Tetrahedron. Vol. 29, pp. 1991 to 2003. Pergamon Press 1973. Printed in Great Britain

FISCHER INDOLIZATION AND ITS RELATED COMPOUNDS—VII[1]

DEVELOPMENT OF ABNORMAL FISCHER INDOLIZATION OF ORTHO-METHOXYPHENYLHYDRAZONE TO PROVIDE A SYNTHETIC METHOD FOR USEFUL INDOLE DERIVATIVES POSSESSING AN ACTIVE METHINE GROUP AT C_6 AND NOVEL 3,6′-BIINDOLE DERIVATIVES

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(*Received in Japan* 13 *November* 1972; *Received in the UK for publication* 22 *February* 1973)

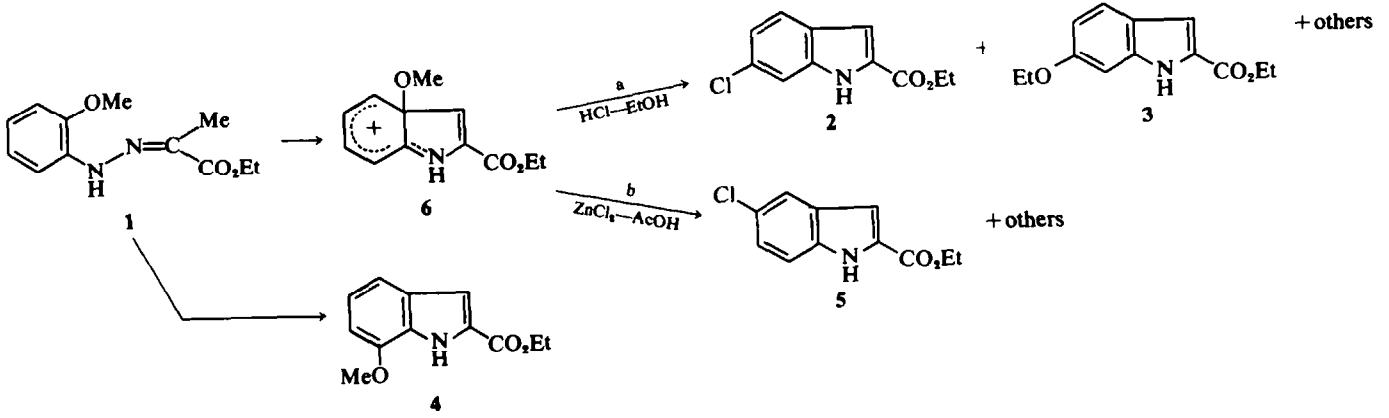
Abstract—Fischer indolization of ethyl pyruvate 2-methoxyphenylhydrazone (**1**) with *p*-toluenesulfonic acid in benzene in the presence of an enolizable dicarbonyl or an indolic compound gave either an indole product having an active methine group at C_6 or a novel type of 3,6′-biindole compound. Structures of the products were established by NMR spectra and chemical evidence.

In preceding papers of this series, we have shown that cyclization of ethyl pyruvate 2-methoxyphenylhydrazone (**1**) with ethanolic hydrogen chloride gives the unexpected ethyl 6-chloro- (**2**) and 6-ethoxy- (**3**) indole-2-carboxylates as main products by ortho-C_6 abnormal Fischer indolization, instead of the expected ethyl 7-methoxyindole-2-carboxylate (**4**);[2] whereas treatment of the same hydrazone (**1**) with zinc chloride in acetic acid gives the unexpected ethyl 5-chloroindole-2-carboxylate (**5**) as a main product by ortho-C_5 abnormal Fischer indolization.[1] We assumed that these transformations proceed via a common key intermediate cation (**6**) which undergoes either addition of a nucleophile such as a chloride anion and/or an ethanol molecule and loss of methanol, or substitution of the OMe group under stronger acidic conditions by an S_N2' (S_Ni' or S_Ni') mechanism. These results suggest that the abnormal Fischer indolization, if carried out under suitable conditions, should provide a synthetic method for indole derivatives having a unique substituent at the C_6 position. In the present paper, we wish to report the successful development of such a method.

