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Abnormal Fischer Indolization and Its Related Compounds. XII.[1] Synthesis of 3,6′-Biindole

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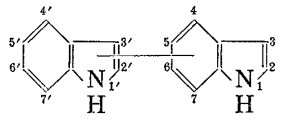
3,6′-Biindole (**1f**), an unsymmetric biindole, was synthesized *via* the advanced Fischer indolization of ethyl pyruvate 2-[(*o*-methoxyphenyl)hydrazone] (**2a**) and ethyl indole-2-carboxylate (**8**).

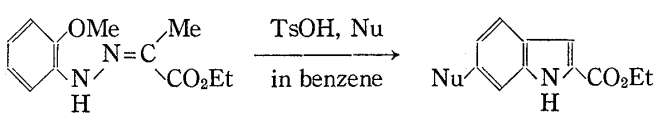
Keywords——unsymmetric biindole; Vilsmeier–Haack reaction; *o*-methoxyphenylhydrazone; 3,6′-biindole; trimerization

Syntheses of several symmetric biindoles involving 2,2′-,[3] 3,3′-,[4] 5,5′-,[5] and 7,7′-[5] biindoles (**1a**, **b**, **c**, **d**) have been reported from various points of view. However, only 2,3′-biindole (**1e**)[6] has been known as an unsymmetric biindole. In the previous paper,[7] we showed the introduction of some nucleophiles into the 6-position of indole nucleus by abnormal Fischer indolization of ethyl pyruvate 2-[(*o*-methoxyphenyl)hydrazone] (**2**). Since this



1a—f

Chart 1



2 **3**

Nu: nucleophile

Chart 2

procedure provides us a synthetic pathway for unsymmetric 3,6′-biindole derivative, we have shown the synthesis of 3,6′-biindole (**1f**) as an example of application of the advanced Fischer indolization in a preliminary communication.[8] In this report, we wish to describe a full detail of experiments on this matter.

Since it is well known that electrophilic replacement[9] could take place at the nitrogen or the C_3-position on indole nucleus but indole itself (**4**) could be polymerized[10] under

1) Part XI: H. Ishii, K. Murakami, Y. Murakami, and K. Hosoya, *Chem. Pharm. Bull.* (Tokyo), **25**, 3122 (1977).
2) Location: *1–33, Yayoi-cho, Chiba, 280, Japan*; *a*) The author to whom correspondence should be addressed; *b*) Present address: *School of Pharmaceutical Science, Toho University*; *2–2–1, Miyama, Funabashi, 274, Japan*.
3) W. Madelung, *Ann.*, **405**, 58 (1914); S.A. Faseeh and J. Harley-Mason, *J. Chem. Soc.*, **1957**, 4141.
4) B. Oddo and L. Raffa, *Gazz. Chim. Ital.*, **69**, 562 (1939) [*Chem. Abstr.*, **34**, 1313 (1940)]; S. Huenig and H.C. Steinmetzer, *Ann. Chem.*, **1976**, 1039.
5) H. Gossler and H. Plieninger, *Ann. Chem.*, **1977**, 1953.
6) O.S. Dumont, K. Hamann, and K.H. Geller, *Ann.*, **504**, 1 (1933); J. Bergman, *J. Heterocycl. Chem.*, **10**, 121 (1973).
7) H. Ishii, Y. Murakami, T. Furuse, K. Hosoya, H. Takeda, and N. Ikeda, *Tetrahedron*, **29**, 1991 (1973).
8) H. Ishii, Y. Murakami, K. Hosoya, T. Furuse, and N. Ikeda, *Chem. Pharm. Bull.* (Tokyo), **20**, 1088 (1972).
9) For a review of electrophilic replacement of indole derivatives, see R.J. Sundberg, "The Chemistry of Indoles," Academic Press, New York, 1970, pp. 1—85; W.A. Remers and R.K. Brown, "Indoles," ed. by W.J. Houlihan, Part I, Wiley Interscience, New York, 1972, pp. 70—126.
10) For a review of polymerization of indole with acid, see R.J. Sundberg, "The Chemistry of Indoles," Academic Press, New York, 1970, pp. 6—8; W.A. Remers and R.K. Brown, "Indoles," ed. by W.J. Houlihan, Part I, Wiley Interscience, New York, 1972, pp. 66—70; G.F. Smith, "Advances in Heterocyclic Chemistry," ed. by A.R. Katritzky, Vol. 2, Academic Press, New York, 1963, pp. 300—309.

