[Chem. Pharm. Bull. 22(9)1981—1989(1974)]

UDC 547.751.057 : 547.574.3.04

# Fischer Indolization and Its Related Compounds. VIII.[1] Formation of 4-Aminoindole Derivatives on the Fischer Indolization of 2-Methoxyphenylhydrazone Derivatives

Hisashi Ishii, Yasuoki Murakami, Haruki Takeda, and Tokuo Furuse

*Faculty of Pharmaceutical Sciences, Chiba University*[2]

(Received October 17, 1973)

Fischer indolization of ethyl pyruvate 5-chloro-2-methoxyphenylhydrazone (**6**) with anhydrous zinc chloride gave ethyl 4-amino-6-chloroindole-2-carboxylate (**12**) as a main product, with three other expected indoles, (**7**), (**8**) and (**5**).

Cyclization of ethyl pyruvate 2-methoxyphenylhydrazone (**1**) with *p*-toluenesulfonic acid in the presence of diethyl malonate afforded ethyl 4-(ethoxycarbonylacetamido)-indole-2-carboxylate (**28**) and diethyl 4-(ethoxycarbonylacetamido)-3,6′-biindole-2,2′-dicarboxylate (**30**) with five other indole derivatives, (**11**), (**10**), (**26**), (**27**), and (**32**).

The pathway leading to such a 4-aminoindole product in the abnormal Fischer indolization of a 2-methoxyphenylhydrazone derivative is discussed.

In the preceding papers[1,3] of this series, we have shown that Fischer indolization of ethyl pyruvate 2-methoxyphenylhydrazone (1) gave various species of indolic products *via* a cyclization to the *ortho*-position occupied by a methoxy group and we developed this transformation to a novel synthetic method for 6-substituted indolic compounds, the advanced Fischer indolization of 2-methoxyphenylhydrazones. In the present paper, we wish to report the formation of 4-aminoindole derivatives.

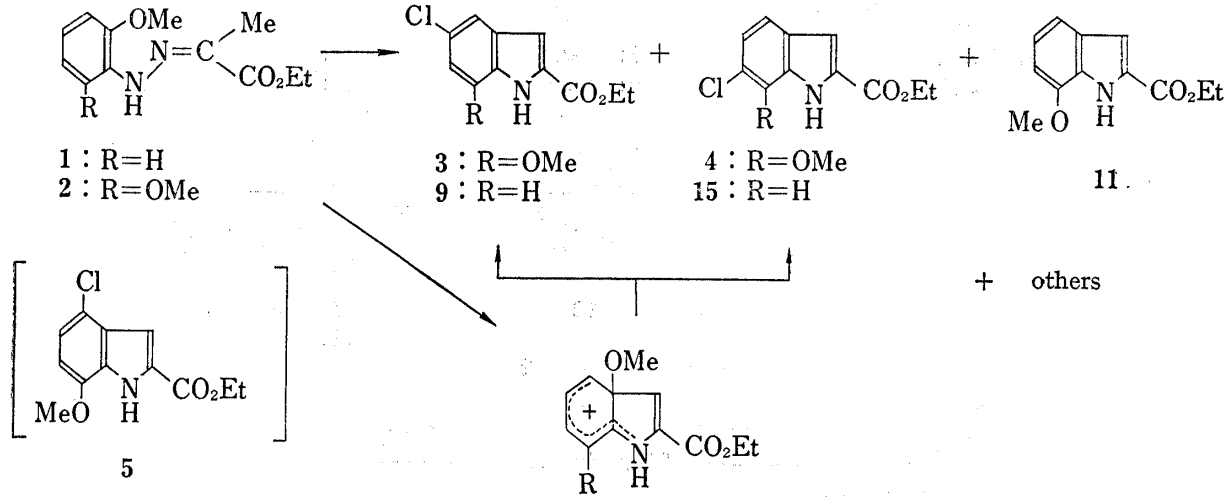



Chart 1

1) Part VII: H. Ishii, Y. Murakami, T. Furuse, K. Hosoya, H. Takeda, and N. Ikeda, *Tetrahedron*, **29**, 1991 (1973).

2) Location: *1–33, Yayoi-cho, Chiba.*

3) *a*) H. Ishii, Y. Murakami, Y. Suzuki, and N. Ikeda, *Tetrahedron Letters*, **1970**, 1181; *b*) H. Ishii, Y. Murakami, K. Hosoya, H. Takeda, Y. Suzuki, and N. Ikeda, *Chem. Pharm. Bull.* (Tokyo), **21**, 1481 (1973); *c*) H. Ishii, Y. Murakami, T. Furuse, K. Hosoya, and N. Ikeda, *Chem. Pharm. Bull.* (Tokyo), **21**, 1495 (1973); *d*) H. Ishii, Y. Murakami, K. Hosoya, T. Furuse, H. Takeda, and N. Ikeda, *Chem. Pharm. Bull.* (Tokyo), **20**, 1088 (1972).

In the course of a study of abnormal Fischer indolization of *ortho*-substituted phenylhydrazones, we had occasion to examine the cyclization[3c] of ethyl pyruvate 2,6-dimethoxyphenylhydrazone (**2**) with ethanolic hydrogen chloride, and obtained a mixture of ethyl 5-chloro-7-methoxyindole-2-carboxylate (**3**) and undefined ethyl chloro-methoxyindole-2-carboxylate. The nuclear magnetic resonance (NMR) spectrum of the latter indole shows two doublets coupled with each other by a rather large coupling constant ($J$=8.6 Hz) due to vicinal aromatic protons. This spectral data allows only two structural possibilities, whether it is ethyl 6-chloro- (**4**) or 4-chloro- (**5**) 7-methoxyindole-2-carboxylate. In order to establish its structure rigidly, we attempted to prepare ethyl 4-chloro-7-methoxyindole-2-carboxylate (**5**) by an alternative pathway *via* Fischer indolization of ethyl pyruvate 5-chloro-2-methoxyphenylhydrazone (**6**). During our studies on dependency of the direction of abnormal Fischer indolization upon species of reagent, we showed that cyclization with anhydrous zinc chloride in acetic acid[3c] gave fewer indole derivatives including mainly the 5-substituted indoles as abnormal products (*ortho*-$C_5$ abnormal Fischer indolization) than that with ethanolic hydrogen chloride which is apt to give the 6-substituted indole products (*ortho*-$C_6$ abnormal Fischer indolization). This condition was, therefore, chosen for preparation of the authentic sample of ethyl 4-chloro-7-methoxyindole-2-carboxylate (**5**). Moreover, the formation of ethyl 5,6-dichloro- (**7**) and 6-chloro-5-methoxy- (**8**) indole-2-carboxylates as by-products under this condition was anticipated on the basis of the previous experimental results[3c] that cyclization of ethyl pyruvate 2-methoxyphenylhydrazone (**1**) gave ethyl 5-chloro- (**9**), 5-methoxy- (**10**) and 7-methoxy- (**11**) indole-2-carboxylates. However, ethyl 4-amino-6-chloroindole-2-carboxylate (**12**) was obtained as one of main product components as described below.