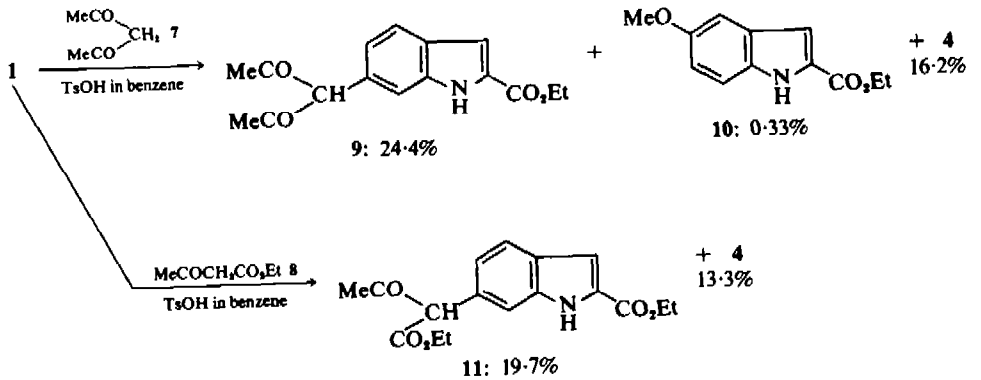
We aimed at inserting an active methine group into the C_6 position of the indole nucleus. We used enolizable dicarbonyl compounds as nucleophiles, expecting that they would serve as suitable acceptors of the electrophilic intermediate (**6**), even under the acidic conditions of Fischer indolization. We chose *p*-toluene-sulfonic acid as a catalyst for the addition, considering that it is not sufficiently nucleophilic to react with the intermediate cation itself. We considered that benzene, or other non-nucleophilic aromatic hydrocarbons would be suitable as the reaction solvent.

Treatment of ethyl pyruvate 2-methoxyphenylhydrazone[2] (**1**) in benzene with *p*-toluenesulfonic acid in the presence of an excess amount of either acetylacetone (**7**) or ethyl acetoacetate (**8**) gave ethyl 6-(1-acetyl-2-oxopropyl)indole-2-carboxylate (**9**) and ethyl α-acetyl-2-ethoxycarbonylindole-6-acetate (**11**) as main products, respectively. (Scheme 2). From the reaction with acetylacetone (**7**), ethyl 5-methoxyindole-2-carboxylate[1] (**10**) was also isolated in a minute yield. The formation of the methoxyindole (**10**) can be explained as a 1,3-migration of the OMe group of the key intermediate cation (**6**) as previously reported.[2] The NMR spectrum of the former indolic product (**9**) shows a 6H singlet due to two acetyl Me groups at 1·85 δ and a 1H singlet due to an enolic proton at 16·48 δ; the spectrum of the latter product (**11**) shows a 3H singlet due to an acetyl Me group at 2·18 δ and a 1H singlet due to an active methine proton at 4·78 δ. These spectral data indicate that both products have the expected substituent in their molecules. Signals due to these aromatic protons appear in each spectra as one 1H quartet having a wide coupling constant (8·5 and 8·0 Hz) and narrow one (2·0 and 2·0 Hz), and two 1H doublets whose coupling constants correspond respectively to those of the quartet. The existence of three protons at the 1, 2 and 4 positions of the benzene ring are thus indicated and, accordingly, the substituent must be at the C_5 or C_6 position in each indole nucleus. The structures were established decisively by the following chemical means.

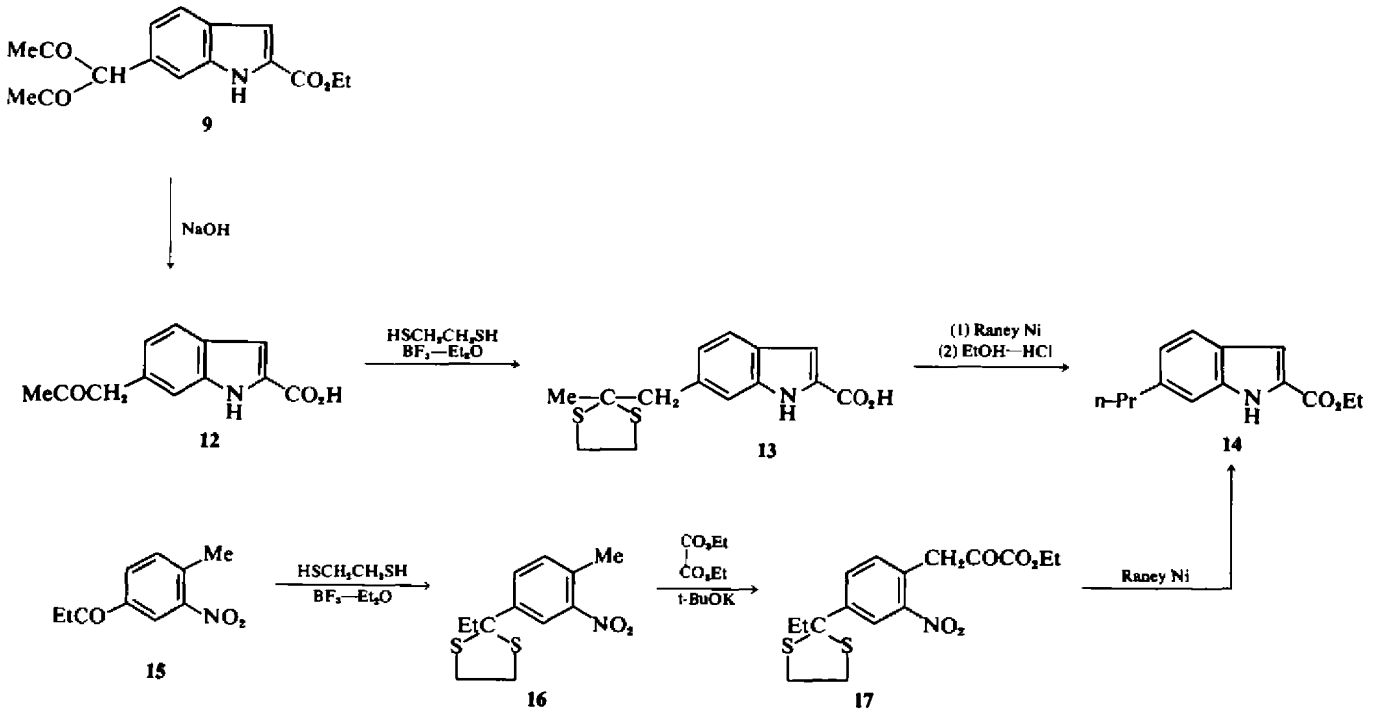
Treatment of ethyl 6-(1-acetyl-2-oxopropyl)-indole-2-carboxylate (**9**) with sodium hydroxide gave 6-(2-oxopropyl)indole-2-carboxylic acid (**12**), whose NMR spectrum shows two singlets due to an



