-Cl	165–166	*d*	0.8	Et	$C_{22}H_{18}ClNO_2$	72.62	4.99	3.85[f]	72.57	5.05	3.83	1.0
17	H	C_6H_5	C_6H_5	H		*i*										0.3
18	H	C_6H_4OH-*p*	C_6H_4OH-*p*	H	212–214	*c*	68	Et–W	$C_{20}H_{16}NO_2$	79.71	5.02	4.65	79.69	5.10	.59	01
19	H	$C_6H_4OC_2H_5$-*p*	$C_6H_4OC_2H_5$-*p*	H	132–133	*c*	53	Et	$C_{24}H_{23}NO_2$	80.64	6.49	3.92	80.85	6.37	1.04	0.1
20	H	$C_6H_4OCH_2CH_2N(C_2H_5)_2$	$C_6H_4OCH_2CH_2N(C_2H_5)_2$-*p*	H	99–101	*c*	38	C	$C_{32}H_{40}N_4O_2$	76.91	8.27	8.41	76.80	8.61	8.36	0
21	H	$C_6H_4OCOCH_3$-*p*	$C_6H_4OCOCH_3$-*p*	H	197–200	*c*	53	M	$C_{24}H_{19}NO_4$	71.79	4.97	3.63	74.53	5.30	3.90	0.1
22	H	C_6H_5	$C_6H_4OCH_3$-*p*	H	188–190.5[j]	*d, k*	50	Me–Et	$C_{21}H_{17}NO$							0.5
23	H	$C_6H_4OCH_3$-*p*	C_6H_5	H	103.5–104.5[l]	*d, m*	68	E–S	$C_{21}H_{17}NO$	84.25	5.72	4.68	84.25	5.76	4.58	0.5
24	H	$C_6H_4OCH_3$-*o*	$C_6H_4OCH_3$-*o*	H	127–129	*d, n, o*	57	Ac–S	$C_{23}H_{19}NO_2$	80.22	5.81	4.25	80.35	5.87	3.88	0.2
25	H	C_6H_4Cl-*p*	C_6H_4Cl-*p*	H	132.5–133.5	*d, p, q*	57	E–S	$C_{20}H_{13}Cl_2N$	71.01	3.87	4.14[f]	71.08	3.41	4.00	0.2
26	H	$C_6H_4OCH_3$-*m*	$C_6H_4OCH_3$-*m*	H	*r*	*d, o, s*	64		$C_{23}H_{19}NO_2$	80.22	5.81	4.25	79.75	6.27	4.27	0
27	H	CH_3	$C_6H_4OCH_3$-*p*	H	129–130[t]	*d, q, u*	17	Et	$C_{16}H_{16}NO$	80.98	6.37	5.90	80.64	6.18	5.95	0
28	H	$C_6H_4OCH_3$-*p*	CH_3	H	119–121[v]	*q, w*	52	E–S	$C_{16}H_{15}NO$	80.98	6.37		80.60	6.26		0.2
29	H	H	$C_6H_4OCH_3$-*p*	H	133.5–134.5[x]	*d, y*	13	Et	$C_{16}H_{13}NO$							0
30	H	$C_6H_4OCH_3$-*p*	H	H	230–231.5	*z*	55	B	$C_{15}H_{13}NO$							0
31	H	C_6H_3-3,4-$(OCH_3)_2$	C_6H_5	H	197.5–198.5	*d, q, dd*	60	Et	$C_{22}H_{19}NO_2$	80.22	5.81	4.25	80.12	5.95	4.27	0.1
32	H	CH_3	$CH_2C_6H_4OCH_3$-*p*	H	117–117.5	*d, aa*	38	Et	$C_{17}H_{17}NO$	81.24	6.82	5.57	80.84	6.44	5.69	0
33	H	$C_6H_4NO_2$-*p*	$C_6H_4NO_2$-*p*	H	331–332	*d, q, bb*	40	T–S	$C_{20}H_{13}N_3O_4$	66.85	3.65	11.70	67.11	3.22	11.47	0
34	H	$C_6H_4OCH_3$-*p*	$COCH_2C_6H_4OCH_3$-*p*	H	170–171.5	*c*	36	Et	$C_{24}H_{21}NO_3$	77.60	5.70	3.77	77.28	5.92	3.88	0
35	H	$C_6H_4OCH_3$-*p*	$CH_2CH_2C_6H_4OCH_3$-*p*	H	80–82	*c*	43	E–P	$C_{24}H_{23}NO_2$	80.64	6.49	3.92	80.23	6.01	3.51	0
36	H	$C_6H_4OCH_3$-*p*	$CH{=}CHC_6H_4OCH_3$-*p*	H	143–144	*c*	43	M	$C_{24}H_{21}NO_2$	81.10	5.96	3.94	81.08	5.93	3.63	0
37	H	$C_6H_4OCH_3$-*p*	$CHOHCH_2C_6H_4OCH_3$-*p*	H	143–144	*c*	57	M	$C_{24}H_{23}NO_3$	77.19	6.21	3.75	77.39	6.31	3.72	0

[a] A, acetic acid; Ac, acetone; B, benzene; C, cyclohexane; E, ether; Ea, ethyl acetate; Et, ethanol; M, methanol; Me, methylene chloride; P, petroleum ether, bp 30–60°; S, Skellysolve B; T, tetrahydrofuran; W, water. [b] Hind paw edema assay, orally in rats; compounds were dissolved in polysorbate 80 in which compound **1** is given an arbitrary potency of 1. For comparative purpose the potencies of **1** and several standard compounds in carboxymethylcellulose and polysorbate 80, respectively, are: **1**, 0.25 and 1; phenylbutazone, 0.25 and 0.38; acetylsalicylic acid, 0.075 and 0.025; cortisol acetate, 0.75 and 0.7. [c] See Experimental Section. [d] Fischer indole was run with EtOH–HCl as described for the synthesis of **1** in the Experimental Section. [e] Prepared the same way as described in the case of **4** in the Experimental Section. [f] Halogen analysis was satisfactory. [g] The $NaHCO_3$ wash was omitted. [h] *o*-Fluorophenylhydrazine hydrochloride was prepared by the method of H. Suchitzky, *J. Chem. Soc.*, 3326 (1953), and converted to the free base in the usual manner. [i] Aldrich Chemical Co., Milwaukee, Wis.; crystallized from ethanol, mp 123–124°. [j] This compound was reported by R. M. Cowper and T. S. Stevens, *J. Chem. Soc.*, 1041 (1947), mp 188–190°, who prepared it from phenyl α-anilino-*p*-methoxybenzyl ketone and also by the present method with the isolation of the intermediate phenylhydrazone. [k] The method described as procedure A by R. L. Huang, *J. Chem. Soc.*, 4089 (1957), was followed for the synthesis of the required *p*-methoxybenzyl phenyl ketone, but phenacyl bromide was used instead of the chloride. The yield was 11.3%. [l] R. M. Cowper and T. S. Stevens, *J. Chem. Soc.*, 1041 (1947), prepared this compound by a similar method and reported mp 140–142° (from alcohol). Our sample showed ultraviolet, infrared, and nmr spectra consistent with the assigned structure. [m] 2.7 *N* ethanolic HCl was used. [n] 2-Methoxy-2-(*o*-methoxyphenyl)acetophenone was prepared according to J. C. Hartwell and S. R. L. Kornberg, *J. Am. Chem. Soc.*, **67**, 1606 (1945), from 2,2′-dimethoxybenzoin which was prepared according to J. C. Irvine, *J. Chem. Soc.*, **79**, 668 (1901). [o] Silica gel and CH_2Cl_2 were used for chromatography. [p] 4-Chloro-2-(*p*-chlorophenyl)acetophenone was prepared according to E. Balaban and F. K. Sutcliffe, British Patent 604,983; *Chem. Abstr.*, **43**, 2235 (1949). [q] This preparation did not require chromatography. [r] Bp 300° (0.3 mm). [s] 3-Methoxy-2-(*m*-methoxyphenyl)acetophenone was prepared according to J. L. Hartwell and S. R. L. Kornberg, *J. Am. Chem. Soc.*, **67**, 1606 (1945), from 3,3′-dimethoxybenzoin, which was prepared according to A. Schönberg and W. Malchow, *Ber.*, **55**, 3746 (1922). [t] Previously prepared by C. M. Atkinson and J. C. E. Simpson, *J. Chem. Soc.*, 1649 (1947), by treatment of 4-*p*-anisyl-3-methylcinnoline with Na and alcohol; mp 127–128°. [u] *p*-Methoxybenzyl methyl ketone was prepared according to F. W. Hoover and H. B. Hass, *J. Org. Chem.*, **12**, 501 (1947). [v] Previously prepared by C. Hell and H. Cohen, *Ber.*, **37**, 866 (1904), from aniline and *p*-methoxyphenyl 1-bromoethyl ketone; mp 123°. [w] The phenyl hydrazone of *p*-methoxypropiophenone was prepared as described in the case of synthesis of **1**. Polyphosphoric acid was used for cyclization as described in footnote *z*. [x] Previously prepared by J. M. Bruce, *J. Chem. Soc.*, 2366 (1959), by reduction of 4-*p*-methoxyphenylcinnoline; mp 134°. [y] *p*-Methoxyphenylacetaldehyde was prepared according to H. Plieninger, German Patent 957,029; *Chem. Abstr.*, **53**, 18870 (1959). [z] J. Szmuszkovicz, U. S. Patent 3,023,221. The maximum scale on which this reaction could be run without deleterious effect on the yield was using 50 g of *p*-methoxyacetophenone. [aa] Chromatography on Florisil was followed by silica gel in CH_2Cl_2. [bb] 4-Nitro-2-(*p*-nitrophenyl)acetophenone was prepared according to F. Kröhnke and I. Vogt, *Ann.*, **589**, 26 (1954), and purified by chromatography on silica gel in CH_2Cl_2. [cc] Prepared the same way as described in the case of **6** in the Experimental Section. [dd] Previously prepared by C. Mentzer and Y. Berguer, *Bull. Soc. Chim. France*, 218 (1952), from aniline and 3,4-dimethoxyphenyl α-bromobenzyl ketone; mp 198°. For the synthesis of benzyl 3,4-dimethoxyphenyl ketone see the Experimental Section.