Treatment of (Z)-ethyl pyruvate 5-chloro-2-methoxyphenylhydrazone (**6a**)[4] with anhydrous zinc chloride in acetic acid gave four indolic products (**7**, **8**, **12** and **5**) (Chart 2).

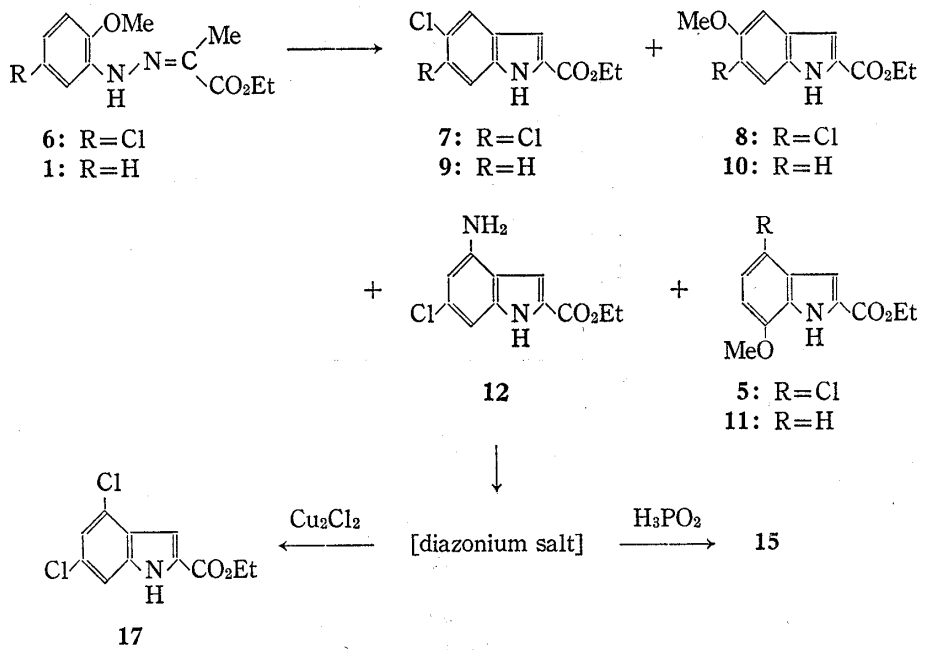



Chart 2

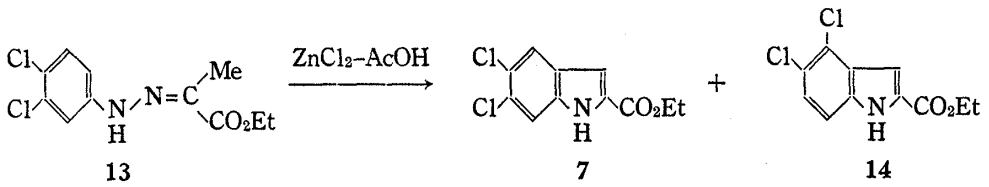
4) Japp-Klingemann[5] reaction of an aniline derivative with ethyl α-methylacetoacetate followed by column chromatography gave two geometrical isomers, (Z)- and (E)-ethyl pyruvate phenylhydrazone derivatives. The structural assignment of these isomers was made from consideration of the spectral data as described in a previous paper.[3b,6]

5) R.R. Philips, "Organic Reactions," Vol. 10, ed. by Adams, John Wiley and Sons, Inc., N. Y., 1959, p. 143.

6) H. Ishii, Y. Murakami, S. Tani, K. Abe, and N. Ikeda, *Yakugaku Zasshi*, **90**, 724 (1970).

The first indolic product (**7**), mp 219—224°, could not be obtained in sufficient amount to determine its structure by chemical means. In the mass spectrum of the compound, two characteristic peaks are observed at *m/e* 259 and 257. As the intensity of the former peak is 73% of that of the latter, the peaks could be assigned respectively as the ($M^+$+2) ion and the parent peak of the expected ethyl 5,6-dichloroindole-2-carboxylate (**7**), $C_{11}H_9O_2NCl_2$.

Treatment of (E)-ethyl pyruvate 3,4-dichlorophenylhydrazone[4] (**13**) with anhydrous zinc chloride in acetic acid gave two isomeric ethyl dichloroindole-2-carboxylates (**7** and **14**). In the NMR spectra, the dichloroindole (**7**), mp 225—226°, which was obtained in the larger yield, shows two 1H singlets due to aromatic protons at 7.67 and 7.95 $\delta$; whereas the other (**14**), mp 212—214°, shows two doublets ($J$=9.0 Hz) at 7.35 and 7.42 $\delta$. This spectral evidence allowed us to assign the former indole as ethyl 5,6-dichloroindole-2-carboxylate (**7**) and the latter as ethyl 4,5-dichloroindole-2-carboxylate (**14**). The former indolic product was identified with the specimen obtained by Fischer indolization of ethyl pyruvate 5-chloro-2-methoxyphenylhydrazone (**6**).




**13** **7** **14**

Chart 3

The second and third indolic product on the reaction of (Z)-ethyl pyruvate 5-chloro-2-methoxyphenylhydrazone (**6a**), (**8**) mp 173—174° and (**5**) mp 133—134°, appear to be isomeric, since both of them gave elemental analysis $C_{12}H_{12}O_3NCl$. In the NMR spectra, these indolic products (**8** and **5**) show a 3H singlet due to a methoxy group at 3.90 and 3.92 $\delta$, respectively. While the aromatic protons of the former product appear as two singlets at 6.37 and 6.94 $\delta$, those of the latter as two doublet ($J$=8.8 Hz) at 7.00 and 6.59 $\delta$. These spectral data allowed us to assign the former as the expected 6-chloro-5-methoxyindole-2-carboxylate (**8**) and the latter as ethyl 4-chloro-7-methoxyindole-2-carboxylate (**5**).