SCHEME 1



SCHEME 2


MeCO
CH
MeCO
N
H
CO2Et
9
NaOH
MeCOCH2
N
H
CO2H
12
HSCH2CH2SH
BF3—Et2O
Me—C—CH2
S
S
N
H
CO2H
13
(1) Raney Ni
(2) EtOH—HCl
n-Pr
N
H
CO2Et
14
Me
EtCO
NO2
15
HSCH2CH2SH
BF3—Et2O
Me
EtC
S
S
NO2
16
CO2Et
CO2Et
t-BuOK
CH2COCO2Et
EtC
S
S
NO2
17
Raney Ni

SCHEME 3

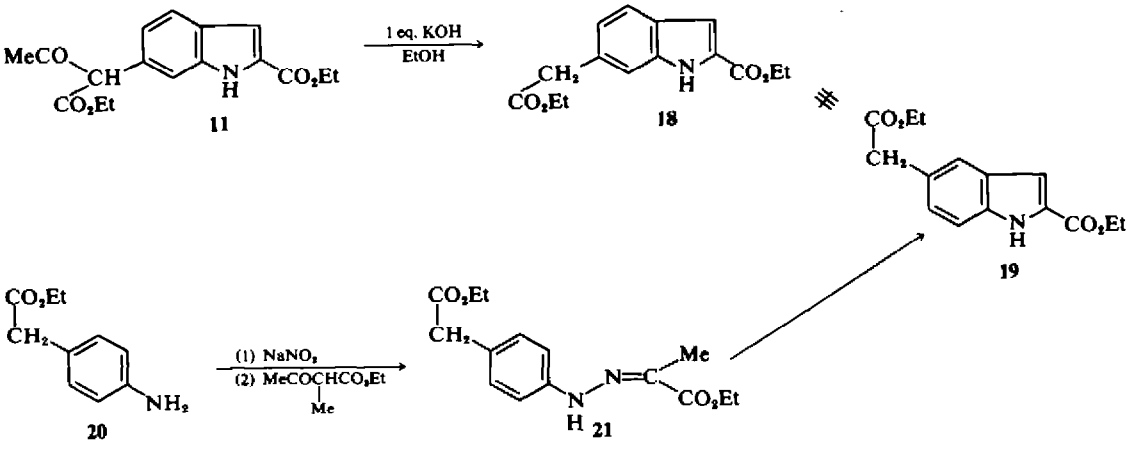
acetyl Me group and an active methylene at 2·10 and 3·78 δ. Thioketalization of the acetonylindole derivative (**12**) with ethanedithiol and boron trifluoride-etherate afforded a dithioketal (**13**). Reduction of the dithioketal (**13**) with Raney Nickel, followed by esterification in ethanol with hydrogen chloride gave ethyl 6-n-propylindole-2-carboxylate (**14**), which was identical with an authentic sample prepared by Reissert's method[3] from 4-methyl-3-nitropropiophenone[4] (**15**) as shown in Scheme 3.

On the other hand, treatment of ethyl α-acetyl-2-ethoxycarbonylindole-6-acetate (**11**) with potassium hydroxide gave ethyl 2-ethoxycarbonylindole-6-acetate (**18**), m.p. 93–94°, shown to be different from a sample of ethyl 2-ethoxycarbonylindole-5-acetate (**19**), m.p. 118·5–120°, prepared from ethyl 4-aminophenylacetate[5] (**20**) by Japp-Klingemann reaction[6] followed by Fischer indolization. These experiments establish the advanced application of the abnormal Fischer indolization of the 2-methoxyphenylhydrazone derivative to the synthesis of the 6-substituted indole derivatives.