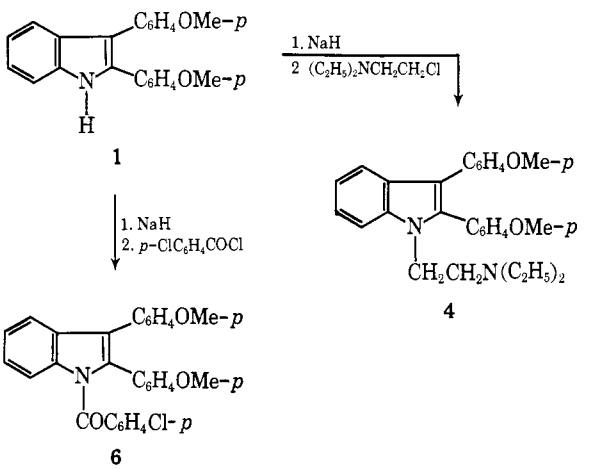






halide (illustrated in the case of the preparation of **4**), or followed by an acid chloride (illustrated in the case of **6**).

CHART II



A few derivatives were prepared by O-alkylation or O-acylation which involved (see Chart III) the reaction of **18** with 2 equiv of sodium hydride in DMF, followed by an alkyl halide (shown in the case of **19**) or an acyl halide (shown in the case of **21**).

CHART III

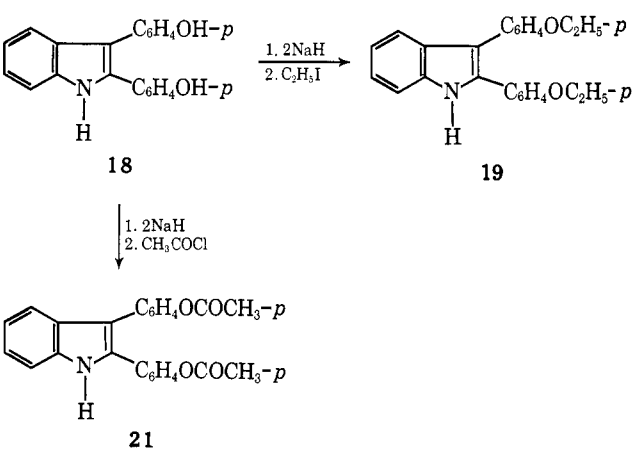
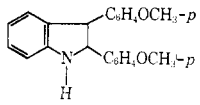
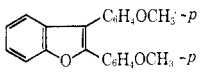
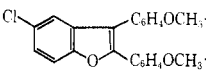
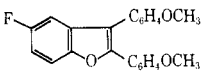
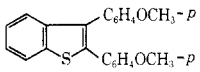
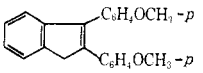
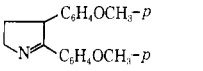
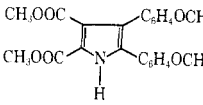
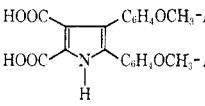
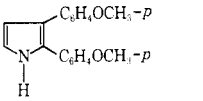
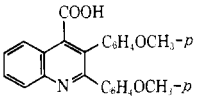
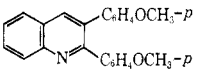


TABLE II

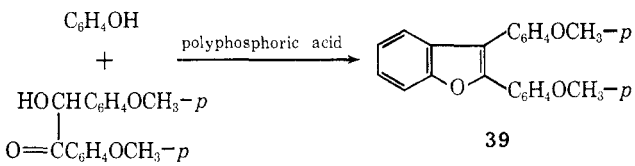
ANALOGS WITH OTHER RING SYSTEMS

No.	Structure	Mp, °C	Method prepn	Yield, %	Recrystn solvents[a]	Formula	Calcd, % C	Calcd, % H	Calcd, % N	Found, % C	Found, % H	Found, % N	Anti-inflammatory act.[b]
38		199–203	*c*	53	Et	$C_{22}H_{21}NO_2 \cdot HCl$	71.82	6.03	3.81[d]	72.00	6.16	3.59	0.2
39		148–149[e]	*c*	24	Ea–S	$C_{22}H_{18}O_3$	79.98	5.49		79.95	5.28		0.2
40		110.5–111.5	*f*	10	Et	$C_{22}H_{17}ClO_3$	72.42	4.70[d]		72.57	4.82		1.0
41		104–105	*f*	15	Et	$C_{22}H_{17}FO_3$	75.85	4.92[d]		76.05	4.95		0.5
42		131–132	*g*	19	Ea–M	$C_{22}H_{18}O_2S$	76.27	5.24[d]		76.62	5.11		0.1
43		101–102.5	*h*	28	M	$C_{23}H_{20}O_2$	84.31	6.33		84.12	6.14		0.2
44		88–89	*c*	21	E	$C_{18}H_{19}NO_2$	76.84	6.81	4.98	76.70	7.39	5.06	0
45		192–193	*c*	14	M	$C_{22}H_{21}NO_6$	66.82	5.35	3.54	67.13	5.52	3.64	0
46		202–204	*c*	95	B–Ac	$C_{20}H_{17}NO_6$	65.39	4.66	3.81	65.46	4.75	3.97	0
47		68–69.5	*c*	49	P	$C_{18}H_{17}NO_2$	77.39	6.13	5.01	76.93	6.55	4.73	0
48		308 (dec)	*i*	71	T–S	$C_{24}H_{19}NO_4$	74.79	4.97	3.63	74.23	4.77	3.68	0
49		98–100[j]	*c*	66	E–S	$C_{23}H_{19}NO_2$	80.91	5.61	4.10	80.99	5.58	4.02	0

[a] See Table I, footnote *a*, for explanation of code. [b] See Table I, footnote *b*. [c] See Experimental Section. [d] Halogen or sulfur analysis was satisfactory. [e] Previously prepared in 4% yield by B. R. Brown, G. A. Somerfield, and P. D. J. Weitzman, *J. Chem. Soc.*, 4305 (1958), from anisoin, phenol, and 8% HCl in aqueous dioxane; mp 147–148°. [f] A solution of anisoin and *p*-chlorophenol (or *p*-fluorophenol) in benzene was evaporated *in vacuo*. Polyphosphoric acid was added and the temperature was maintained at 45° for 15 min. The product was chromatographed on Florisil in CH_2Cl_2. [g] A mixture of anisoin, thiophenol, and polyphosphoric acid was heated during 33 min to 146°. [h] Prepared from 2-*p*-methoxyphenylindanone and *p*-methoxyphenylmagnesium bromide according to the general method described by D. Lednicer, J. C. Babcock, P. E. Marlatt, S. C. Lyster, and G. W. Duncan, *J. Med. Chem.*, **8**, 52 (1965). We are indebted to Dr. D. Lednicer of these laboratories for making this compound available to us. [i] Prepared according to N. P. Buu-Hoi, M. Sy, and N. D. Xuong, *Bull. Soc. Chim. France*, 629 (1956), who reported mp 335–336°; ultraviolet, λ_{max} 220 sh mμ (ε 36,900), 239 (45,400), 273 (22,750), 342 (9350). [j] Lit.[i] mp 110° for this compound, crystallized from ethanol.

The synthesis of benzofurans[8a] (see Chart IV) is illustrated in the case of **39**. It involved the reaction

CHART IV



39

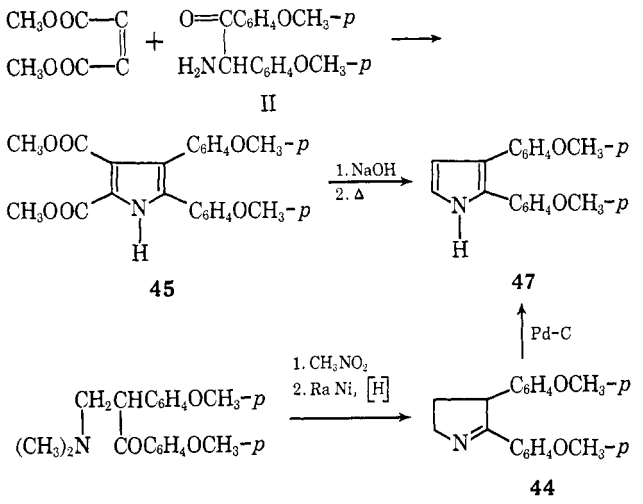
of a phenol (or thiophenol) with anisoin and polyphosphoric acid.

Compound **47** (Table II) was prepared by two routes (see Chart V).

The first route *via* **45** was patterned after the recently described pyrrole synthesis,[8b] which involves an intra-

(8) (a) R. C. Elderfield and V. B. Meyer in "Heterocyclic Compounds," Vol. 2, R. C. Elderfield Ed., John Wiley and Sons, Inc., New York, N. Y., 1951, p 16; (b) J. B. Hendrickson, R. Rees, and J. F. Templeton, *J. Am. Chem. Soc.*, **86**, 107 (1964).