The fourth product (**12**), mp 174.5—176° [$C_{11}H_{11}O_2N_2Cl$; $M^+$: *m/e* 238] contains both nitrogen atoms of the starting phenylhydrazone in its molecule. Close resemblance of its ultraviolet (UV) spectrum to that of ethyl 6-chloroindole-2-carboxylate[3b] (**15**) suggested that the product (**12**) might be a derivative of ethyl indole-2-carboxylate. The presence of a primary amino group was clarified by coupling color test. Treatment of its diazonium salt with hypophosphorus acid gave a deaminated product which was identified with an authentic sample of ethyl 6-chloroindole-2-carboxylate (**15**). Since the NMR spectrum of the original aminoindole derivative (**12**) shows two 1H doublets ($J$=2.0 Hz) attributable to two aromatic protons situated *meta* to each other, we assigned the compound as ethyl 4-amino-6-chloroindole-2-carboxylate. Although all attempts to synthesize this compound by the Reissert method[7] from 4-chloro-2,6-dinitrotoluene[8] (**16**) failed, the assignment was confirmed by transformation of the diazonium salt of **12** with cuprous chloride to ethyl 4,6-dichloroindole-2-carboxylate (**17**), mp 185—187° (lit.[9] mp 183.5—184°).

Many research groups have attempted to give a chemical proof of the dienone imine intermediate (**18**) which Robinson's mechanism postulates to be present in the Fischer indoliza-

7) R.K. Brown, "The Chemistry of Heterocyclic Compounds: Indoles (Part one)," ed. by W.J. Houlihan, John Wiley and Sons, Inc., N. Y., 1972, pp. 396—413.
8) G.D. Parkes and A.C. Farthing, *J. Chem. Soc.*, **1948**, 1275.
9) G. Pappalardo and T. Vitali, *Gazz. Chim. Ital.*, **88**, 1147 (1958) [*C.A.*, **53**, 21877*c* (1959)].

tion,[10] though nobody has yet succeeded in obtaining the enehydrazine type of intermediate. Among these attempts, that of Brown, *et al.*[11] assumed that the ortho disubstituted enamine written by formula (**19**) should give a dienone imine product (**20**) under the conditions of Fischer indolization. However, their attempt to prepare this enamine (**19**) by condensation of $N_1$-methyl-2,6-dichlorophenylhydrazine (**21**) with cyclohexanone without aid of an acid catalyst afforded a 4-aminoindole derivative, 5-amino-6-chloro-9-methyl-1,2,3,4-tetrahydrocarbazole (**22**), instead of the desired enamine (**19**). They then proposed a tentative mechanism including a cyclization process through a sigmatropic reaction as shown in Chart 4. As described before,[3] the *ortho*-$C_5$ or *ortho*-$C_6$ abnormal Fischer indolization [for example, (**3**)

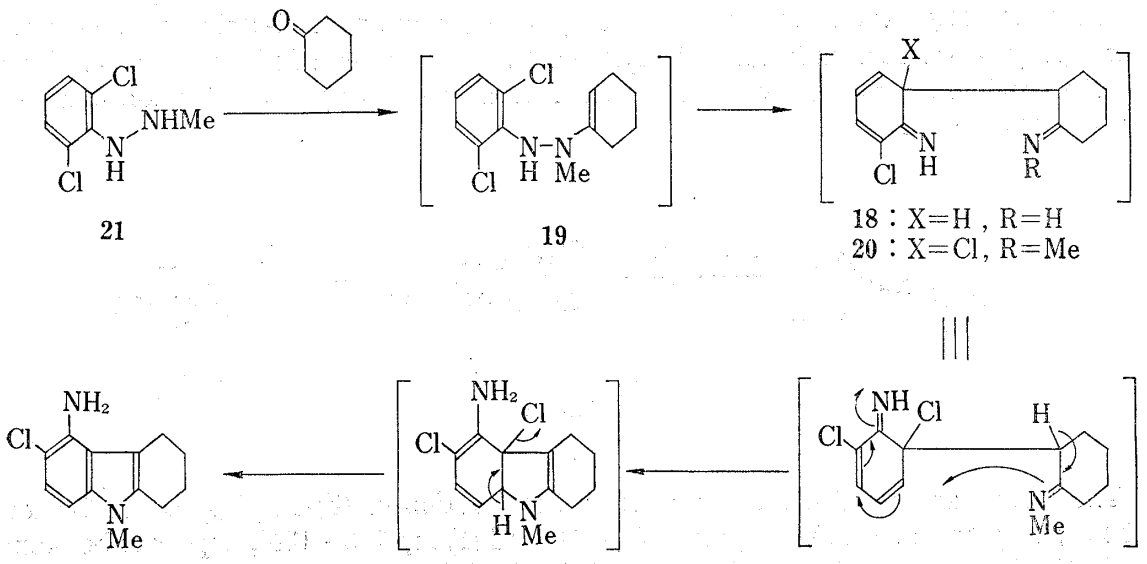



Chart 4

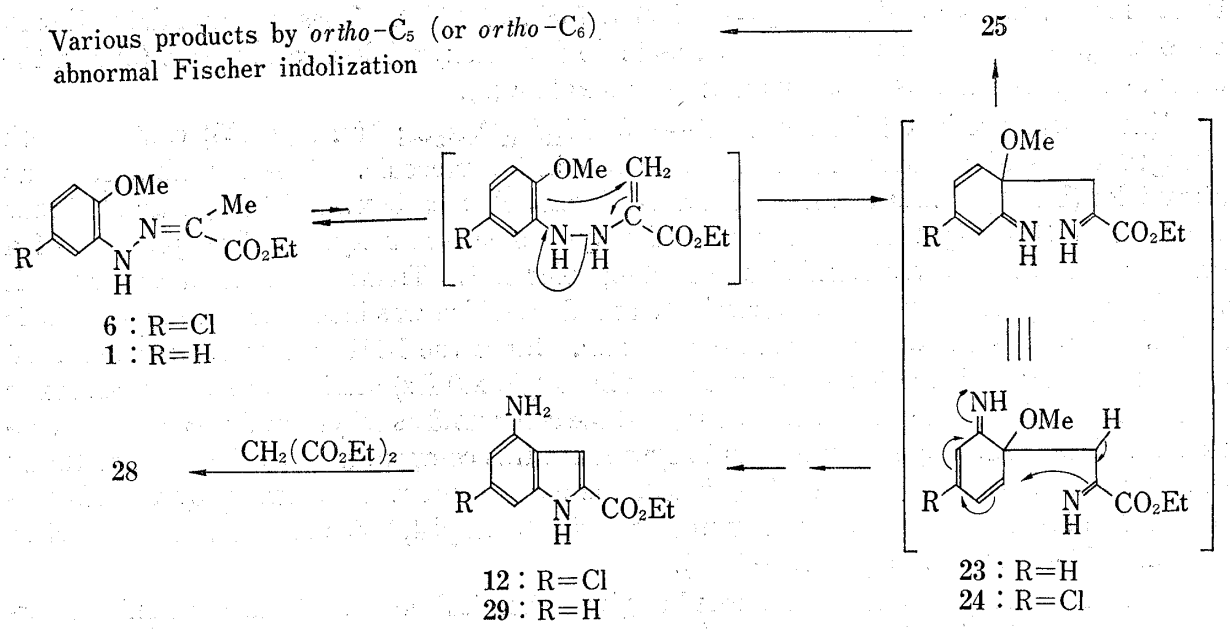



Chart 5

10) For reviews of the Fischer indolization, see B. Robinson, *Chem. Rev.*, **63**, 373 (1963); *idem, ibid.*, **69**, 227 (1969); R.K. Brown, "The Chemistry of Heterocyclic Compounds: Indoles (Part one)," ed. by W.J. Houlihan, John Wiley and Sons, Inc., N. Y., 1972, pp. 232—317.