definitely acidic conditions, we examined applicability of indole itself (**4**) as a nucleophile in the advanced Fischer indolization.[7]

Treatment of *E*-ethyl pyruvate 2-[(*o*-methoxyphenyl)hydrazone][11] (**2a**) with *p*-toluenesulfonic acid in benzene in the presence of indole itself (**4**) gave a mixture of the isomerized starting hydrazone (**2b**) (mp 87°), the indole-ester (**5**) (mp 170.5—171.5°) and the new indole trimer (**6**) (mp 105—107°), in 11.3%, 25.6%, and 17.3% yields, respectively, in the order of elution on column chromatography.

The first product was identified with an authentic sample[11] of *Z*-ethyl pyruvate 2-[(*o*-methoxyphenyl)hydrazone] (**2b**). The isomerization of an *E*-form of phenylhydrazone to a *Z*-form is a common phenomenon when treated under acidic condition.

The second product (**5**) gave elemental analysis in agreement with the molecular formula $C_{21}H_{20}N_2O_2$. The infrared (IR) spectrum of it shows an NH band at 3410 cm^{-1} and an ester band at 1720 cm^{-1}. The nuclear magnetic resonance (NMR) spectrum of it revealed the

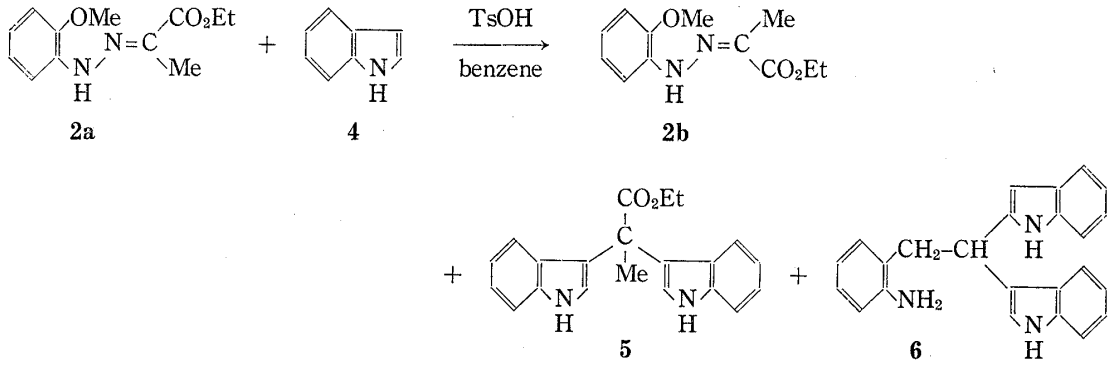


Chart 3

presence of an ethoxy group [1.07 δ (3H, t, J=7.5 Hz) and 4.11 δ (2H, q, J=7.5 Hz)], one tertiary methyl group [2.07(2H, s)], two 2H signals attributable to a C_2-proton of an indole nucleus [6.82 δ (2H, d, J=3.0 Hz, changed into a singlet by addition of D_2O]. These data could be rationalized only by supposing that the indole-ester has the structure (**5**), which could be formed by repetition of a nucleophilic attack of indole at the carbon atom of azomethine group in ethyl pyruvate 2-[(*o*-methoxyphenyl)-hydrazone] (**2**).