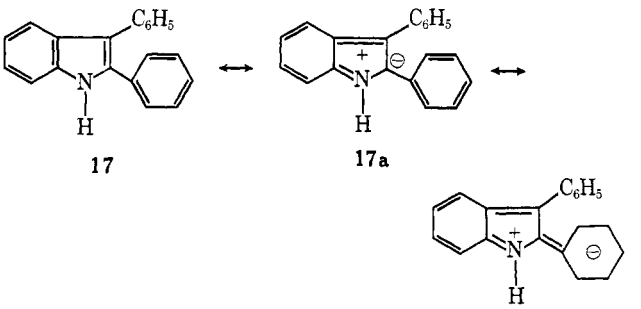
CHART V



molecular acylation of the intermediate enamine[9] to give **45**. Alkaline hydrolysis followed by thermal decarboxylation led to the desired **47**. The second route involved a Mannich base–nitromethane[10] condensation to the pyrroline derivative **44**, followed by dehydrogenation. The formulation of **44** as the 1- rather than the 2-pyrroline (*cf.* references on p 20 in footnote 9) is supported by the absence of NH band in the infrared spectrum and nmr evidence (see Experimental Section).

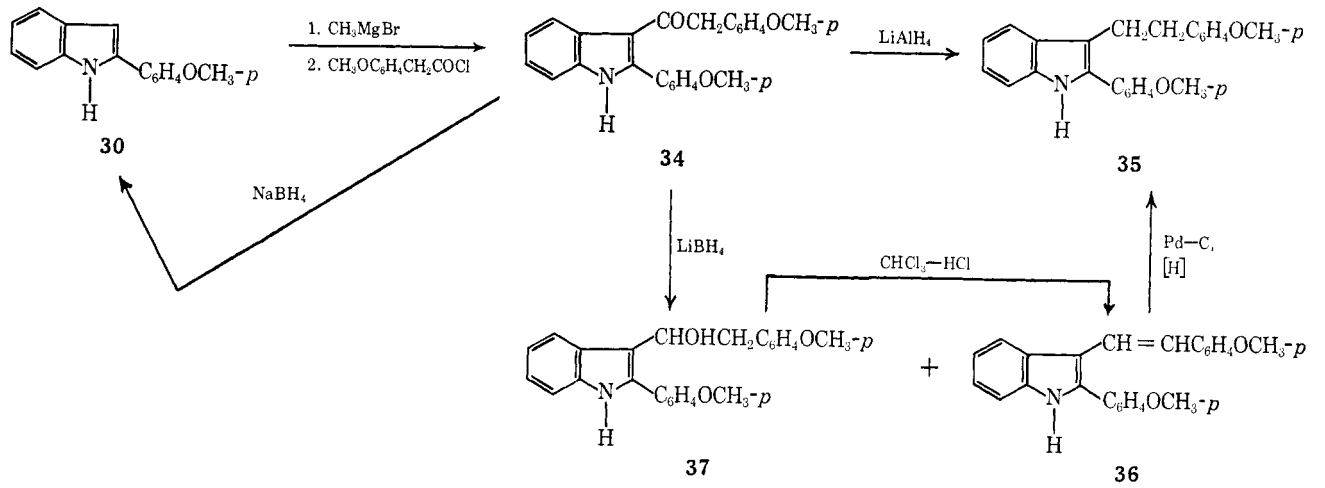
The vinylog of **1**, namely **36**, was prepared from ketone **34** (see Chart VI). The three metal hydride agents used to reduce **34** showed three different patterns of decomposition of the intermediate alkoxide formed in this reaction. In the case of sodium borohydride 1,2 elimination occurred to give **30**.[11a] Lithium aluminum hydride reduction was accompanied by 1,4 elimination followed by reduction to give a hydrogenolysis product **35** (*cf.* reference in footnote 11a). Lithium borohydride afforded a mixture of the normal reduction product **37** and a product of a different 1,2 elimination, the desired **36**.[11b] Hydrogenation of **36** led to dihydro derivative which was identical with **35**.

Correlation of Structure and Ultraviolet Absorption.—Since a detailed account of the ultraviolet spectra of 2-arylindoles has already been published,[12a] we would just like to focus attention on two points. The first point concerns the nature of the two longer wavelength absorption bands in the ultraviolet spectra of 2-aryl ndoles (see Table III): the band at 248 mμ may arise from the $\pi-\pi^*$ excitation of the aromatic ring (**17**), and the 308-mμ band may derive from the *trans*-



stilbene chromophore (which involves the 2-phenylindole portion of the molecule) red shifted by the nitrogen (*cf.* **17a**). Second, we would like to emphasize the inherent difficulty of assignment of structures, based on differences in ultraviolet absorption, as 4- or 6-substituted indoles in this series in the absence of one of the isomers.[12b]

CHART VI



Biological Studies.—The compounds presented in Tables I and II were tested[14a] for antiinflammatory activity in the hind paw edema assay by a slight modification of the method of Winter.[14] Compounds dissolved in 0.2–0.5 ml of polysorbate 80[14] were administered orally 1 hr prior to induction of edema in

(9) For a review see J. Szmuszkovicz in "Advances in Organic Chemistry, Methods and Results," Vol. 4, R. A. Raphael, E. C. Taylor, and H. Wynberg, Ed., Interscience Publishers, Inc., New York, N. Y., 1963, p 69.

(10) (a) G. A. Youngdale, D. G. Anger, W. C. Anthony, J. P. DaVanzo, M. E. Greig, R. V. Heinzelman, H. H. Keasling, and J. Szmuszkovicz, *J. Med. Chem.*, **7**, 415 (1964); (b) S. Kessar and M. C. Kloetzel, *J. Org. Chem.*, **27**, 1314 (1962).

(11) (a) The formation of **30** from **34** is reminiscent of the likely intermediacy of indole in the reaction reported by E. Leete and L. Marion, *Can. J. Chem.*, **31**, 775 (1953), who isolated 3,3,-methylenediindole on boiling indole-3-methanol with water. (b) For other examples of 3-vinylindoles see, *e.g.*, W. E. Noland and D. N. Robinson, *J. Org. Chem.*, **22**, 1134 (1957); W. E. Noland and R. J. Sundberg, *ibid.*, **28**, 884 (1963); E. Leete, *J. Am. Chem. Soc.*, **82**, 1180 (1960).

(12) (a) M. J. Kamlet and J. C. Dacons, *J. Org. Chem.*, **26**, 220 (1961). (b) Compare the discussion on this topic in ref 12a with the account given earlier in the present paper concerning **8** and **10**.

(13) C. A. Winter, E. A. Risley, and G. W. Nuss, *Proc. Soc. Exptl. Biol. Med.*, **111**, 544 (1962).

(14) For a description of this vehicle see "The Pharmacopeia of the United States of America," Mack Publishing Co., Easton, Pa., USP XVI, p 558.

TABLE III

ULTRAVIOLET SPECTRA[a-c]

No.	λ_{max}, mμ	ε	λ_{max}, mμ	ε
1	252.5	32,700	308	20,600
2	249	31,500	301	15,800
3	240	30,950	299	14,900
4	239	30,600	299	15,400
5	241	30,000	299	15,200
6	246	37,750	300	19,750
7	241	28,300	298	15,700
8	254	33,100	310	18,750
9	252	25,350	316	24,950
10	253	31,400	323	19,900
11	256	34,200	306	20,150
12	254	30,600	313	20,900
13	253	31,200	308	19,400
14	251	28,650	310	22,300
15	253	35,000	305	19,650
16	257	29,950	314	17,100
17[d]	248	22,500	308	17,150
18	253	32,700	309	20,350
19	253	33,350	309	21,000
20	253	33,850	309	21,450
21	248	22,250	309	18,500
22	249	28,050	308	17,650
23	253	28,050	309	19,900
24	248	22,750	303	16,250
25	248	21,050	311	18,400
26	249	23,950	312	17,650
27	270	16,000		
28	245	20,950	308	22,750
29	264.5	17,250		
30	248	17,625	310	26,450
31	257	25,200	315	20,350
33	264	15,050	360	14,850

[a] For structural formulas see Table I. [b] Determined in 95% ethanol. [c] Maxima below 232 mμ and shoulders are not reported. [d] No change was observed in 0.01 *N* ethanolic H_2SO_4.

the right hind paw of rats by subplantar injection of 0.1 ml of 0.5% carrageenin. Drugs were assayed at four to six doses employing 10 rats/group. The comparative potencies were estimated from the log dose–response obtained from the individual assays. Vehicle-treated controls were used in each assay. For comparative purposes phenylbutazone was found to be 1.5 times as active in polysorbate 80 as in carboxymethylcellulose.

Because many of the compounds bear some structural resemblance to synthetic estrogens and since high doses of estrogens show antiinflammatory activity due to adrenal hypertrophy, a typical active member of our series, compound **1**, was studied for estrogenic activity. Immature and mature castrate female rats were dosed orally twice daily for 7 days. In contrast to stilbestrol and estrone controls, no adrenal stimulatory effects, no loss of body weight, and no changes in uterus weight were noted at very high doses, indicating a complete lack of estrogenic activity.