11) F.P. Robinson and R.K. Brown, *Can. J. Chem.*, **42**, 1940 (1964).

and (**4**)] was explained by assuming a dienone imine intermediate (**23**) (Chart 5). Since the supposed intermediate (**23**) corresponded to that of Brown's mechanism, formation of 4-aminoindole (**12**) from a 2-methoxyphenylhydrazone derivative might also be rationalized as a branch reaction from the same corresponding dienone imine intermediate (**24**), a cyclization in a fashion of the Michael reaction (Chart 5).

We have also another examples of formation of a 4-aminoindole on Fischer indolization of a simple 2-methoxyphenylhydrazone. In a previous paper we reported that Fischer indolization of ethyl pyruvate 2-methoxyphenylhydrazone (**1**) with *p*-toluenesulfonic acid in benzene in the presence of an enolizable dicarbonyl compound, acetylacetone or ethyl acetoacetate, gave an indolic product having an active methine group at the $C_6$ position of the indole nucleus. We presumed that no unenolizable active methylene compounds are incorporated into an indolic product, since they are not acceptors of the key intermediate (**25**) (Chart 1) under such acidic conditions as used in Fischer indolization. In order to examine this postulation, we treated ethyl pyruvate 2-methoxyphenylhydrazone (**1**) with diethyl malonate under the above conditions; we obtained seven indolic products, but, as expected, none having a malonyl group at its $C_6$ position.

The first four indolic products were identified as known derivatives of ethyl indole-2-carboxylate: 7-methoxy-[3b] (**11**), [mp 114—115.5°, 15.4%]; 5-methoxy-[3c] (**10**), [mp 153—158°, 0.32%]; 5-tosyloxy-[1] (**26**), [mp 161—162.5°, 1.2%]; and diethyl 7-methoxy-3,6′-biindole-2,2′-dicarboxylate[1] (**27**), [mp 206—207.5°, 2.6%].

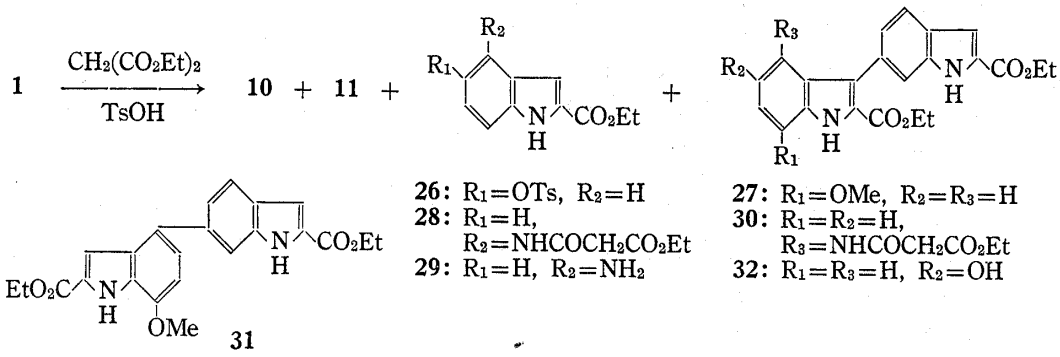



Chart 6

The other three products were recognized as new indolic compounds. The first of these (**28**), mp 129—133°, has an empirical formula $C_{16}H_{18}O_5N_2$, ($M^+$: at *m/e* 318). Its IR spectrum shows ester and amide bands at 1723 and 1663 $cm^{-1}$ respectively. Its NMR spectrum indicates the presence of the following functional groups in its molecule; two ethoxy groups [1.31 and 1.38 (3H, t, $J$=7.5 Hz; 4.25 and 4.38 (2H, q, $J$=7.5 Hz)], two NH groups [9.52 and 10.17 (1H, br. s)], an active methylene group [3.52 (2H, s)], one $C_3$-proton [7.18 (1H, d, $J$=2.4 Hz)], and three aromatic protons [7.04—7.50 (3H, m)]. This evidence indicates the formation of an ethyl indole-2-carboxylate possessing an ethoxycarbonylacetamido group. The structure of the indolic product having these functional groups may be established from consideration of the reaction process. We may assumed that in our experiment ethyl 4-aminoindole-2-carboxylate (**29**) formed was trapped by partial amidation of it with diethyl malonate added in the reaction mixture. This consideration allows us to assign the compound (**28**) as ethyl 4-(ethoxycarbonylacetamido)indole-2-carboxylate.

The second new indolic product (**30**) mp 203—204°, $C_{27}H_{27}O_7N_3$ ($M^+$: *m/e* 505) was also related to the 4-aminoindole (**29**) described above. In its IR spectrum it shows two ester and one amide bands, at 1716 and 1697 $cm^{-1}$. Its NMR spectrum exhibits the presence of the following functional groups in its molecule: three ethoxy groups [1.25—1.48 (9H, m); 4.36 (6H, q, $J$=7.5 Hz)], one active methylene [3.58 (2H, s)], three NH groups [9.31, 9.71 and 10.45 (1H, br. s)], one $C_3$ proton [7.35 (1H, d, $J$=2.4 Hz)], and six aromatic protons [7.13—

7.80 (6H, m)]. This evidence indicates that the compound is a dimeric indole having an ethoxycarbonylacetamido group and two ester groups in its molecule. As described in detail in a previous paper,[3b] an indolic product can be an acceptor of the key intermediate (**25**) at the $C_3$ position in *ortho*-$C_6$ abnormal Fischer indolization. Therefore, the dimeric product can be assigned as diethyl 4-(ethoxycarbonylacetamido)-3,6′-biindole-2,2′-dicarboxylate (**30**), which would be expected to be formed by reaction of ethyl 4-aminoindole-2-carboxylate (**29**) or its N-ethoxycarbonylacetyl derivative (**28**) with the key intermediate (**25**). Although we could determine that one terminus of the linkage between the two indolic units was located at the $C_6$ position; we could not strictly confirm that the other terminus is at the $C_3$ position, because ethyl 4-aminoindole-2-carboxylate (**29**) and its N-ethoxycarbonylacetyl derivative (**28**) have two points susceptible to an electrophile, the $C_5$ and $C_7$ carbon atoms, additional to those in the common indole derivative. Indeed, in a previous experiment[1] treatment of ethyl pyruvate 2-methoxyphenylhydrazone (**1**) with *p*-toluenesulfonic acid in the presence of an excess amount of ethyl 7-methoxyindole-2-carboxylate (**11**) afforded a mixture of diethyl 7-methoxy-3,6′- (**27**) and -4,6′- (**31**) biindole-2,2′-dicarboxylates. Unfortunately, since the dimeric product (**30**) was isolated in such a minute amount it was impossible for us to establish the structure by chemical transformation; this is a problem we hope to solve in future.