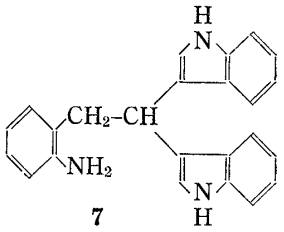


Chart 4

The results of elemental analysis and mass spectrum of the third product (**6**) coincided with the calculated values for an indole trimer, $(C_8H_7N)_3$. However, we recognized that our indole trimer was different from a sample of the well-known indole trimer (**7**), mp 173—177°, prepared by treatment of indole itself (**4**) according to the reported method[10] and also confirmed the formation of our indole trimer by treatment of indole itself (**4**) in benzene with *p*-toluenesulfonic acid in the absence of ethyl pyruvate 2-[(*o*-methoxyphenyl)hydrazone] (**2**). This observation became a clue for reinvestigation of indole trimerization[1] in our laboratory.

Then, we changed a nucleophile in the advanced Fischer indolization of ethyl pyruvate 2-[(*o*-methoxyphenyl)hydrazone] (**2**) from indole itself (**4**) to ethyl indole-2-carboxylate (**8**) which is not able to polymerize by itself under acid condition.

Treatment of ethyl pyruvate 2-[(*o*-methoxyphenyl)hydrazone] (**2b**) with *p*-toluenesulfonic acid in benzene in the presence of an equivalent of ethyl indole-2-carboxylate (**8**) gave a mixture of desired diethyl 3,6′-biindole-2,2′-dicarboxylate (**9**) and ethyl 7-methoxyindole-

11) H. Ishii, Y. Murakami, K. Hosoya, H. Takeda, Y. Suzuki, and N. Ikeda, *Chem. Pharm. Bull.* (Tokyo), **21**, 1481 (1973).