Toxicity.—Compounds of Tables I and II were nontoxic in mice[15] with intraperitoneal LD_{50} values of 1000 mg/kg or greater, except for compounds **5**, **18**, **44** (562), **20** (178), and **46** (422). The therapeutic ratio of the more active compounds compared well with aspirin (1500), hydrocortisone acetate (2000), and especially with phenylbutazone (233).

(15) LD_{50} values were determined as described in ref 10a.

Structure–Activity Relationships.—From the tables it is apparent that certain compounds have significant antiinflammatory activity, whereas other very closely related structures are much less active or even inactive. Small alkyl or acyl groups on the indole nitrogen effect activity only slightly (*e.g.*, **2** and **7**), whereas larger groups of this type decrease activity significantly (*e.g.*, **3** and **6**). Substituents such as methyl (**10** and **13**), methoxyl (**8**–**11**), or halogen (**14**–**16**) in the benzene ring of the indole moiety seem to have in general little influence on activity, no matter what the position of the substitution.

It is in the 2 and 3 positions of the indole ring that the influence of substitution is clearly seen. Phenyl substitution on both positions is the minimum requirement for activity. Furthermore, the type of substitution on these phenyl rings is most critical. Optimal activity is present when both groups are *p*-anisyl (**1**). If the methoxyl groups are moved to the *ortho* or *meta* positions (**24** and **26**) activity is eliminated as is also the case if the *p*-methoxyl substituents are replaced by *p*-ethoxyl (**14**), *p*-hydroxyl (**18**), *p*-chloro (**25**), *p*-nitro (**33**), or *p*-diethylaminoethoxyl (**20**). Activity is reduced progressively as one (**22** and **23**) and then both methoxyl groups (**17**) are removed.

When the indole nitrogen in **1** is replaced by oxygen or sulfur (**39** and **42**) activity is not eliminated but is reduced. Substitution of halogen into the benzofuran ring (**40** and **41**) again yields highly active compounds. On the other hand, the indene analog of **1**, in which the nitrogen is replaced by methylene (**43**) has little activity. The corresponding pyrrole (**47**), 1-pyrroline (**44**), and quinoline (**49**) are devoid of antiinflammatory activity.

It is difficult to rationalize the above pattern of structure–activity interrelationships solely on the basis of electronic, spatial or solubility factors. Clearly a more complicated set of requirements[16] is involved here such as a multiple point of attachment in the agonist–enzyme complex.

Experimental Section[17,18]

Synthesis of 2,3-Bis(*p*-methoxyphenyl)indole (1). A. By the Fischer Indole Synthesis.—A mixture of phenylhydrazine (53 g, 0.49 mole), deoxyanisoin (125 g, 0.49 mole), 4.3 ml of acetic acid, and 530 ml of benzene was refluxed under N_2 for 3 hr, and 9.2 ml of water was collected using a water separator. The

(16) (a) "Molecular Pharmacology," E. J. Ariens, Ed., Academic Press Inc., New York, N. Y., 1964; (b) W. C. Holland, R. L. Klein, and A. H. Briggs, "Introduction to Molecular Pharmacology," The Macmillan Co., New York, N. Y., 1964, p 167.

(17) Melting points were taken in a capillary tube and are corrected. Ultraviolet spectra were determined in 95% ethanol using a Cary spectrophotometer Model 14. Infrared spectra were determined in Nujol using a Perkin-Elmer recording infrared spectrophotometer Model 21. The nmr spectra were measured in 60 Mc, using $CDCl_3$ as solvent (unless otherwise specified); frequencies are reported in cycles per second downfield from internal tetramethylsilane. Florisil is magnesium–silica gel adsorbent manufactured by Floridin Co., Pittsburgh, Pa. Silica gel (0.05–0.20 mm) was from Merck, Darmstadt. Skellysolve B is commercial hexane, bp 60–70°, made by Skelly Oil Co., Kansas City, Mo. Petroleum ether refers to fraction, bp 30–60°. $LiAlH_4$ refers to lithium aluminum hydride. All the compounds described in Tables I and II showed consistent infrared and nmr spectra but only those cases described in detail in the Experimental Section are reported.

(18) The authors are indebted to Dr. W. A. Struck and his associates for microanalyses, to Mr. P. A. Meulman for infrared spectra, to Miss Betty Zimmer for ultraviolet spectra, to Messrs. J. F. Zieserl and F. A. MacKellar for nmr spectra, to Dr. M. F. Grostic, Messrs. D. A. Griffith and R. J. Wnuk for the mass spectra, and to Messrs. D. B. Hooker, T. Koslowski, L. G. Laurian, and M. L. Myers for laboratory assistance.

resulting solution was evaporated to dryness, 960 ml of 3 *N* ethanolic HCl was added, and the mixture was refluxed for 1.25 hr.[19] It was evaporated to dryness and shaken with 400 ml each of CH_2Cl_2 and water. The aqueous layer was extracted with 200 ml of CH_2Cl_2. The combined organic layer was washed with two 200-ml portions of water, three 100-ml portions of 5% NaOH, and 200 ml of saturated NaCl solution, then dried (Na_2SO_4), and evaporated to give 170 g of a brown oil. The oil was dissolved in 300 ml of methylene chloride and chromatographed on 3 kg of Florisil. Methylene chloride was used as eluent and 400-ml fractions were collected. Fractions 9–17 afforded 82.5 g of product. Crystallization from ethanol afforded 60.5 g melting at 151–152°, and a second crop of 6.1 g melting at 150–151°. The infrared spectrum (cm^{-1}) showed NH, 3440; C=C, 1610, 1575, 1555, 1520, 1495; CO/CN, 1255, 1225, 1175, 1030; aromatic, 830, 820, 750; nmr showed two singlets at 223, 227 (OCH_3 area 6), complex at 402–462 (aromatic area 12), NH at 484.5.

The aqueous wash of the crude reaction mixture (from a 5-mole run) was allowed to stand for 1 week. The resulting suspension was filtered, and the solid was washed with a little water to give 41.1 g (2.7%) of 2-amino-4′-methoxy-2-(*p*-methoxyphenyl)-acetophenone hydrochloride melting at 249–251°, raised to 253–255° dec on crystallization from ethanol (lit.[20] mp 258–259° dec). The ultraviolet spectrum showed λ_{max} 224 mμ (ε 18,350), 276 sh (15,750), 286 (16,650), sh 292 (16,200); the infrared (cm^{-1}) showed amine salt, 3000, 2680, 2600; C=O, 1690; C=C, 1610, 1600, 1575, 1510; CO/CN, 1255, 1240, 1180, 1170, 1030, 1015; aromatic, 850, 830, 810, 780; the mass spectrum showed a peak at *m/e* 271 (307 − HCl); the strongest peak was at *m/e* 136 which by isotope analysis was $C_8H_{10}NO$ (H_2NCH-$C_6H_4OCH_3$); nmr (in D_2O) showed two singlets at 228.5 and 230 (OCH_3 area 6), singlet at 379 (H on carbon bearing NH_2, area 1), and complex at 408–484.5 (aromatic, area 8).

Anal. Calcd for $C_{16}H_{17}NO_3 \cdot HCl$: C, 62.43; H, 5.89; Cl, 11.52; N, 4.55. Found: C, 62.66; H, 5.94; Cl, 11.33; N, 4.66.

The aqueous filtrate from above was washed with 100 ml of CH_2Cl_2 (discard organic layer), cooled in ice, basified with 20% NaOH and extracted with four 200-ml portions of ether. The extract was washed with saturated NaCl solution and evaporated. The resulting brown oil was dissolved in ether and treated with ethereal HCl. The crude product was crystallized from cold ethanol to give 28.2 g (4.3% yield) of aniline hydrochloride, mp 196–197°. It was identified by comparison of infrared and ultraviolet spectra to those of an authentic sample and a mixture melting point determination.

B. From Anisoin and Aniline[7] without Isolation of Intermediate.—A mixture of aniline (37.3 g, 0.25 mole), anisoin (13.6 g, 0.05 mole), and 3.3 ml of concentrated HCl was refluxed for 30 min (inside T = 110°). The mixture was then distilled until the inside temperature reached 180° and kept at this temperature for 1 hr. It was allowed to stand overnight. Water and ether were added, and the aqueous layer was extracted once more with ether. The ether extract was washed with forty 50-ml portions of 10% HCl, water, 5% NaOH, water, and saturated NaCl solution, dried ($NaSO_4$), and evaporated. A solution of the crude product (16.2 g) in methylene chloride was stirred with 100 g of Florisil. The suspension was filtered and evaporated. Two crystallizations of the residue (15.8 g) from ethanol gave 5.2 g of **1** melting at 148–149°. The ultraviolet showed λ_{max} 253 mμ (ε 32,200), 308 (20,450). The filtrates were evaporated to dryness and a solution of the residue in CH_2Cl_2 was passed through a column of Florisil (339 g). Elution with seven 200-ml portions of CH_2Cl_2 and crystallization from ethanol afforded 4.3 g of **1** melting at 150–151°. The ultraviolet showed λ_{max} 282 mμ (ε 33,150), 308 (20,950); yield 58%.