The last product (**32**), mp 201—203°, $C_{22}H_{20}O_5N_2$, was also recognized as a dimeric indole derivative. We tentatively propose that it is diethyl 5-hydroxy-3,6′-biindole-2,2′-dicarboxylate (**32**) by an argument similar to the above, but we will not give the details here because the formation of this compound is unrelated to the present subject. However, we believe that its formation involves reaction of the key intermediate with ethyl 5-tosyloxyindole-2-carboxylate (**26**) produced in the reaction, followed by hydrolysis of the tosyloxy group.

There are no reports that described an isolation of a 4-aminoindole product on Fischer indolization of 2-methoxyphenylhydrazone derivatives until now. However, our results indicate the general formation of a 4-aminoindole derivative in such a reaction system. Since in general the indolic product yielded by Fischer indolization were extracted with organic solvent in acid solution, any aminoindole would have remained in the acidic aqueous layer. This could be one of reason why the Fischer indolization of 2-methoxyphenylhydrazone derivatives gave a poor yield of indole products.

## Experimental[12]

**(Z)-Ethyl Pyruvate 5-Chloro-2-methoxyphenylhydrazone (6a)**——A solution of diazonium salt prepared from 11 g of commercial 5-chloro-2-methoxyaniline (Nakarai Chemicals Ltd.), mp 81—83° (lit[13] mp 82°), in 78 ml of $H_2O$, 12.4 ml of conc. HCl, and 5.8 g of $NaNO_2$, was added to a solution of 10.1 g of ethyl α-methylacetoacetate[14] and 4.84 g of KOH (in 5.06 ml of $H_2O$) in 92 ml of EtOH at below 0°. The mixture was stirred for 1 hr, poured into ice-water and extracted with benzene. The organic layer was dried over $MgSO_4$ and evaporated to dryness *in vacuo*. The residue, 18.1 g, was dissolved in a mixed solution of 5.8 ml of 85% $H_3PO_4$ and 52 ml of EtOH, refluxed for 25 min, poured into ice-water and extracted with benzene. The benzene extract was dried over $MgSO_4$ and evaporated to dryness *in vacuo*. The residue was dissolved in benzene was chromatographed on silicic acid. The first portion of the benzene eluate gave 6.80 g of yellow pillars, mp 108.5—110°, which were recrystallized from hexane. *Anal.* Calcd. for $C_{12}H_{15}O_3N_2Cl$: C, 53.24; H, 5.59; N, 10.35. Found: C, 53.31; H, 5.60; N, 10.51. IR $\nu_{max}^{Nujol}$ $cm^{-1}$: 3255(NH), 1679 (C=O).

12) All melting points were observed on a microscopic hot stage and are uncorrected. All NMR spectra were obtained with tetramethylsilane as an internal standard on a JEOL JNM-4H-100 NMR spectrometer (100 Mc). Assignment of the NH and the $C_3$-H signals of each indole products was confirmed by the fact that the former disappeared and the latter changed its pattern from a doublet to a singlet after addition of $D_2O$. Mass spectra were recorded on Hitachi RMU-6E mass spectrometer with a direct inlet system. Silicic acid, 100 mesh, Mallinckrodt Chemical Works, was used for column chromatography. Identification of products with authentic sample, was done by comparison of IR spectra, mixed melting test, and TLC.

13) F. Reverdin and F. Eckhard, *Ber.*, 38, 2622 (1899).

14) A. Michael, *Ber.*, 38, 2083 (1905).

NMR ($CCl_4$) $\delta$: 1.33 (3H, t, $J$=7.5 Hz, $CH_2CH_3$), 2.11 (3H, s, N=$CCH_3$), 3.85 (3H, s, $OCH_3$), 4.22 (2H, q, $J$=7.5 Hz, $OCH_2CH_3$), 6.67 (2H, m, $C_3$- and $C_4$-H), 7.41 (1H, d, $J$=2.0 Hz, $C_6$-H), 12.03 (1H, br. s, NH). Mass Spectrum *m/e*: 272 ($M^+$+2, 34.8% intensity of $M^+$), 270 ($M^+$).

**(E)-Ethyl Pyruvate 5-Chloro-2-methoxyphenylhydrazone (6b)**——Further elution with benzene gave 9.50 g of pale orange pillars, mp 123—124°, which were recrystallized from cyclohexane. *Anal.* Calcd. for $C_{12}H_{15}O_3N_2$: C, 53.24; H, 5.59; N, 10.35. Found: C, 53.34; H, 5.48; N, 10.09. IR $\nu_{max}^{Nujol}$ $cm^{-1}$: 3355 (NH), 1690 (C=O). NMR ($CCl_4$) $\delta$: 1.37(3H, t, $J$=7.5 Hz, $CH_2CH_3$), 2.04(3H, s, N=$CCH_3$), 3.85 (3H, s, $OCH_3$), 4.24(2H, q, $J$=7.5 Hz, $OCH_2CH_3$), 6.66(1H, d, $J$=8.0 Hz, $C_3$-H), 6.73(1H, dd, $J$=8.0 and 2.5 Hz, $C_4$-H), 7.46(1H, d, $J$=2.5 Hz, $C_6$-H), 7.85(1H, br, s, NH). Mass Spectrum *m/e*: 272($M^+$+2, 34% intensity of $M^+$), 270 ($M^+$).

**Fischer Indolization of (Z)-Ethyl Pyruvate 5-Chloro-2-methoxyphenylhydrazone (6a) with Anhydrous Zinc Chloride in Acetic Acid**——To a solution of 5.00 g of (Z)-ethyl pyruvate 5-chloro-2-methoxyphenylhydrazone (**6a**) in 75 ml of acetic acid was added 20 g of anhydrous zinc chloride. The mixture was refluxed for 15 min, poured into ice-water and extracted with ether. The ethereal solution was washed with 5% $NaHCO_3$ aq, dried over $MgSO_4$ and evaporated to dryness *in vacuo* to give 3.92 g of an oily residue. The aqueous layer was basicified with $Na_2CO_3$ and extracted with ether. The ethereal solution was dried over $MgSO_4$ and evaporated to dryness to give 0.18 g of an oily residue. Both of these oily residues were combined after confirmation of identity of their components on thin-layer chromatography (TLC), dissolved in benzene, and chromatographed on silicic acid. Elution with benzene was monitored by TLC and the eluate was divided into four fractions (Fractions A, B, C, and D in the order of elution).