In our previous paper,[2] we reported the isolation of a minute amount of an indolic dimer, m.p. 236–240°, having a Cl atom in its molecule, when ethyl pyruvate 2-methoxyphenylhydrazone (**1**) was cyclized with saturated ethanolic hydrogen chloride. It was reasonable to assume that the dimer arises from nucleophilic addition of ethyl 6-chloroindole-2-carboxylate (**2**), the main product in the cyclization, to the key intermediate cation (**6**) to give diethyl 6-chloro-3,6′-biindole-2,2′-dicarboxylate (**22**). The elemental analysis of the dimer, corresponding to the formula $C_{22}H_{19}O_4N_2Cl$ (M^+: *m/e* 410), supports this assumption. This led us to consider that cyclization of ethyl pyruvate 2-methoxyphenylhydrazone (**1**) in the presence of an excess amount of ethyl 6-chloroindole-2-carboxylate (**2**) under the conditions used for the present advanced application would provide the dimer (**22**) in better yield.

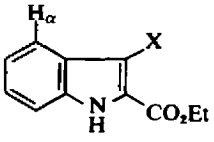
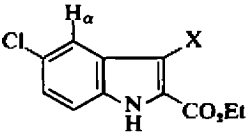
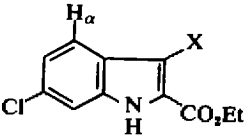
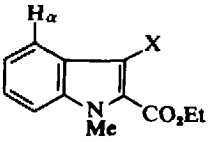
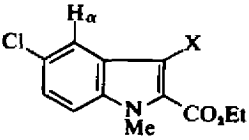
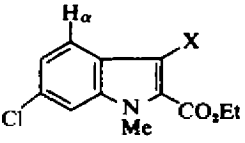
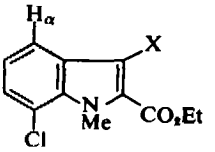
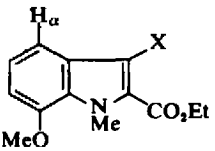
Treatment of a mixture of ethyl pyruvate 2-methoxyphenylhydrazone (**1**) and ethyl 6-chloroindole-2-carboxylate[2] (**3**) in benzene with *p*-toluenesulfonic acid followed by column chromatography gave two new indolic products, (**22** and **23**), besides ethyl 5-methoxyindole-2-carboxylate[1] (**10**, *vide ante*) and the expected ethyl 7-methoxyindole-2-carboxylate[2] (**4**). The first new product (**22**) was found to be identical with a specimen of the dimer previously isolated from the cyclization of ethyl pyruvate 2-methoxyphenylhydrazone (**1**) with saturated hydrogen chloride.[2] The NMR spectrum of the product (**22**) shows signals due to C_3—H and two NH groups at 7·06, 11·82 and 11·95 δ in the lower field region. The fact that the dimer (**22**) lacks one C_3—H signal means that one of its indolic units is linked with the benzene portion of the other indolic unit at the C_3 position. However, as the signals due to the six aromatic protons are too complicated to analyse, due to overlapping of the two indolic units, we could not obtain any information about the other side of the linkage from the NMR spectrum of the dimer itself.

A comparison of the signals due to the C_4 proton of C_3—H indole derivatives with those of the corresponding C_3-formyl compounds suggests that the introduction of a formyl group into the C_3 position causes the signals due to a C_4—H, which is situated at a position peri to the formyl group, to shift downfield by 60–100 Hz through the anisotropic effect of the CO group (Table 1). Formylation of the dimer (**22**) with Vilsmeier reagent yielded a product (**24**) possessing one formyl group in its molecule. The dimer (**22**) has three points which are vulnerable to the electrophilic reagent, the C_3 carbon and the two N atoms, but the occurrance of formylation only at the C_3 position is proved by the appearance of two NH



SCHEME 4

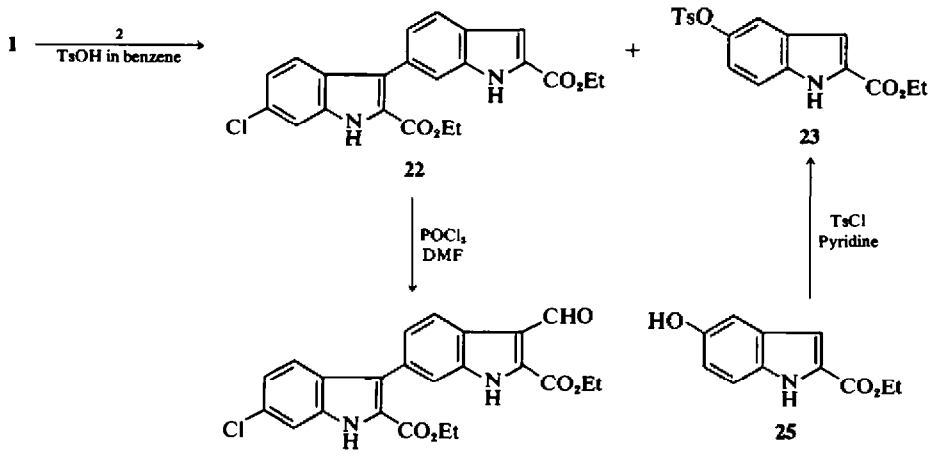
Table 1

Compounds	Chemical shifts of C_4—H (Hα): δ indole (X=H)	3-formyl deriv. (X=CHO)	Δ (cps)
	7·58	8·22	64
	7·62	8·24	62
	7·60	8·22	62
	7·51	8·52	101
	7·53	8·48	95
	7·46	8·23	77
	7·42	8·31	89
	7·07	7·98	91