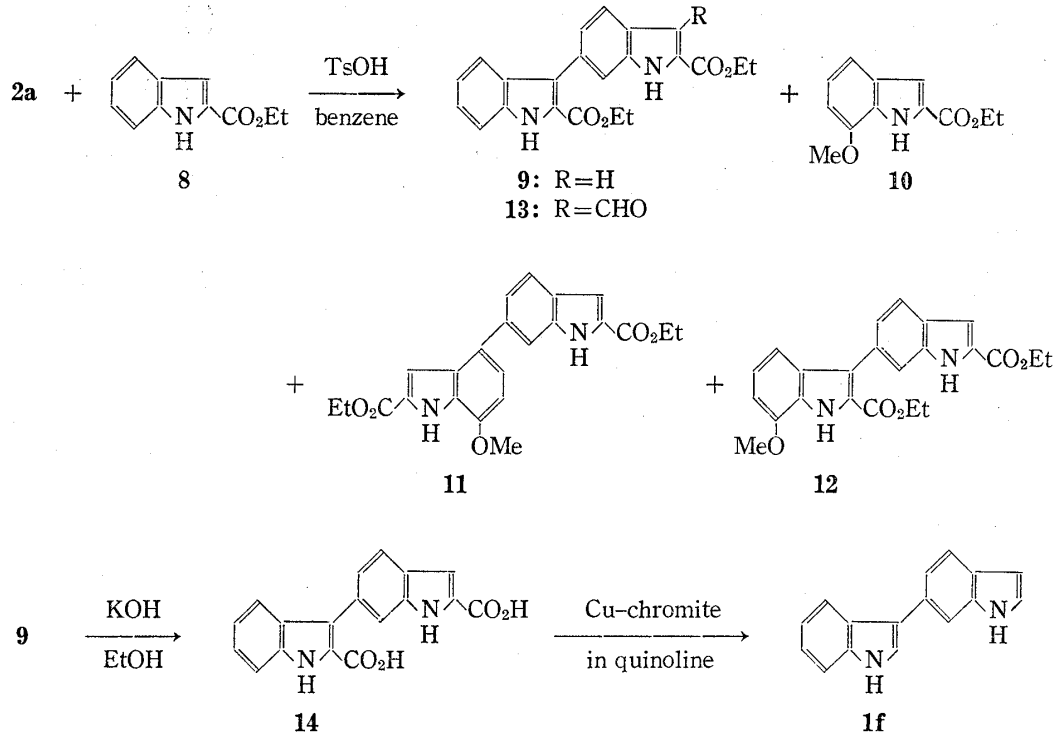


Chart 5

2-carboxylate (**10**) (the normally cyclized product) in 28.4% and 12.2% yield, respectively, together with minute amounts of known diethyl 7-methoxy-4,6′-biindole-2,2′-dicarboxylate[7] (**11**, 0.6%) and diethyl 7-methoxy-3,6′-biindole-2,2′-dicarboxylate[7] (**12**, 0.9%) as by-products.

The structure of the desired product (**9**) was confirmed as follows. Elemental analysis and a mass spectrum agreed with the desired product. In the NMR spectrum of it, a 1H singlet at 7.19 δ due to an indolic C_3-proton and a 2H singlet at 9.19 δ attributable to two NH-protons were observed together with the signals due to seven aromatic protons and two ethoxy groups. Since the presence of only one C_3-proton in this molecule means that one terminus of the linkage of the two indole units should be at the C_3-position, the data mentioned above established the structure of the biindole product except another terminus of the linkage of two indole units. Vilsmeier-Haack formylation of the product (**9**) resulted in formation of the mono-formyl derivative (**13**). In the NMR spectrum of the formyl derivative (**13**), we could find an aldehydic proton at 10.63 δ as a 1H singlet and two NH protons at 11.87 and 12.74 δ as a 1H broad singlet, but no signal due to an indolic C_3-proton, indicating that the insertion of a formyl group took place at the C_3-position of the product. Moreover, an aromatic proton was observed to be shifted to a lower field as a 1H doublet (J=8.8 Hz) in the NMR spectrum of the formyl-derivative (**13**). Since the aromatic proton was assignable to the peri-proton of the aldehyde group, we may safely conclude that the product should be depicted by the formula (**13**). The yield of the desired product (**9**) was increased to 36.0% when two equivalents of ethyl indole-2-carboxylate (**8**) were used in the same reaction.

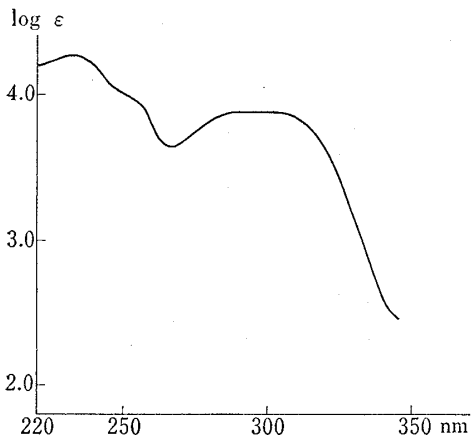


Fig. 1. UV Spectra of 3,6′-Biindole (**1f**)

Hydrolysis of the biindole (**9**) with potassium hydroxide in ethanol gave the dicarboxylic acid (**14**)

as monohydrate, mp 276—277.5° (dec.). Decarboxylation of the dicarboxylic acid (**14**) with copper chromite[12] in quinoline provided the desired 3,6′-biindole (**1f**), mp 157—158.5°, the ultraviolet spectrum of which is shown in Fig. 1.