**Ethyl 5,6-Dichloroindole-2-carboxylate (7)**——Fraction A gave a trace amount of colorless needles, mp 219—224°, which were recrystallized from benzene–hexane. Mass Spectrum *m/e*: 259 ($M^+$+2, 73% intensity of $M^+$), 257 ($M^+$). This material was identified with an authentic sample of ethyl 5,6-dichloroindole-2-carboxylate (7) prepared from (E)-ethyl 3,4-dichlorophenylhydrazone (**13**) by Fischer indolization.

**Ethyl 6-Chloro-5-methoxyindole-2-carboxylate (8)**——Fraction B gave 38 mg of colorless needles, mp 173—174°, which were recrystallized from hexane–benzene. *Anal.* Calcd. for $C_{12}H_{12}O_3NCl$: C, 56.81; H, 4.77; N, 5.52. Found: C, 56.97; H, 4.63; N, 5.52. IR $\nu_{max}^{Nujol}$ $cm^{-1}$: 3326 (NH), 1680 (C=O). NMR ($CCl_4$) $\delta$: 1.43 (3H, t, $J$=7.5 Hz, $CH_2CH_3$), 3.90 (3H, s, $OCH_3$), 4.39 (2H, q, $J$=7.5 Hz, $OCH_2CH_3$), 6.37 (1H, s, $C_4$-H), 6.94 (1H, s, $C_7$-H), 7.17 (1H, d, $J$=2.0 Hz, $C_3$-H), 9.45 (1H, br. s., NH). Mass Spectrum *m/e*: 255 $M^+$+2, 35% intensity of $M^+$), 253 ($M^+$).

**Ethyl 4-Chloro-7-methoxyindole-2-carboxylate (5)**——Fraction C gave 620 mg of colorless needles, mp 133—134°, which were recrystallized from benzene–hexane. *Anal.* Calcd. for $C_{12}H_{12}O_3NCl$: C, 56.81; H, 4.77; N, 5.52. Found: C, 57.00; H, 4.85; N, 5.75. IR $\nu_{max}^{Nujol}$ $cm^{-1}$: 3285 (NH), 1701 (C=O). NMR ($CDCl_3$) $\delta$: 1.40 (3H, t, $J$=7.5 Hz, $CH_2CH_3$), 3.92 (3H, s, $OCH_3$), 4.39 (2H, q, $J$=7.5 Hz, $OCH_2CH_3$), 6.59 (1H, d, $J$= 8.8 Hz, $C_6$-H), 7.00 (1H, d, $J$=8.8 Hz, $C_5$-H), 7.24 (1H, d, $J$=1.5 Hz, $C_3$-H), 9.17 (1H, br. s, NH). Mass Spectrum *m/e*: 255 ($M^+$+2, 34% intensity of $M^+$), 253 ($M^+$).

**Ethyl 4-Amino-6-chloroindole-2-carboxylate (12)**——Fraction D gave 660 mg of colorless needles, mp 174.5—176°, which were recrystallized from benzene. *Anal.* Calcd. for $C_{11}H_{11}O_2N_2Cl$: C, 55.36; H, 4.65; N, 11.74. Found: C, 55.53; H, 4.54; N, 11.96. IR $\nu_{max}^{Nujol}$ $cm^{-1}$: 3400, 3285, 3180 (NH), 1689 (C=O). UV $\lambda_{max}^{EtOH}$ m$\mu$ (log $\varepsilon$): 251.5(4.49), 297(4.14)sh, 304(4.21), 337(3.86). NMR ($CDCl_3$) $\delta$: 1.39 (3H, t, $J$=7.5 Hz, $CH_2CH_3$), 3.70—4.20 (2H, br. s., $NH_2$, disappeared after addition of $D_2O$), 4.38 (2H, q, $J$=7.5 Hz, $OCH_2CH_3$), 6.34 (1H, d, $J$=2.0 Hz, $C_5$-H), 6.80 (1H, d, $J$=2.0 Hz, $C_7$-H), 7.11 (1H, d, $J$=2.5 Hz, $C_3$-H), 8.89 (1H, br. s., NH). Mass Spectrum *m/e*: 240 ($M^+$ +2, 35% intensity of $M^+$), 238 ($M^+$). A diazotized solution of this material coupled with $\beta$-naphthol to give a red colored product.

**Ethyl 6-Chloroindole-2-carboxylate (15) from Ethyl 4-Amino-6-chloroindole-2-carboxylate (12)**——A saturated aqueous solution of $NaNO_2$ (36 mg) was added to a solution of 100 mg of ethyl 4-amino-6-chloroindole-2-carboxylate (**12**) in 2 ml of conc. HCl with stirring at 0°. The diazotized solution was added to 2.5 ml of 30% $H_3PO_2$ dropwise under ice cooling and the mixture was stirred for 4.5 hr. The mixture was allowed to stand overnight at room temperature, poured into water and extracted with ether. The ethereal solution was dried over $MgSO_4$ and the solvent was distilled off. The residue was dissolved in benzene and chromatographed on silicic acid. Elution with benzene gave 30 mg of colorless needles, mp 180—181°, which were recrystallized from hexane–benzene. The product was identified with an authentic sample of ethyl 6-chloroindole-2-carboxylate[3b] (**15**).

**Ethyl 4,6-Dichloroindole-2-carboxylate (17)**——A diazotized solution of 100 mg of ethyl 4-amino-6-chloroindole-2-carboxylate (**12**) prepared as above was added to a freshly prepared solution of 28 mg of $Cu_2Cl_2$ in 2.3 ml of conc. HCl with stirring at 0°. The reaction mixture was stirred for 1 hr, poured into water and extracted with ether. The ethereal solution was washed with 10% HCl aq. and 5% $NaHCO_3$ aq, dried over anhydrous $K_2CO_3$ and evaporated. The residue (26 mg) was purified by column chromatography on silicic acid followed by recrystallization from cyclohexane to give 20 mg of colorless leaflets, mp 185—187° (lit[9] mp 183.5—184°). *Anal.* Calcd. for $C_{11}H_9O_2NCl_2$: C, 51.19; 3.52; N, 5.43. Found: C, 51.52; H, 3.39; N, 5.62. IR $\nu_{max}^{Nujol}$ $cm^{-1}$: 3300 (NH), 1699 (C=O). NMR ($CDCl_3$) $\delta$: 1.40 (3H, t, $J$=7.5 Hz, $CH_2CH_3$), 4.42 (2H, q, $J$=7.5 Hz, $OCH_2CH_3$), 7.14 (1H, d, $J$=2.0 Hz, $C_5$- or $C_7$-H), 7.25 (1H, d, $J$=1.3 Hz, $C_3$-H), 7.30 (1H,

d, $J$=2.0 Hz, $C_5$- or $C_7$-H), 9.29 (1H, br. s., NH). Mass Spectrum $m/e$: 259 ($M^+$+2, 66.7% intensity of $M^+$), 257 ($M^+$).