C. From Anisoin and Aniline with Isolation of Intermediate.—A mixture of aniline (10.2 g, 0.11 mole), anisoin (27.2 g, 0.1 mole), *p*-toluenesulfonic acid monohydrate (0.95 g, 0.005 mole), and 100 ml of benzene was refluxed under nitrogen for 22 hr using a water separator (1.6 ml of aqueous layer was collected). The mixture was filtered, the filtrate was washed with 5% NaOH, water, and saturated NaCl solution, dried (Na_2SO_4), and evaporated. Crystallization from methanol afforded 26.75 g (77% yield) of 2-anilino-4′-methoxy-2-(*p*-methoxyphenyl)acetophenone as yellow prisms, mp 114–115°[21] unchanged on recrystallization. The ultraviolet showed λ_{max} 223 mμ (ε 21,050), 248 (17,000), sh 276 (18,650), 282 (18,800); the infrared (cm^{-1}) showed NH, 3400; C=O, 1670; C=C, 1600, 1580, 1505, 1480; CO/CN, 1260, 1245, 1165, 1030; aromatic, 835, 750, 690; nmr showed two singlets at 219, 225 (OCH_3 area 6), 322 (NH area 1), 357 (NCHCO area 1), and complex at 393–485.5 (aromatic area 13).

Anal. Calcd for $C_{22}H_{21}NO_3$: C, 76.06; H, 6.09; N, 4.03. Found: C, 75.83; H, 5.86; N, 3.99.

A solution of the above amino ketone (6.94 g, 0.02 mole) and 0.3 g of *p*-toluenesulfonic acid in 100 ml of *p*-cymene was refluxed under nitrogen for 2 hr using a water separator. The mixture was cooled, washed with three 50-ml portions of 5% HCl, three 50-ml portions of 5% NaOH, water, and saturated NaCl, dried (Na_2SO_4), and evaporated. The product (6.2 g) was chromatographed on 372 g of silica gel with 5% ethyl acetate–cyclohexane as eluent and 250-ml fractions were collected. Fractions 8 and 9 gave a solid, which was crystallized twice from petroleum ether to give 80 mg of 2,3-dimethyl-2,3-di-*p*-tolylbutane, mp 155–156.5°.[22] The ultraviolet showed λ_{max} 221 mμ (ε 17,900), sh 253 (433), 259 (586), 265 (760), 273 (655); the infrared (cm^{-1}) showed CH, 3090, 3060, 3020; C=C, 1510, 1190, 1080, 1015; aromatic: 815; nmr showed a peak at 76.5 (CH_3, area 12), 138.5 (CH_3, area 6), and 420 (aromatic, area 8). Carbon and hydrogen analysis also conformed with the above structure.

Fractions 10–19 gave oils (discarded). Elution was continued with 20% ethyl acetate–cyclohexane. Fraction 2 crystallized from ethanol to give 0.9 g (12.7% yield) of **1** melting at 144–147°. It was identical with an authentic sample as shown by comparison of ultraviolet spectra and mixture melting point determination.

Example for N-Alkylation. 1-[2-(Dimethylamino)ethyl]-2,3-bis(*p*-methoxyphenyl)indole (4).—Sodium hydride (0.46 g of a 53% dispersion in mineral oil; 0.01 mole) was added under N_2 to a stirred solution of **1** (3.3 g, 0.01 mole) in 50 ml of DMF. After 2 hr, 2.71 g of a solution of diethylaminoethyl chloride in xylene (1:1 by wt, 0.01 mole) was added, and the mixture was stirred for 19 hr. It was evaporated on the steam bath *in vacuo*. The residue was treated with 100 ml of 10% HCl and ether. An insoluble colloidal hydrochloride resulted. It was washed three times by shaking with ether and decantation. The mixture was then cooled, basified with NaOH, and extracted with ether. The ether extract was washed with water and a saturated salt solution, dried by passage through sodium sulfate, and evaporated; 4.1 g, mp 108–110°. The infrared (cm^{-1}) showed C=C, 1610, 1575, 1555, 1515, 1495; CO/CN, 1245, 1175, 1105, 1035, 1025; aromatic, 825, 740; nmr showed triplet centered at 52 (CCH_3 area 6), multiplet centered at 149 (CH_2N aliphatic area 6), two singlets at 223.5, 226.5 (OCH_3 area 6), multiplet centered at 249 (CH_2N indole area 2); complex at 403.5–471 (aromatic area 12).

Example for N-Acylation. 1-(*p*-Chlorobenzoyl)-2,3-bis(*p*-methoxyphenyl)indole (6).—The reaction was run as described in the case of **4**, but using 1.75 g (0.01 mole) of benzoyl chloride and $NaHCO_3$ instead of NaOH in the work-up. The crude product was chromatographed on 90 g of silica gel using 20% ethyl acetate–cyclohexane as the eluent. Elution with 275 ml gave fractions containing the desired compound. Further elution gave some unchanged **1**. The desired product was crystallized from ether–petroleum ether; pale yellow prisms, 2 g, mp 151–152°. The infrared (cm^{-1}) showed C=O, 1685; C=C, 1620, 1610, 1600, 1590, 1570, 1515, 1500, 1495; CO/CN, 1245, 1230, 1175, 1085, 1030; aromatic, 845, 830, 750; nmr showed two singlets at 222, 228.5 (OCH_3 area 6), complex at 392.5–470 (aromatic area 16).

Synthesis of 4-Methoxy-2,3-bis(*p*-methoxyphenyl)indole (8) and 6-Methoxy-2,3-bis(*p*-methoxyphenyl)indole (10). A. *m*-Methoxyphenylhydrazine Hydrochloride.—Concentrated HCl (750 ml) was added to a mixture of *m*-methoxyaniline (246.3 g, 2.0 moles) and 750 ml of water. The resulting mixture was cooled with stirring to −20° and treated dropwise with a solution of $NaNO_2$ (142 g, 2.06 moles) in 500 ml of water. (The temperature of the reaction mixture was kept at −15 to −20° during this addition.) This solution was warmed to 0° and added dropwise to a stirred solution of $SnCl_2 \cdot 2H_2O$ (915 g, 4.05 moles) in 1 l. of concentrated HCl maintained at 0°. The resulting mixture was stirred at 0° for 2 hr; the solid was collected by filtration and dissolved in water (2 l.), and the solution was

(19) The time varied from 30 min to 24 hr. The longer period was required in the case of disubstituted hydrazines.

(20) G. Drefahl and M. Hartmann, *Ann.*, **589**, 82 (1954).

(21) (a) A. Novelli and J. C. Somaglino, *Chem. Abstr.*, **38**, 2957[7] (1944), reported mp 115°; (b) E. F. Pratt and M. J. Kamlet, *J. Org. Chem.*, **28**, 1366 (1963).

(22) G. Ciamician and P. Silber, *Ber.*, **43**, 1536 (1910).

saturated with NaCl. This was cooled below 10°, made alkaline with 50% NaOH, and extracted with four 1-l. portions of ether. The combined ether extract was dried ($MgSO_4$) and acidified with ethereal HCl. The resulting hydrochloride was collected by filtration and crystallized from 2-propanol to yield 130 g (37%) of *m*-methoxyphenylhydrazine hydrochloride, mp 141° dec (lit.[23] mp 140–141°).

B. Fischer Indole Reaction.—To a stirred mixture of 3 *N* NaOH (100 ml) and ether (100 ml) cooled to 0°, was added *m*-methoxyphenylhydrazine hydrochloride (20.5 g, 0.115 mole). The aqueous layer was saturated with NaCl, separated from the ether layer, and extracted twice with 200-ml portions of ether. The combined ether extract was washed once with 50 ml of saturated NaCl solution, dried ($MgSO_4$), and concentrated under reduced pressure at room temperature. A solution of the resulting light yellow oil in benzene (1 l.) was treated with 25.6 g (0.10 mole) of deoxyanisoin and 2 ml of acetic acid. The resulting solution was refluxed under N_2 for 30 min with azeotropic distillation of water and concentrated under reduced pressure at 35°. The residue was treated with ice-cold 3 *N* ethanolic HCl (200 ml), refluxed for 30 min under N_2, cooled, and treated with 1 l. of ice water. This mixture was extracted with four 500-ml portions of methylene chloride. The combined CH_2Cl_2 extract was washed with saturated NaCl solution (500 ml), dried ($MgSO_4$), and concentrated under reduced pressure at 35°. Chromatography of the residue on Florisil (1.5 kg) with CH_2Cl_2 resulted in a preliminary purification of the two isomeric products. A good separation of these compounds was obtained by careful chromatography on silica gel (1.2 kg, E. Merck AG) with 20% ethyl acetate–cyclohexane (200 50-ml fractions were collected). The first product eluted from the column (fractions 40–69) was dissolved in CH_2Cl_2–ethanol, decolorized with Darco G 60, and crystallized to yield 1.06 g of **8**, mp 164.5–165.5°. The infrared (cm^{-1}) showed NH, 3360; C=C, 1610, 1575, 1550, 1515, 1500, 1495; CO/CN, 1235, 1180, 1020; aromatic, 830, 740; nmr showed three sharp peaks corresponding to 9 methoxyl hydrogens at 221, 224, and 228 cps, the indole NH at 488 cps, a pair of doublets (apparent J = 2 and 7 cps) centered at 390.5 cps corresponding to H-5 of the indole nucleus, and a complex multiplet extending from 402 to 446 cps corresponding to the remaining aromatic hydrogens.

The second product eluted from the column (fractions 83–200) was crystallized from CH_2Cl_2–ethanol to yield 11.88 g of 6-methoxy-2,3-bis(*p*-methoxyphenyl)indole, mp 183.5–184.5°. The infrared (cm^{-1}) showed NH, 3340; C=C, 1615, 1585, 1575, 1555, 1520 and 1495; CO/CN, 1265, 1240, 1200, 1180, 1175, 1165, 1035; aromatic, 830, 870, 810, 795; nmr showed two peaks at 228 and 230 cps corresponding to 9 methoxyl hydrogens, a multiplet extending from 403 to 446 cps corresponding to 11 aromatic hydrogens, and a broad peak at 482 cps corresponding to the indole NH.