Experimental[13]

Fischer Indolization of *E*-Ethyl Pyruvate 2-[(*o*-Methoxyphenyl)hydrazone] (2a) in the Presence of Indole with *p*-Toluenesulfonic Acid——A solution of 4.73 g of *E*-ethyl pyruvate 2-[(*o*-methoxyphenyl)hydrazone][11] (**2a**), 23.4 g of indole (**4**) and 13.78 g of anhydrous *p*-toluenesulfonic acid (TsOH, prepared from 15.22 g of monohydrate using Dean–Stark water separator) was refluxed for 3 hr. After cooling, the benzene layer was separated from a tar-like product by decantation and washed with dil. $NaHCO_3$ aq. The tar-like product was dissolved in $CHCl_3$, and washed with dil. $NaHCO_3$ aq. The combined organic layer was passed through Celite 545 to remove an insoluble material. The filtrate was dried over $MgSO_4$ and evaporated to dryness *in vacuo*. The residue (36.05 g) was taken up in benzene and chromatographed on silicic acid and divided into two eluants with $CHCl_3$ (0.60 g) and 5% EtOH in $CHCl_3$ (25.2 g).

***Z*-Ethyl Pyruvate 2-[(*o*-Methoxyphenyl)hydrazone] (2b)**——The $CHCl_3$ fraction was re-chromatographed on silicic acid (45 g) using benzene as a solvent to give 0.534 g of pale yellow pillars, mp 87°, which were recrystallized from hexane and EtOH. This material was identical with an authentic sample of *Z*-ethyl pyruvate 2-[(*o*-methoxyphenyl)hydrazone].[11]

Ethyl 2,2-[Bis(indol-3-yl)]propionate (5)——The 5% EtOH in $CHCl_3$ fraction was re-chromatographed on silicic acid (250 g) using $CHCl_3$ as a solvent to give an oil, which was solidified by triturating with cyclohexane. Recrystallization of the solid from EtOH gave 1.70 g of colorless needles, mp 170.5—171.5°. *Anal.* Calcd. for $C_{21}H_{20}N_2O_2$: C, 75.88; H, 6.07; N, 8.43. Found: C, 75.67; H, 5.99; N, 8.29. IR: ν_{max}^{Nujol} cm^{-1}: 3410 (NH), 1720 (C=O). UV: λ_{max}^{EtOH} nm (log ε): 276 (4.08, sh.), 283 (4.11), 291 (4.02). NMR ($CDCl_3$) δ: 1.07 (3H, t, J=7.5 Hz, $CH_2C\underline{H}_3$), 2.07 (3H, s, C–CH_3), 4.11 (2H, q, J=7.5 Hz, $OC\underline{H}_2CH_3$), 6.82 (2H, d, J=3.0 Hz, 2×C_2–H), 6.95—7.55 (8H, m, aromatic protons), 7.90 (2H, br.s, 2×NH).

Indole Trimer [2,3′-(*o*-Aminophenethylidene)diindole] (6)——Further elution with the same solvent gave 4.01 g of colorless fine needles, mp 105—107°, which were recrystallized several times from benzene. The characterization of this compound has been reported.[1]

Diethyl 3,6′-Biindole-2,2′-dicarboxylate (9)——A solution of 1.180 g of *E*-ethyl pyruvate 2-[(*o*-methoxyphenyl)hydrazone] (**2a**), 0.950 g [one equivalent for the starting hydrazone (**2a**)] of ethyl indole-2-carboxylate[11,14] (**8**), and 2.58 g of anhydrous TsOH (prepared from 2.80 g of its monohydrate using Dean–Stark water separator) was refluxed for 30 min. After cooling the reaction mixture was poured onto ice-water and extracted with ether. The ethereal solution was washed with H_2O, dried over $MgSO_4$, and evaporated to dryness *in vacuo*. The residue (1.876 g) was dissolved in benzene and chromatographed on Al_2O_3 (Woelm, acidic grade II, 60 g) with monitoring by TLC. After the first eluant containing 479 mg of the starting ethyl indole-2-carboxylate (**8**) and 134 mg of ethyl 7-methoxyindole-2-carboxylate[11] (**10**) was removed, the second eluant gave 481 mg of colorless prisms, mp 203—204°, which were recrystallized from benzene. *Anal.* Calcd. for $C_{22}H_{20}N_2O_4$: C, 70.20; H, 5.36; N, 7.44. Found: C, 70.52; H, 5.41; N, 7.53. IR: ν_{max}^{Nujol} cm^{-1}: 3298, 3270 (br.) (NH), 1685, 1665 (C=O). NMR ($CDCl_3$) δ: 1.17 (3H, t, J=7.5 Hz, $CH_2C\underline{H}_3$), 1.42 (3H, t, J=7.5 Hz, $CH_2C\underline{H}_3$), 4.26 (2H, q, J=7.5 Hz, $OC\underline{H}_2CH_3$), 4.42 (2H, q, J=7.5 Hz, $OC\underline{H}_2CH_3$), 7.00—7.75 (7H, m, aromatic protons), 7.19 (1H, d, J=1.5 Hz, C_3′–H), 9.19 (2H, br. s, 2×NH). Mass Spectrum *m/e*: 376 (M^+).