**(Z)- Ethyl Pyruvate 3,4-Dichlorophenylhydrazone (13)**——A solution of the diazonium salt prepared from 8.10 g of 3,4-dichloroaniline, mp 72—74° (lit[15] mp 71.5°), 11.0 g of conc. HCl, 3.45 g of $NaNO_2$ and 60 ml of $H_2O$ was added dropwise to a solution of 7.2 g of ethyl α-methylacetoacetate[14] and 5.8 g of 50% KOH aq. in 70 ml of EtOH under ice cooling. The mixture was stirred for 1 hr, poured into ice-water and extracted with benzene. The benzene layer was dried over $MgSO_4$ and evaporated to dryness *in vacuo*. The oily residue (11.5 g) was dissolved in a mixture of 6 ml of 85% $H_3PO_4$ and 30 ml of EtOH, refluxed for 15 min, poured into water and extracted with benzene. The organic layer was dried over $MgSO_4$ and evaporated to dryness *in vacuo*. The residue (10.0 g) was dissolved in benzene and repeatedly chromatographed on silicic acid to give two fractions. The first fraction eluted gave 443 mg of pale yellow fine needles, mp 48.5—50.5°, which were recrystallized from EtOH. *Anal.* Calcd. for $C_{11}H_{12}O_2N_2Cl_2$: C, 48.02; H, 4.40; N, 10.18. Found: C, 48.21; H, 4.27; N, 10.32. IR $\nu_{max}^{CHCl_3}$ $cm^{-1}$: 3250 (NH), 1679 (C=O). NMR ($CCl_4$) $\delta$: 1.37 (3H, t, $J$=7.3 Hz, $CH_2C\underline{H}_3$), 2.13 (3H, s, N=$CCH_3$), 4.26 (2H, q, $J$=7.3 Hz, $OC\underline{H}_2CH_3$), 6.94 (1H, dd, $J$=8.5 and 2.7 Hz, $C_6$-H), 7.77 (1H, d, $J$=2.7 Hz, $C_2$-H), 7.77 (1H, d, $J$=8.5 Hz, $C_5$-H), 11.98 (1H, br. s, NH). Mass Spectrum $m/e$: 276 ($M^+$+2, 67% intensity of $M^+$), 274 ($M^+$).

**(E)-Ethyl Pyruvate 3,4-Dichlorophenylhydrazone (13)**——The second fraction eluted gave 3.904 g of pale orange leaflets, mp 126—128°, which were recrystallized from benzene–hexane. *Anal.* Calcd. for $C_{11}H_{12}O_2N_2Cl_2$: C, 48.02; H, 4.42; N, 10.18. Found: C, 48.06; H, 4.31; N, 10.21. IR $\nu_{max}^{CHCl_3}$ $cm^{-1}$: 3350 (NH), 1704 (C=O). NMR ($CDCl_3$) $\delta$: 1.37 (3H, t, $J$=7.3 Hz, $CH_2C\underline{H}_3$), 2.07 (3H, s, N=$CCH_3$), 4.32 (2H, q. $J$=7.3 Hz, $OC\underline{H}_2CH_3$), 7.01 (1H, dd, $J$=9.0 and 2.5 Hz, $C_6$-H), 7.32 (1H, d, $J$=9.0 Hz, $C_5$-H), 7.33 (1H, d, $J$=2.5 Hz, $C_2$-H), 7.68 (1H, br. s, NH). Mass Spectrum $m/e$: 276 ($M^+$+2, 63.5% intensity of $M^+$), 274 ($M^+$).

**Fischer Indolization of (E)-Ethyl Pyruvate 3,4-Dichlorophenylhydrazone (13) with Anhydrous Zinc Chloride in Acetic Acid**——To a solution of 500 mg of (E)-ethyl pyruvate 3,4-dichlorophenylhydrazone (13) in 15 ml of AcOH was added 6.0 g of anhydrous zinc chloride. The mixture was refluxed for 1.5 hr, poured into water and extracted with ether. The ethereal solution was washed with 5% $NaHCO_3$ aq, dried over $MgSO_4$ and the solvent distilled off. The residue was dissolved in benzene and chromatographed on silicic acid.

**Ethyl 5,6-Dichloroindole-2-carboxylate (7)**——The first benzene eluate gave 111 mg of colorless needles, mp 225—226°, which were recrystallized from benzene–hexane . *Anal.* Calcd. for $C_{11}H_9O_2NCl_2$: C, 51.18; H, 3.51; N, 5.42. Found: C, 51.28; H, 3.42; N, 5.51. IR $\nu_{max}^{Nujol}$ $cm^{-1}$: 3300 (NH), 1689 (C=O). NMR (DMSO-$d_6$) $\delta$: 1.37 (3H, t, $J$=7.3 Hz, $CH_2C\underline{H}_3$), 4.38 (2H, q, $J$=7.3 Hz, $OC\underline{H}_2CH_3$), 7.15 (1H, diffused s, $C_3$-H), 7.67 (1H, s, $C_4$- or $C_7$-H), 7.95 (1H, s, $C_7$- or $C_4$-H), 12.06 (1H, br. s, NH). Mass Spectrum $m/e$: 259 ($M^+$+2, 67% intensity of $M^+$), 257 ($M^+$).

**Ethyl 4,5-Dichloroindole-2-carboxylate (14)**——Subsequent elution with benzene gave 69 mg of colorless needles, mp 215—216°, which were recrystallized from benzene. *Anal.* Calcd. for $C_{11}H_9O_2NCl_2$: C, 51.18; H, 3.51; N, 5.42. Found: C, 51.09; H, 3.39; N, 5.71. IR $\nu_{max}^{Nujol}$ $cm^{-1}$: 3297 (NH), 1969 (C=O). NMR (DMSO-$d_6$) $\delta$: 1.37 (3H, t, $J$=7.3 Hz, $CH_2C\underline{H}_3$), 4.37 (2H, q, $J$=7.3 Hz, $OC\underline{H}_2CH_3$), 7.09 (1H, d, $J$=2.3 Hz, $C_3$-H), 7.39 (1H, d, $J$=9.0 Hz, $C_6$- or $C_7$-H), 7.42 (1H, d, $J$=9.0 Hz, $C_7$- or $C_6$-H), 12.35 (1H, br. s, NH). Mass Spectrum $m/e$: 259 ($M^+$+2, 66% intensity of $M^+$), 257 ($M^+$).