4,4′-Indole-2,3-diyldiphenol (18).—Aluminum chloride (66.5 g, 0.5 mole) was added all at once to a solution of **1** (33 g, 0.1 mole) in 1 l. of dry benzene, while stirring and cooling under nitrogen. The mixture was then refluxed for 4 hr. It was cooled in ice and decomposed by addition of a solution of 500 ml of concentrated HCl in 1500 ml of water. The resulting suspension was filtered and the product was washed with water. The product was dissolved in 750 ml of 5% NaOH, and the resulting dark green solution was filtered, cooled, and acidified with 250 ml of concentrated HCl. The product was filtered and washed with water to give 33.6 g. It was passed through a column of silica gel (1000 g) in ethyl acetate. Elution with four 400-ml portions of ethyl acetate afforded solid fractions, which were triturated with chloroform to give 11.2 g, mp 212–214°, and 3 g, mp 198–211°. Further elution with two 400-ml portions of ethyl acetate gave fractions which were combined with the filtrates from the above trituration and rechromatographed on 330 g of silica gel using 5% methanol–$CHCl_3$ as eluent. Elution with nine 250-ml portions afforded the product which was crystallized from ethyl acetate; 6.1 g, mp 213–214°. The infrared (cm^{-1}) showed NH/OH, 3450, 3420, 3260; C=C, 1605, 1590, 1555, 1515, 1495; CO/CN, 1230; aromatic, 745; nmr (in DMF-*d*,) showed aromatic H's at 407–457.5, phenolic OH at 578, indole NH at 672.

Example for O-Alkylation. 2,3-Bis(*p*-ethoxyphenyl)indole (19).—Sodium hydride (0.92 g of 53% dispersion in oil; 0.02 mole) was added portionwise during about 1 min to a solution of **18** (3.0 g, 0.01 mole) in 50 ml of DMF, and the mixture was stirred for 30 min. A green solution resulted. Ethyl iodide (3.12 g, 0.02 mole) was added dropwise during 3 min, and the solution was stirred for 21 hr. The mixture was evaporated *in vacuo* on the steam bath. Water was added and the product was extracted with ether. The extract was washed four times with 5% NaOH solution (total 100 ml), then with water, and saturated NaCl solution. It was dried (Na_2SO_4) and evaporated. The product was passed through a column of Florisil (114 g) in CH_2Cl_2 to give 3.17 g which could not be crystallized. Chromatography on 94 g of silica gel in 20% ethyl acetate–cyclohexane afforded some oil in the first two 50-ml fractions. The third fraction (50 ml) gave 2.13 g which crystallized from ethanol; 1.9 g of colorless prisms, mp 132–133°. The infrared (cm^{-1}) showed NH, 3430; C=C, 1610, 1570, 1520, 1495; CO/CN, 1255, 1240, 1190, 1175, 1050; aromatic, 840, 740; nmr showed two triplets centered at 83, 85 (CH_3 area 6), two quartets centered at 240, 247 (CH_2 area 4), complex at 404–464 (aromatic area 12), 485 (NH area 1).

2,3-Bis{*p*-[2-(diethylamino)ethoxy]phenyl}indole (20).—The reaction was run as described in the case of the synthesis of **19**, but using 0.02 mole of diethylaminoethyl chloride (diluted 1:1 with xylene). Water and CH_2Cl_2 were added, and the product was extracted with a total of 125 ml of 10% HCl. The acid extract was cooled, basified, and extracted three times with CH_2Cl_2. The extract was washed with water, NaCl solution, dried by passage through Na_2SO_4, and evaporated to give 4.7 g of dark brown oil. The oil was dissolved in 20 ml of benzene and chromatographed on 141 g of neutral alumina (Woelm, activity I). Elution with 600 ml of ether, 250 ml of 0.5% methanol–ether, and 250 ml of 1% methanol–ether afforded 2.88 g of product. It was crystallized from Skellysolve B, followed by recrystallization from cyclohexane to give 1.9 g, mp 99–101°. The infrared (cm^{-1}) showed NH, 3340, 3200; N-alkyl, 2800; C=C, 1610, 1575, 1555, 1515, 1490; CO/CN, 1235, 1180, 1045; aromatic, 835, 745; nmr showed triplet centered at 63 (CH_3 area 12), multiplet at 148–179 (CH_2N area 12), two triplets centered at 240.5, 244 (OCH_2 area 4), complex at 454–462 (aromatic area 12), singlet at 497.5 erased by D_2O (NH area 1).

Example for O-Acylation. 4,4′-Indole-2,3-diyldiphenol Diacetate (21).—The reaction was run as described in the case of the synthesis of **19**, but using acetyl chloride (1.57 g, 0.02 mole). The mixture was evaporated *in vacuo* on the steam bath. Water was added, and the product was extracted with ether. The ether extract was washed with water, saturated NaCl solution, dried (Na_2SO_4), and evaporated. The residue was dissolved in 25 ml of chloroform and chromatographed on 123 g of silica gel using 5% methanol–chloroform as the eluent. The first three 100-ml fractions afforded the product which was crystallized from methanol as colorless prisms, 2.03 g, mp 197–200°. The infrared (cm^{-1}) showed NH, 3400; C=O, 1750, 1735; C=C, 1600, 1590, 1560, 1515, 1490; CO/CN, 1225, 1200, 1165, 1015; aromatic, 855, 750; nmr showed singlet at 137.5 (CH_3 area 6), complex at 416.5–465 (aromatic area 12), broad peak at 497 (NH area 1).

Benzyl 3,4-Dimethoxyphenyl Ketone.—A stirred mixture of phenylacetic acid (27.2 g, 0.20 mole), veratrole (27.6 g, 0.20 mole), and polyphosphoric acid (600 g) was heated slowly on the steam bath to 95° and allowed to remain at this temperature for 30 min. It was then poured into 3 l. of stirred ice–water. The mixture was stirred for 1.5 hr. The product was collected by filtration, washed successively with water, Na_2CO_3, and water, and crystallized from methanol to yield 41.0 g (80%) of material, mp 86–88° (lit.[24] mp 87–88°).

Synthesis of 2-(*p*-Methoxyphenyl)-3-(*p*-methoxystyryl)-indole (36). A. *p*-Methoxybenzyl 2-(*p*-Methoxyphenyl)indol-3-yl Ketone (34).—A suspension of 2-(*p*-methoxyphenyl)indole (prepared according to footnote *z*, Table I) (75.2 g, 0.337 mole) in 2 l. of benzene was heated to boiling and then cooled to 40–50°. An ethereal solution of methylmagnesium bromide (114 ml of 3 *M* or 0.342 mole) was added dropwise during 30 min. The resulting solution was refluxed for 1.5 hr. It was then cooled to room temperature and *p*-methoxyphenylacetyl chloride (62 g, 0.337 mole) was added over a 20-min period. The mixture was refluxed for 1.5 hr and allowed to stand overnight. It was decomposed by addition of a solution of 95 ml of concentrated HCl in 350 ml of water. The suspension was filtered and the solid was washed with benzene, then with water; 13.1 g, mp 196–206°. It was crystallized from chloroform to give 4 g of

(23) C. Alberti and C. Tivoni, *Farmaco* (Pavia), *Ed. Sci.*, **17**, 443 (1962).

(24) M. O. Faroog, W. Rahman, and M. Ilyas, *Ber.*, **92**, 2555 (1959).

recovered 2-(*p*-methoxyphenyl)indole. The benzene filtrate was separated into layers. The benzene layer was washed with water and saturated NaCl solution, dried by passage through Na_2SO_4, and evaporated. The resulting colored solid was triturated with ether and filtered. The solid was then crystallized from ethanol; 31.5 g, mp 170–171.5°. The second crop amounted to 14 g, mp 168–171°, yield 36%. The ultraviolet showed λ_{max} 211 mμ (ε 39,300), 258 (24,450), sh 284 (12,950), 308 (14,950); the infrared (cm^{-1}) showed NH, 3170, 3140; C=O, 1600; C=C, 1575, 1545, 1510, 1500; CO/CN, 1250, 1175, 1125, 1105, 1035; aromatic, 830, 815, 790, 765; nmr showed two singlets at 221.5, 229 (OCH_3), singlet at 226 (CH_2), complex at 406–500 (aromatic), broad 536 (NH).

B. Treatment of 34 with $LiAlH_4$.—A solution of **34** (37.1 g, 0.1 mole) in 500 ml of THF was added under nitrogen to a solution of $LiAlH_4$ (37.1 g) in 2500 ml of THF during 20 min. The mixture was refluxed with stirring for 17 hr. It was then cooled in ice and decomposed by successive addition of 37 ml of water, 37 ml of 15% NaOH, and 111 ml of water. The suspension was filtered, the solid was washed with THF, and the filtrate was evaporated. The residue (37.8 g of brown oil) was dissolved in 20 ml of methylene chloride and 50 ml of 15% acetone–Skellysolve B and chromatographed on 1134 g of Florisil. Elution with 15% acetone–Skellysolve B (350-ml fractions were collected) gave 26.5 g of an oil (fractions 11–17). Crystallization from ether–petroleum ether gave 15.26 g of **35** as prisms, mp 80–82°. The ultraviolet showed λ_{max} 228 mμ (ε 30,700), sh 245 (24,000), sh 280 (10,800), sh 288 (13,900), 306 (20,200); the infrared (cm^{-1}) showed NH, 3340; C=C, 1605, 1580, 1575, 1550, 1510; CO/CN, 1250, 1235, 1175, 1030, 1020; aromatic, 830, 745; nmr showed two triplets centered at 180, 181.5 (CH_2 area 4), two singlets at 223, 226 (OCH_3 area 6), complex at 402–463 (aromatic area 12), NH at 470.