The mother liquor of the recrystallization of the above biindole (**9**) was evaporated to dryness *in vacuo*. The residue was chromatographed on SiO_2 using 3% AcOEt in $CHCl_3$ as a solvent followed by purification by preparative TLC on SiO_2 (AcOEt: $CHCl_3$: benzene=1: 20: 10 v/v) to give 12 mg of diethyl 7-methoxy-

12) W.A. Lazier and H.R. Arnold, "Organic Syntheses," Coll. Vol. II, ed. by A.H. Blatt, John Wiley and Sons, Inc., New York, 1943, p. 142.

13) All mp's were measured on a micro-melting hot-stage (Yanagimoto) and are uncorrected. IR and UV spectra were obtained with Hitachi EPI-G III and Hitachi EPS-3T spectrometers. NMR spectra were obtained with JEOL JNM-MH-100 using tetramethylsilane as internal standard, and the abbreviations of singlet, doublet, triplet, quartet, and multiplet were represented as s, d, t, q, and m, respectively. Assignment of the NH and the C_3–H signals of indole products was confirmed by the fact that the former disappeared and the latter changed its pattern from a doublet to singlet after addition of D_2O. Mass spectra were recorded on Hitachi RMU-6E at 70 eV of Chamber Voltage on direct inlet system. Silicic acid, 100 mesh, Mallinckrodt Chemical Works, was used for column chromatography. Identification of a product with an authentic sample was performed by comparison of IR spectrum, mixed melting point test and TLC.

14) W.E. Noland, F.J. Baude, "Organic Syntheses," Coll. Vol. V, ed. by H.E. Baumgarten, John Wiley and Sons, Inc., New York, 1973, p. 567.

4,6′-biindole-2,2′-dicarboxylate[7] (**11**), 18 mg of diethyl 7-methoxy-3,6′-biindole-2,2′-dicarboxylate[7](**12**), and further 53 mg of diethyl 3,6′-biindole-2,2′-dicarboxylate (**9**) [total yield; 534 mg (28.4%)].

When used two equivalents of ethyl indole-2-carboxylate (**8**), the yield of the desired biindole (**9**) was raised to 36.0%.