signals at 11·98 and 12·78 δ in the NMR spectrum. The formyl derivative (**24**) also has a 1H doublet ($J = 8·5$ Hz) shifted 60–130 Hz from the signals due to the aromatic protons of the starting dimer (**22**). We can safely assign this signal to the C_4—H of the formylated indole unit. Irradiation at 8·27 δ, the centre of the C_4—H doublet, changed the splitting pattern of the signal at 7·25 δ from a quartet ($J = 8·5$ and 2·0 Hz) to a doublet ($J = 2·0$ Hz), and *vice versa*. These spectral data show the presence of protons at the C_5 and C_7 positions of the formylated indole unit, indicating that the formylated indole unit is linked to the other indolic unit of the dimer (**24**) at the C_6 carbon atom. This evidence leads us to conclude that the indolic dimer (**22**) is diethyl 6-chloro-3,6′-biindole-2,2′-dicarboxylate.

The second and minor new indolic product (**23**) contains a S atom in its molecule. The presence of a tosyloxy substituent in its molecule is confirmed by its elemental analysis (M^+: at *m/e* 359), absorption bands at 1377, 1181 and 1170 cm^{-1} in its IR spectrum, and the newly appearing Me signal as a singlet at 2·42 δ in its NMR spectrum. Unfortunately, the yield of the product (**23**) was too low to allow determination of the position of the tosyloxy group by chemical transformation, though we can postulate its position from the mechanism previously proposed by us.[2] As it is well-known that the tosyloxy ion is a weak nucleophile, and it is natural to assume that the *p*-toluenesulfonic acid molecule has not sufficient nucleophilicity to add to the key intermediate cation (**6**) at the C_6 position (ortho-C_6 Abnormal Fischer indolization) but would be subject to an S_N2' (S_N1' or S_Ni') reaction with a OMe group of the cation (**6**) at the C_5 position (ortho-C_5 Abnormal Fischer indolization) to give ethyl 5-tosyloxyindole-2-carboxylate (**23**). The correctness of this assumption has been verified by the fact that the tosyloxyindolic product (**23**) is identical to an authentic sample prepared by tosylation of ethyl 5-hydroxyindole-2-carboxylate[7] (**25**).

In 1969, Gannon *et al.*[8] reported the isolation of a different indolic dimer, m.p. 233–235°, having a OMe group in its molecule, from the cyclization of ethyl pyruvate 2-methoxyphenylhydrazone (**1**) with saturated hydrogen chloride. In view of the formation of diethyl 6-chloro-3,6′-biindole-2,2′-dicarboxylate (**22**) under the same conditions in our experiment, it may be supposed that Gannon's product is also the result of abnormal Fischer indolization. In other words, the normally expected ethyl 7-methoxyindole-2-carboxylate (**4**) was subject to a further nucleophilic attack by the key intermediate cation (**6**) in the reaction mixture to give Gannon's dimer. However, electrophilic attack of ethyl 7-methoxyindole-2-carboxylate (**4**) differs from that of ethyl 6-chloroindole-2-carboxylate (**2**), because the latter has only two points



SCHEME 5

susceptible to an electrophile, at the nitrogen and C_3 carbon atoms on the pyrrole ring, while the former has two additional points, the positions ortho- and para- to the methoxy group on the benzene ring. In fact, treatment of a mixture of ethyl 7-methoxyindole-2-carboxylate[2] (**4**) and ethyl pyruvate 2-methoxyphenylhydrazone[2] (**1**) in benzene with *p*-toluenesulfonic acid gave a mixture of two dimeric indoles in the yields of 10·8% (dimer I; **26**) and 16·3% (dimer II; **27**). Both of these dimeric products have the same empirical formula, $C_{23}H_{22}O_5N_2$, determined from their elemental analyses and mass spectra (M^+: at *m/e* 406). The first product, dimer I (**26**), m.p. 234–236°, has the same m.p. as that reported by Gannon *et al.* for their dimer, m.p. 233–235°. It is easily shown that dimer I is not a 3,6′-biindole derivative, since its NMR spectrum shows two NH and two C_3—H signals, as shown in Table 2. These spectral data leave only two possible structures, diethyl 7-methoxy-4,6′-biindole-2,2′-dicarboxylate (**26**) or diethyl 7-methoxy-6,6′-biindole-2,2′-dicarboxylate (**26a**) for dimer I.