C. Treatment of 34 with Sodium Borohydride.—Solid $NaBH_4$ (3.7 g) was added during 10 min to a warm (*ca.* 40°) solution of **34** (3.71 g, 0.01 mole) in 250 ml of ethanol. The mixture was stirred overnight. The resulting solution was evaporated to dryness and 100 ml of water was added. The solid was filtered and washed with water. Crystallization from ethanol afforded 1.2 g (54%) of 2-(*p*-methoxyphenyl)indole (**30**), mp 228–229°. It was identified by comparison of the ultraviolet and infrared spectra with those of the authentic sample.

D. Treatment of 34 with Lithium Borohydride.—A solution of **34** (20.2 g, 0.0545 mole) in 270 ml of THF was added to a suspension of $LiBH_4$ (20.2 g) in 220 ml of THF, and the mixture was stirred overnight at room temperature. It was then cooled in ice and decomposed by successive addition of 21 ml of water, 21 ml of 15% NaOH solution, and 63 ml of water. After stirring another 30 min, the suspension was filtered, and the filtrate was evaporated to dryness *in vacuo*. The residue was stirred with 1 l. of water and 700 ml of ether. The layers were separated and the aqueous layer was extracted with three 100-ml portions of CH_2Cl_2. The combined organic extract was washed with water, saturated NaCl solution, dried (Na_2SO_4), and evaporated. The residue was crystallized from methanol to give 11.7 g of alcohol **37**, mp 143–144° (mixture melting point with **36** showed a depression: 125–135°). The ultraviolet showed λ_{max} 213 sh mμ (ε 33,400), 224 (33,200), 243 sh (23,800), 287 sh (15,500), 300 (18,700); the infrared (cm^{-1}) showed NH/OH, 3520, 3330; C=C, 1610, 1585, 1575, 1550, 1510, 1485; CO/CN, 1250, 1180, 1160, 1105, 1025; aromatic, 845, 820, 750. Nmr was at first run in $CDCl_3$ and was compatible with the dehydration product **36**. This was likely caused by presence of acid in $CDCl_3$, since a later experiment (see below) showed that the alcohol was stable in pure chloroform. The nmr spectrum in acetone-d_6 was in accord with the hydroxy structure and showed doublet at 145.5, 153 (CH_2 area 2), two singlets at 222.5, 229 (OCH_3) with a shoulder on 229 (OH) (total area 7), sextet centered at 311 (CHO split by OH; became a triplet on addition of D_2O; area 1), complex 398–487 (aromatic area 12), broad NH at 602.

The methanolic filtrates from above were combined, evaporated to dryness, and chromatographed on Florisil (650 g). Elution with 2 l. of CH_2Cl_2 afforded fractions which were combined and crystallized from methanol to give 8.34 g of **36**, mp 143–144°. The ultraviolet showed λ_{max} 248 mμ (ε 24,900), sh 265 (22,100), 299 (25,400), 338 (22,600); the infrared (cm^{-1}) showed NH, 3440; C=C, 1630, 1600, 1575, 1545, 1515, 1495; CO/CN, 1240, 1180, 1170, 1030, 1020; aromatic, 835, 740, nmr (in acetone-d_6) showed two singlets at 225.5, 230.5 (OCH_3 area 6), complex at 409–458 (vinyl and aromatic area 14), 626 (NH area 1).

In another experiment which was run the same way as above, the crude mixture was chromatographed on Florisil (without first separating the hydroxy compound by crystallization). Elution with CH_2Cl_2 and crystallization afforded 40% yield of the vinyl compound. The hydroxy compound was still adsorbed on the column and could not be eluted even with methanol.

E. Hydrogenation of 36.—A solution of **36** (0.33 g, 0.94 mmole) was dissolved in 200 ml of ethanol and hydrogenated during 30 min in the presence of 0.3 g of 10% Pd–C at initial pressure of 3.71 kg/cm^2 of hydrogen. The mixture was filtered, the filtrate was evaporated to dryness, and the residue was passed through a column of Florisil (16 g) in CH_2Cl_2. Elution with 30 ml of CH_2Cl_2 gave 0.259 g, which crystallized from ether–petroleum ether (30–60°); 45 mg, mp 78–80°. This product was identical with **35** as shown by comparison of the ultraviolet and infrared spectra and a mixture melting point determination.

F. Dehydration of 37.—The hydroxy compound **37** (0.373 g, 1 mmole) was dissolved in 25 ml of chloroform (Mallinckrodt, AR) and the solution was allowed to stand for 1 hr. Examination of an aliquot by ultraviolet and by thin layer chromatography on Florisil showed only the starting material. (Note that the nmr of **37** showed previously the occurrence of dehydration in $CDCl_3$, which must have been due to traces of acid in the solvent.) One milliliter of 2 *N* ethereal HCl was added. The solution turned brown, and examination by tlc after 1 min showed complete absence of starting material. The solution was evaporated to dryness, the resulting brown oil was dissolved in CH_2Cl_2 and passed through a column of Florisil (5 g). Elution with ml of CH_2Cl_2 afforded 0.3 g of product which was crystallized from methanol; 0.23 g, mp 142–143°. This compound was identical with **36** as shown by comparison of ultraviolet and infrared spectra, and a mixture melting point determination.

2,3-Bis(*p*-methoxyphenyl)indoline Hydrochloride (38).—A mixture of **1** (3.3 g, 0.01 mole), 2 g of zinc dust, and 50 ml of 18% aqueous HCl was refluxed with stirring for 2 hr. A further 2 g of zinc dust and 50 ml of ethanol were added and reflux continued for 1.5 hr. The resulting solution was filtered and evaporated *in vacuo* until an oil appeared.[25] The product was shaken with dilute HCl and ether, and the layers were separated. The aqueous layer was basified and extracted with methylene chloride. The extract was washed with water, dried (Na_2SO_4), and evaporated to give 3.1 g of a gummy product. It was dissolved in 20 ml of ether and passed through a column of neutral alumina (93 g, Woelm activity I). Elution with ether gave 2.6 g of product. It was dissolved in ether and converted to the hydrochloride with ethereal HCl. Crystallization from ethanol afforded 1.94 g, mp 198–203°, raised to 199–203° on recrystallization. The ultraviolet showed λ_{max} mμ 226 (ε 24,700), 277 (5150), 284 (4850), 299 (3100). In 0.01 *N* alcoholic acid λ_{max} 255 sh mμ (ε 3850), 261 (3700), 269 (3850), 276 (3900), 283 sh (3450), 298 (1550); the infrared (cm^{-1}) showed amine salt, 2760, 2690, 2660, 2560, 2530, 2450, 2400; C=C, 1610, 1580, 1570, 1565, 1510, 1485; CO/CN, 1250, 1180, 1025; aromatic, 825, 755; nmr (in DMSO-d_6) showed a single peak at 299.5 cps corresponding to the two hydrogens at C-2 and C-3. In pyridine, however, two pairs of doublets were obtained centered at 265, 302 with a coupling constant of 10 cps. In the absence of a second isomer, stereochemistry cannot be assigned with certainty. However, the large coupling constant would indicate *cis* structure based on examination of the Dreiding model.

Example for Benzofuran Synthesis.[5] 2,3-Bis(*p*-methoxyphenyl)benzofuran (39).—A mixture of phenol (9.41 g, 0.1 mole), anisoin (27.2 g, 0.1 mole), and 300 g of polyphosphoric acid was heated slowly to 100° under N_2. It was then cooled, poured into ice–water, and extracted with ether. The ether solution was washed in succession with water, dilute NaOH, water, and brine. It was dried ($MgSO_4$), and evaporated. The residue was chromatographed on silica gel (500 g) with 20% ethyl acetate–cyclohexane. The first band eluted from the column was crystallized to give **39**. The ultraviolet showed λ_{max} 228 sh mμ (ε 18,950), 246 (20,550), 310 (27,650); the infrared (cm^{-1}) showed C=C, 1610, 1590, 1515, 1500; CO, 1250, 1235, 1175, 1070, 1030; aromatic, 845, 835, 750; nmr showed two OCH_3 at 227, 231 (area 6), aromatic complex 406–462 (area 12).

2,3-Bis(*p*-methoxyphenyl)pyrrole (47). A. *Via* the Dicarbomethoxy Compound. Condensation of Dimethyl Acetylenedicarboxylate with Amino Ketone II.—A mixture of amino ketone

(25) Probably a $ZnCl_2$–amine complex; *cf.* footnote 35 in I. K. Lewis, G. B. Russell, R. D. Topsom, and J. Vaughan, *J. Org. Chem.*, **29**, 1183 (1964).