Diethyl 3′-Formyl-3,6′-biindole-2,2′-dicarboxylate (13)——To a solution of 530 mg of $POCl_3$ in 2 ml of DMF was added a solution of 130 mg of diethyl-3,6′-biindole-2,2′-dicarboxylate (**9**) in 1 ml of DMF. The mixed solution was heated at 100—110° (bath) for 2 hr. After cooling, the reaction mixture was poured onto water, made basic with 10% Na_2CO_3 aq., and extracted with AcOEt. The organic layer was washed with water, and dried over $MgSO_4$. Removal of the solvent *in vacuo* gave 124 mg (87.6%) of pale yellow fine needles, mp 290°, which were recrystallized from dioxane–EtOH–H_2O. *Anal.* Calcd. for $C_{23}H_{20}N_2O_5$: C, 68.30; H, 4.99; N, 6.93. Found: C, 67.95; H, 5.07; N, 6.54. IR: ν_{max}^{Nujol} cm^{-1}: 3310, 3175 (NH), 1725, 1680 (ester), 1644 (CHO). NMR (DMSO-d_6) δ: 1.17 (3H, t, J=7.5 Hz, $CH_2C\underline{H}_3$), 1.42 (3H, t, J=7.5 Hz, $CH_2C\underline{H}_3$), 4.22 (2H, q, J=7.5 Hz, $OC\underline{H}_2CH_3$), 4.48 (2H, q, J=7.5 Hz, $OC\underline{H}_2CH_3$), 7.00—7.75 (6H, m, aromatic protons), 8.30 (1H, d, J=8.8 Hz, $C_{4'}$–H), 10.63 (1H, s, C$\underline{H}$O), 11.87 (1H, br.s, NH), 12.74 (1H, br.s, NH). Mass Spectrum *m/e*: 404 (M^+).

3,6′-Biindole-2,2′-dicarboxylic Acid Monohydrate (14)——To a solution of 200 mg of KOH in 10 ml of EtOH was added 200 mg of diethyl 3,6′-biindole-2,2′-dicarboxylate (**9**). The mixture was refluxed for 2 hr. The crystal mass of the starting material (**9**) was dissolved once, and, immediately, formation of other precipitates was observed. When the reaction was complete, most of the solvent was evaporated *in vacuo*. The product was dissolved in a large amount of water. The solution was made acidic with dil.HCl aq. and the precipitates were collected by filtration. The recrystallization of the precipitates gave 175 mg of colorless fine pillars, mp 276—277.5° (dec., partly melted at 165°). *Anal.* Calcd. for $C_{18}H_{12}N_2O_4 \cdot H_2O$: C, 63.90; H, 4.17; N, 8.28. Found: C, 63.85; H, 4.22; N, 8.18. IR: ν_{max}^{Nujol} cm^{-1}: 3500 (H_2O), 3358, 3245 (NH), 1680 (CO_2H). NMR (DMSO-d_6) δ: 6.95—7.90 (10H, aromatic protons, C_3–H and 2×NH), 11.65 (2H, dif.s, 2×CO_2H). Mass Spectrum *m/e*: 320 (M^+, as $C_{18}H_{12}N_2O_4$).

3,6′-Biindole (1f)——A mixture of 100 mg of 3,6′-biindole-2,2′-dicarboxylic acid monohydrate (**14**) and 20 mg of copper chromite[12] in 1.5 ml of quinoline was heated at 200° (bath) for 1 hr with stirring, diluted with ether, and filtered off. The filtrate was successively washed with 5% HCl aq., 5% $NaHCO_3$ aq. and H_2O, and dried over K_2CO_3. Removal of solvent gave 47 mg of an oil. Purification of the resulting oil by column chromatography on SiO_2 (2 g) using benzene as a solvent gave 41 mg of colorless leaflets, mp 157.5—158.5° (once melted at 142° and crystallized again), which were recrystallized from benzene–cyclohexane. *Anal.* Calcd. for $C_{16}H_{12}N_2$: C, 82.73; H, 5.21; N, 12.06. Found: C, 82.67; H, 5.22; N, 11.72. Mass Spectrum *m/e*: 232 (M^+). IR: ν_{max}^{Nujol} cm^{-1}: 3395, 3370 (NH), no C=O. NMR ($CDCl_3$) δ: 6.55 [1H, m, $C_{3'}$–H; changed to doublet (J=3.5 Hz) by addition of D_2O], 7.10—8.15 (11H, m, aromatic protons and 2×NH). UV: λ_{max}^{EtOH} nm (log ε): 232.5 (4.27), 255 sh. (3.95), 289 (3.88), 302 (3.88).