Conclusive evidence for preference of the former structure (**26**) was obtained by comparison (Table 2) of the NMR spectrum of the dimer I with that of its diformyl derivative (**28**), synthesized by formylation of dimer I (**26**) with Vilsmeier reagent. The diformyl derivative (**28**) shows signals due to two aldehydic and two NH protons but no signal due to C_3—H.This suggests the introduction of formyl groups into both of two C_3-positions of dimer I (**26**) to give diethyl 3,3′-diformyl-7-methoxy-4,6′-biindole-2,2′-dicar oxylate (**28**). In spite of the presence of CO groups at the C_3-position of each indolic unit, the diformyl derivative (**28**) shows only one 1H doublet in the lower field at the aromatic proton region, compared with the signals due to aromatic protons of dimer I (**26**) itself. This spectral evidence shows that the diformyl derivative (**28**) has only one C_4—H in its molecule. Therefore, structure **26**, not **26a** must be supposed for dimer I.

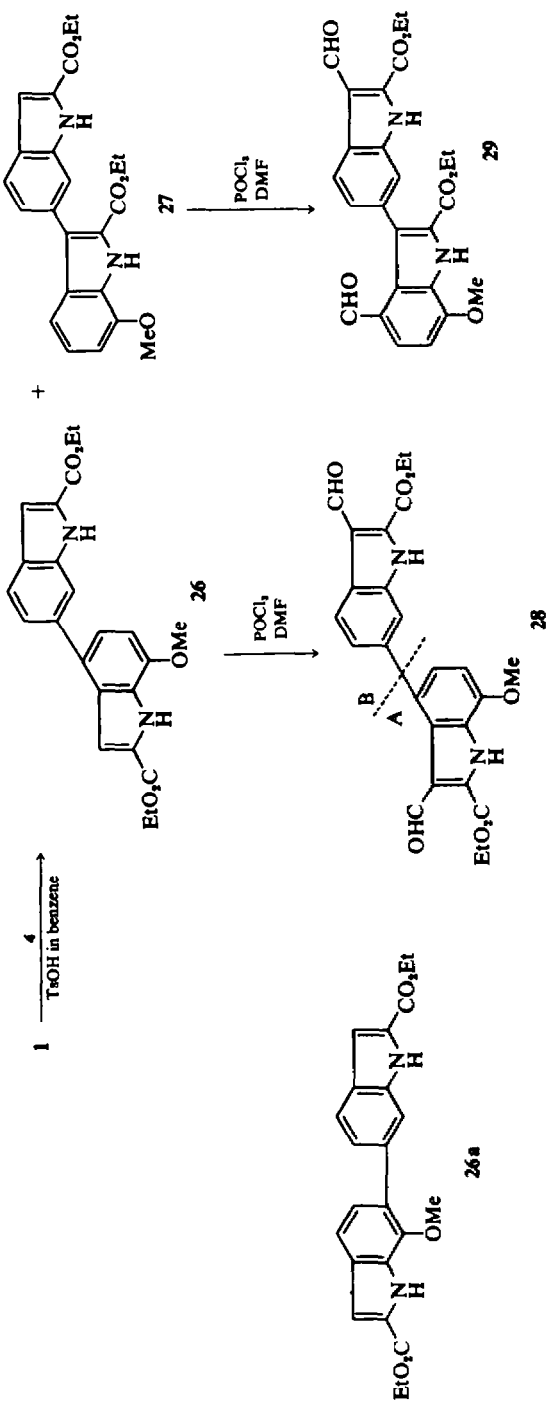
The structural establishment of dimer II (**27**) was made as follows: The NMR spectrum shows signals due to two NH protons and one C_3—H proton as shown in Table 2. This suggests that dimer II (**27**) is a 3,6′-biindole derivative. Formylation of dimer II (**27**) gave a diformyl derivative (**29**) whose NMR spectrum shows a 1H doublet in the lower field of aromatic proton region. Therefore, we can safely assign the signal to C_4—H. Double resonance technique reveals that the formylated indole unit has three benzenoid protons at 4, 5, and 7 positions. The formyl derivative shows two undefined 1H doublets ($J = 8{\cdot}2$ Hz) at 7·71 and 7·03 δ due to two aromatic protons. Although the coupling constant indicates that these two protons are situated vicinally, whether they should be assigned to the C_4—C_5 positions or to the C_5—C_6 positions cannot be made for certain from the data available so far. However, we tentatively place the second formyl group at the C_4 position, since the formation of dimer I allows us to assume that electrophilic attack of the ethyl 7-methoxyindole-2-carboxylate derivative takes place at the C_4 position in preference to the C_6 position. These considerations lead us to the conclusion that dimer II is assigned as diethyl 7-methoxy-3,6′-biindole-2,2′-dicarboxylate (**27**) and its diformyl derivative as diethyl 3′,4-diformyl-7-methoxy-3,6′-biindole-2,2′-dicarboxylate (**29**).