II (obtained as a by-product from the synthesis of **1** (176 g, 0.573 mole)), dimethyl acetylenedicarboxylate (81.5 g, 0.573 mole), sodium acetate (47 g, 0.573 mole), and 1440 ml of methanol was refluxed 15 min. It was then cooled, 1440 ml of 4 *N* methanolic HCl was added, and reflux was continued for 0.5 hr. The mixture was evaporated to dryness with stirring *in vacuo* at 40°. The residue was diluted with 1 l. of water and stirred to obtain a nice suspension. It was filtered and the yellow solid was washed with 200 ml of water. A suspension of this solid in 2 l. of water was heated on the steam bath with stirring until all of the starting material went into solution. The suspension was filtered hot, and the undissolved yellow solid was washed with 200 ml of hot water; 38 g, mp 180–187°. The combined aqueous filtrate (2.2 l.) was cooled for about 1 week and afforded 91.6 g (52%) of recovered II (mp 245–251°). The filtrate was evaporated to *ca.* 500 ml and cooled for a few days to give a further 30 g (17%) of recovered II (mp 252–255°).

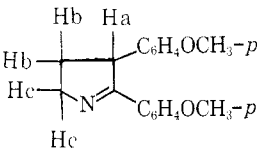
The yellow solid was dissolved in 2.6 l. of methanol, the solution was filtered, evaporated to 1.2 l., and cooled while swirling; yield 29 g, mp 190–192°, raised to 192–193° on recrystallization. The second crop amounted to 1.9 g, mp 189–191°. The ultraviolet showed λ_{max} 236 mμ (ε 22,800), sh 260 (15,300), sh 283, sh 303 (18,550), 310 (18,650); the infrared (cm^{-1}) showed NH, 3320; C=O, 1735, 1690; C=C, 1610, 1580, 1575, 1560, 1525, 1485; CO/CN, 1250, 1210, 1195, 1180, 1100, 1020; aromatic, 835, 825; nmr showed four singlets at 225, 226, 227.5, 230 (OCH_3 area 12), complex at 403.5–437 (aromatic area 8), broad at 574 (NH area 1).

4,5-Bis(*p*-methoxyphenyl)pyrrole-2,3-dicarboxylic Acid (46).—A mixture of dimethyl ester **45** (29 g, 0.0735 mole), 580 ml of methanol, and 580 ml of 20% NaOH solution was heated on the steam bath under nitrogen with stirring. After 5 min the mixture began refluxing and a solution resulted. After 5 min of refluxing a thick suspension was obtained. After an additional 5 min of refluxing, methanol was distilled. The aqueous suspension was cooled in ice and acidified with 300 ml of concentrated HCl. The resulting precipitate was filtered and washed with water. During the washing the solid turned oily. The oily solid was crystallized from 50 ml of acetic acid and 120 ml of water to give 25.7 g of a pale yellow product, mp 202–204° dec. The ultraviolet showed λ_{max} 237.5 mμ (ε 22,400), 281 (41,400), 296 sh (12,850), 318 sh (9950); in 0.01 alcoholic acid, λ_{max} 238 mμ (ε 24,400), 270 sh (14,100), 329 (9900); in 0.01 *N* alcoholic base, λ_{max} 231 mμ (ε 14,800), 257.5 (19,700), 288 (17,700), 298 (18,700); the infrared showed NH, 3300, 3240; acid OH, 2660, 2540, 2480; C=O, 1690; C=C, 1610, 1595, 1570, 1560, 1520, 1485; CO/CN, 1250, 1200, 1180, 1030; aromatic, 845, 835, 380; nmr (in acetone-d_6) showed two singlets at 227, 229 (OCH_3), complex at 405–438 (aromatic), broad 519.5 (NH).

Decarboxylation to 47.—Dicarboxylic acid **46** (24.16 g, 0.066 mole) was heated in an oil bath under N_2 at 200–220° (outside temperature) during 20 min. Distillation from an oil-jacketed flask at 240–255° (outside temperature) (0.2–0.5 mm) afforded 12.91 g of a yellow oil. A solution of this oil in 200 ml of ether was washed with two 100-ml portions of 5% NaOH solution, then with water, and saturated NaCl solution, dried (Na_2SO_4), and evaporated. The residue (12.8 g) was dissolved in 200 ml of 20% ethyl acetate–cyclohexane and chromatographed on 756 g of silica gel. Elution with the same solvent (3.5 l.) afforded 12.56 g of crude **47**. It was crystallized from petroleum ether (30–60°) with seeding to give 5 g of prisms, mp 68–69.5°, unchanged on recrystallization. The filtrates were evaporated to dryness, the residue was passed through a column of silica gel (15 g) and the product was crystallized as before, but the whole operation was performed as rapidly as possible to avoid the considerable reddening of the compound. This afforded additional 3.9 g of pink crystals, mp 68–70°. The ultraviolet showed λ_{max} 247 mμ (ε 20,100), 294.5 (15,150); the infrared (cm^{-1}) showed NH, 3470; C=C, 1610, 1580, 1515, 1510; CO/CN, 1245, 1185, 1165, 1105, 1030; aromatic, 840; nmr showed singlet at 228 (OCH_3 area 6), complex at 380–443 (aromatic area 10), NH at about 488 (area 1).

B. *Via* the Mannich Base Reaction. 2,3-Bis(*p*-methoxyphenyl)-1-pyrroline (44).—3-(Dimethylamino)-4′-methoxy-2-(*p*-methoxyphenyl)propiophenone hydrochloride[26] (42.6 g, 0.122 mole) was released to the free base. A mixture of the base, 213 ml of nitromethane, and 0.77 g of $NaOCH_3$ was refluxed with stirring for 6 hr while passing a stream of nitrogen through. After standing overnight, 150 ml of water was added, and the mixture was extracted twice with ether. The ether extract was washed with three 50-ml portions of 10% HCl, and saturated NaCl solution, dried (Na_2SO_4), and evaporated to give 50.1 g of crude oil. It was dissolved in 1500 ml of ethanol and hydrogenated in presence of 4 teaspoons of Raney nickel at initial pressure of 2.1 kg/cm^2. After 3 hr, the uptake stopped. The mixture was filtered through Filtercel, and the filtrate was evaporated. The residue was dissolved in 1 l. of ether, 400 ml of 10% HCl was added, and the resulting oily hydrochloride was washed with ether by decantation. After the addition of ice the aqueous mixture was basified and extracted with ether. The ether extract was washed with water, saturated salt solution, dried (Na_2SO_4), and evaporated to give 29 g of oil. It was chromatographed on 900 g of silica gel using 50% ethyl acetate-cyclohexane and 1% triethylamine as the eluent. Elution with ten 250-ml portions afforded crystalline fractions which were purified from ether to give 0.8 g of deoxyanisoin (identified by infrared and ultraviolet).

Further elution with three 250-ml portions gave oily fractions which were not investigated. Elution with four 250-ml portions gave crystalline fractions. Crystallization from ether (Nuchar 190-N) afforded 7.2 g of **44**, mp 88–89°. The ultraviolet showed λ_{max} 268 mμ (ε 18,200), 286 sh (10,450), 295 sh (5300); infrared (cm^{-1}) showed C=C/C=N, 1665, 1600, 1580, 1510; CO, 1250, 1175, 1030; aromatic, 835; nmr showed complex at 100–170 (Hb area 2), singlet at 224 (OCH_3 area 6), complex at 237–274 (Hc + Ha, area 3), complex at 400–470 (aromatic area 8).



44

Dehydrogenation of 44.—A mixture of 0.8 g of crude **44** (not purified by chromatography), 0.8 g of 5% Pd–C, and 10 ml of decalin was refluxed with stirring for 6.5 hr. It was cooled, chloroform was added to dissolve the oil which separated, and the solution was filtered through Filtercel. The solution was washed with 10% HCl, water, saturated NaCl solution, dried (Na_2SO_4), and evaporated (0.1 mm) to give 0.7 g of oil. It was dissolved in methylene chloride and chromatographed on 42 g of Florisil. Elution with 45 ml of CH_2Cl_2 afforded 0.22 g, which was rechromatographed on 22 g of silica gel. Elution with seven 10-ml portions of 10% ethyl acetate–cyclohexane afforded 0.07 g which was discarded. Further elution with 10 ml gave 0.138 g of oil which was identical with **47** as shown by comparison of ultraviolet, infrared, and nmr spectra. The mass spectrum showed a mass peak at 279 (calcd mol wt 279.72).

2,3-Bis(*p*-methoxyphenyl)quinoline (49).—A flask containing 25 g of 2,3-bis(*p*-methoxyphenyl)cinchoninic acid (**48**, see Table II, footnote *i*) was heated in a Wood's metal bath at 325° until CO_2 evolution stopped (*ca.* 10 min). The residual material was dissolved in 500 ml of methylene chloride. The solution was washed with two 100-ml portions of 5% NaOH solution and 200 ml of water, dried ($MgSO_4$), and evaporated. The residual oil was dissolved in acetone–Skellysolve B and adsorbed on a column of Florisil. The column was eluted with an increasing proportion of acetone in Skellysolve B mixtures. The solid obtained was crystallized twice from acetone–Skellysolve B and once from ether–Skellysolve B to give 14.6 g of ivory prisms, mp 98–100° (see Table II, footnote *j*).

Anal. Calcd for $C_{23}H_{19}NO_2$: C, 80.91; H, 5.61; N, 4.10. Found: C, 80.99; H, 5.58; N, 4.02.

The ultraviolet showed λ_{max} 217 mμ (ε 11,950), 239 (43,800), 271 (29,300), 341 (9750); the infrared showed C=C/C=N, 1610, 1575, 1550, 1515; C-O, 1245, 1170, 1030; aromatic, 830, 760; nmr showed singlet at 225 (OCH_3 area 6), complex at 400–495 (aromatic area 13).

(26) Sterling Drug, Inc., British Patent 828,762 (1960).