**Fischer Indolization of Ethyl Pyruvate 2-Methoxyphenylhydrazone*,[16] (1) in the Presence of Diethyl Malonate**——A solution of 11.50 g of $TsOH \cdot H_2O$ in 100 ml of abs. benzene was refluxed for 1 hr using a Dean-Stark trap. To the solution was added 36.05 g of diethyl malonate and 4.77 g of a mixture of (Z)- and (E)-ethyl pyruvate 2-methoxyphenylhydrazone*,[3b] (1). The mixture was refluxed for 30 min, poured into ice-water and extracted with ether. The ethereal solution was washed with water and dried over $MgSO_4$ and evaporated to give 49.51 g of an oily residue. After an excess of diethyl malonate had been removed by distillation under reduced pressure, the residue (5.93 g) was taken up in benzene, chromatographed on silicic acid and fractionated into seven portions, Fr. A—G in the order of elution, by eluting with benzene and/or $CHCl_3$.

**Ethyl 7-Methoxyindole-2-carboxylate* (11)**——Recrystallization of Fr. A from benzene–hexane gave 681 mg (15.4%) of colorless pillars, mp 114—115.5°, which were identified with a sample of ethyl 7-methoxyindole-2-carboxylate[3b] (11).

**Ethyl 5-Methoxyindole-2-carboxylate* (10)**——Recrystallization of Fr. B (40 mg) from benzene–hexane gave 14 mg (0.32%) of colorless plates, mp 153—158°, which were identified with a sample of ethyl 5-methoxyindole-2-carboxylate[3b] (10).

**Ethyl 5-Tosyloxyindole-2-carboxylate* (26)**——Recrystallization of Fr. C (112 mg) from benzene–hexane gave 84 mg (1.2%) of colorless needles, mp 161—162.5°, which were identified with a sample of ethyl 5-tosyloxyindole-2-carboxylate[3c] (26).

15) F. Beilstein and A. Kurbatow, *Lieb. Ann.*, **196**, 214 (1879).
16) Preparation and physical constants of the compound marked with an asterisk in this paper are described in detail in our previous paper.

**Diethyl 7-Methoxy-3,6′-biindole-2,2′-dicarboxylate*** (27)——Recrystallization of Fr. D (250 mg) from benzene–hexane gave colorless pillars, mp 206—207.5°, which were identified with a sample of diethyl 7-methoxy-3,6′-biindole-2,2′-dicarboxylate[3c] (27).

**Ethyl 4-(Ethoxycarbonylacetamido)indole-2-carboxylate** (28)——Recrystallization of Fr. E (366 mg) from benzene–hexane gave 165 mg (2.6%) of colorless needles, mp 136—138°. *Anal.* Calcd. for $C_{16}H_{18}O_5N_2$: C, 60.37; H, 5.70; N, 8.80. Found: C, 60.52; H, 5.69; N, 8.47. IR $\nu_{max}^{Nujol}$ $cm^{-1}$: 3326; 3235 (NH), 1723 (ester), 1662 (amide). NMR ($CDCl_3$) $\delta$: 1.31 (3H, t, $J$=7.5 Hz, $CH_2C\underline{H}_3$), 1.38 (3H, $J$=7.5 Hz, $CH_2C\underline{H}_3$), 3.52 (2H, s, $COC\underline{H}_2CO_2Et$), 4.25 (2H, q, $J$=7.5 Hz, $OC\underline{H}_2CH_3$), 4.38 (2H, q, $J$=7.5 Hz, $OC\underline{H}_2CH_3$), 7.04 (2H, m, $C_6$- and $C_7$-Hs), 7.18 (1H, d, $J$=2.4 Hz, $C_3$-H), 7.50 (1H, dd, $J$=5.4 and 3.2 Hz, $C_5$-H), 9.52 (1H, br. s, NH), 10.17 (1H, br. s, NH). Mass Spectrum $m/e$: 318 ($M^+$).

**Diethyl 4-(Ethoxycarbonylacetamido)-3,6′-biindole-2,2′-dicarboxylate** (30)——Recrystallization of Fr. F (158 mg) from benzene gave 85 mg (1.7%) of leaflets, mp 203—204°. *Anal.* Calcd. for $C_{27}H_{27}O_7N_3$: C, 64.15; H, 5.38; N, 8.31. Found: C, 64.04; H, 5.35; N, 7.84. IR $\nu_{max}^{Nujol}$ $cm^{-1}$: 3327, 3220 (NH), 1716, 1697 (ester), 1646 (amide). NMR ($CDCl_3$) $\delta$: 1.25—1.48 (9H, m, 3×$CH_2C\underline{H}_3$), 3.58 (2H, s, $COC\underline{H}_2CO_2Et$), 4.36 (6H, q, $J$=7.5 Hz, 3×$OC\underline{H}_2CH_3$), 7.35 (1H, d, $J$=2.4 Hz, $C_3$′-H), 7.13—7.80 (6H, m, aromatic Hs), 9.31 (1H, br. s, NH), 9.71 (1H, br. s, NH), 10.45 (1H, br. s, NH). Mass Spectrum $m/e$: 505 ($M^+$).

**Diethyl 5-Hydroxy-3,6′-biindole-2,2′-dicarboxylate** (32)——Recrystallization of Fr. G (128 mg) from benzene gave 92 mg (2.3%) of pale yellow needles, mp 201—203°. *Anal.* Calcd. for $C_{22}H_{20}O_5N_2$: C, 67.33; H, 5.14; N, 7.14. Found: C, 67.14; H, 5.09; N, 6.86. IR $\nu_{max}^{Nujol}$ $cm^{-1}$: 3310, 3185 (NH and OH), 1713, 1680 (ester). NMR ($CDCl_3$) $\delta$: 1.18 (3H, t, $J$=7.5 Hz, $CH_2C\underline{H}_3$), 1.38 (3H, t, $J$=7.5 Hz, $CH_2C\underline{H}_3$), 1.80 (1H, br. s, OH), 4.32 (4H, q, $J$=7.5 Hz, 2×$OC\underline{H}_2CH_3$), 7.15 (1H, d, $J$=2.0 Hz, $C_3$′-H), 6.90—7.66 (6H, m, aromatic Hs), 8.87 (1H, br. s, NH), 9.47 (1H, br. s, NH). Mass Spectrum $m/e$: 392 ($M^+$).