So we have succeeded in developing the ortho-C_6 abnormal Fischer indolization to provide a synthetic method for C_6-substituted indole derivative. The fact that ethyl 7- (**4**) and 5- (**10**) methoxyindole-2-carboxylates are produced as by-products is compensated for by the ready availability of the starting materials and by the difficulty of synthesizing the desired products by other methods.

Table 2

		Dimer I (26)	Diformyl dimer I (28)	Dimer II (27)	Diformyl dimer II (29)
NH		11·82 (1H, br, s) 11·98 (1H, br, s)	12·68 (1H, br, s) 12·91 (1H, br, s)	11·68 (1H, br, s) 11·82 (1H, br, s)	12·46 (2H, br, s)
$C_{3,3'}$—H		7·17 (1H, d, J = 1·5) 7·24 (1H, d, J = 1·5)	———	7·17 (1H, d, J = 1·5)	———
CHO		———	9·94 (1H, s) 10·62 (1H, s)	———	9·38 (1H. s) 10·61 (1H, s)
	C_4—H	———	———	7·12 (1H, q, J = 7·5, 2·0)	———
A	C_5—H	7·12 (1H, d, J = 8·0)	7·14 (1H, d, J = 8·0)	6·99 (1H, t, J = 7·5)	7·71 (1H, d, J = 8·2)
	C_6—H	6·87 (1H, d, J = 8·0)	7·00 (1H, d, J = 8·0)	6·81 (1H, q, J = 7·5, 2·0)	7·03 (1H, d, J = 8·2)
	$C_{4'}$—H	7·74 (1H, d, J = 8·2)	8·19 (1H, d, J = 8·4)	7·67 (1H, d, J = 8·0)	8·19 (1H, d, J = 8·4)
B	$C_{5'}$—H	7·34 (1H, q, J = 8·2, 1·7)	7·24 (1H, q, J = 8·4, 1·5)	7·20 (1H, q, J = 8·0, 1·5)	7·24 (1H, q, J = 8·4, 1·5)
	$C_{7'}$—H	7·70 (1H, d, J = 1·7)	7·45 (1H, d, J = 1·5)	7·56 (1H, d, J = 1·5)	7·56 (1H, d, J = 1·5)
$OCH_2\underline{C}H_3$		1·30 (3H, t, J = 7·5) 1·34 (3H, t, J = 7·5)	1·36 (3H, t, J = 7·5) 1·43 (3H, t, J = 7·0)	1·15 (3H, t, J = 7·0) 1·34 (3H, t, J = 7·5)	0·99 (3H, t, J = 7·0) 1·42 (3H, t, J = 7·0)
OCH_3		3·94 (3H, s)	4·00 (3H, s)	3·93 (3H, s)	4·07 (3H, s)
$OC\underline{H}_2CH_3$		4·28 (2H, q, J = 7·5) 4·34 (2H, q, J = 7·5)	4·38 (2H, q, J = 7·5) 4·47 (2H, q, J = 7·0)	4·16 (2H, q, J = 7·0) 4·34 (2H, q, J = 7·5)	4·09 (2H, q, J = 7·0) 4·48 (2H, q, J = 7·0)

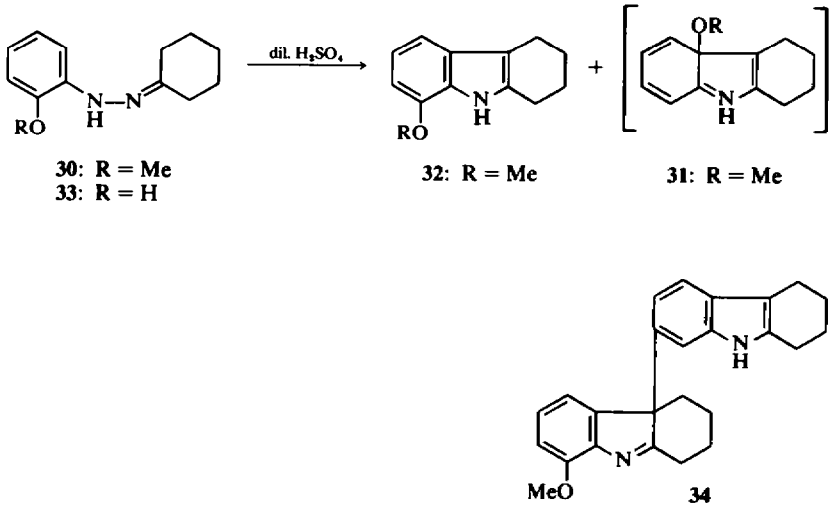
Measured in $DMSO_6$ (J : Hz)



Scheme 6

Finally, in connection with our studies, we would like to make a proposal for the structure of Pausacker's so-called 12-methoxy-1,2,3,4-tetrahydroisocarbazole.[9] In 1949, Pausacker[9] *et al.* reported that Fischer indolization of cyclohexanone 2-methoxyphenylhydrazone (**30**) in dilute sulfuric acid gave an interesting by-product (**31**), m.p. 145–146°, having a OMe group in its molecule, together with the expected 8-methoxy-1,2,3,4-tetrahydrocarbazole (**32**). From its weak basicity and the formation of 1-methoxycarbazole on dehydrogenation with chloranil, they claimed that the by-product is 12-methoxy-1,2,3,4-tetrahydroisocarbazole (**31**). Later, Tomlinson *et al.*[10] re-examined Pausacker's procedure with cyclohexanone 2-hydroxyphenylhydrazone (**33**), and their results cast doubt on Pausacker's assignment. Recently, Gannon *et al.*[8] repeated the published method with cyclohexanone 2-methoxyphenylhydrazone (**30**) and indeed obtained crystals having almost the same m.p., 152–155°, as that reported by Pausacker.[9] Their reported data for the characterization of the product is as follows: Elemental analysis consistent with empirical formula $C_{25}H_{26}ON_2$; the mass spectrum displays a parent peak at *m/e* 470, and the NMR spectrum exhibits one NH, one OMe and six or seven aromatic protons in a complex system. Taking our results on the ortho-C_6 abnormal Fischer indolization into consideration, Gannon's description allows us to postulate that the products of both Pausacker and Gannon (at least that of Gannon) is the dimer shown by structure (**34**).

Chemical experiments on the reactivity of the C_3 position of 3-substituted indole derivatives to electrophiles are going on in our laboratory.



30: R = Me
33: R = H

32: R = Me

31: R = Me

34

SCHEME 7

EXPERIMENTAL

All m.ps were measured on a micro-melting hot-stage (Yanagimoto) and are uncorrected. IR, NMR, and mass spectra were obtained with Hitachi EPI-G3, JEOL JMN-4H-100, and Hitachi RMU-6-E spectrometers, respectively. Assignments of all NH and C_3—H signals in the NMR spectra of the indole derivatives were confirmed by disappearance of the NH signal and change of shape of the C_3—H signal from doublet to singlet after addition of D_2O. For column chromatography, Silicic acid (100 mesh, Mallinckrodt Chemical Works) and Aluminum Oxide (neutral, M. Woelm) was used. Details of the synthetic methods used and the physical properties of the starting materials and authentic samples of the products appeared in preceding papers.[1,2] All identification of the products was made by IR, mixed m.p., and TLC

Ethyl 6-(1-*acetyl*-2-*oxopropyl*)*indole*-2-*carboxylate* (**9**)

A soln of 14·5 g of $TsOH \cdot H_2O$ in 150 ml of abs benzene was refluxed for 1 hr using a Dean-Stark water collection apparatus. To the soln was added a mixture of 6·00 g of **1**[2] and 25·4 g of acetylacetone. The mixture was refluxed for 1 hr, diluted with water and extracted with ether. The ethereal soln was dried over $MgSO_4$ and evaporated to dryness *in vacuo*. The residue (5·463 g) was taken up in benzene and chromatographed on Al_2O_3 (grade I) and divided into two fractions, eluants with benzene (1·927 g) and with chloroform (2·029 g). The benzene fraction was rechromatographed on silicic acid. First elution with benzene gave 909 mg of colourless needles, m.p. 114–116·5°, which were recrystallized from hexane–benzene and identified with an authentic sample of **4**.[2] Second elution with benzene gave 17 mg of colourless pillars, m.p. 158–161·5°, which were recrystallized from hexane–benzene and identified with an authentic sample of **10**.[1]

The chloroform eluant was purified by rechromatography on silicic acid to give 1·776 g of light yellow needles, m.p. 149–151°, which were recrystallized from cyclohexane–benzene; IR ν_{max}^{Nujol} cm^{-1}; 3265 (**NH**), **1707**

(C=O); NMR (CCl_4) δ: 1·44 (3H, t, J = 7·3 Hz, CH_2CH_3), 1·85 (6H, s, 2×$COCH_3$), 4·42 (2H, q, J = 7·3 Hz, OCH_2CH_3), 6·90 (1H, q, J = 2·0 Hz, J = 8·5 Hz, C_5—H), 7·14 (1H, d, J = 2·0 Hz, C_3—H), 7·20 (1H, d, J = 2·0 Hz, C_7—H), 7·61 (1H, d, J = 8·5 Hz, C_4—H), 9·48 (1H, br, s, NH), 16·48 (1H, s, enolic OH, disappeared by addition of D_2O). Mass spectrum *m/e*: 287 (M^+). (Found: C, 66·62; H, 5·88; N, 5·01. $C_{16}H_{17}O_4$ requires: C, 66·88; H, 5·96; N, 4·88%).

6-(2-Oxopropyl)indole-2-carboxylic acid (**12**)

To a soln of **9** (200 mg) in 3 ml EtOH was added 0·42 ml 20% NaOH aq. The mixture was refluxed for 30 min, evaporated to dryness *in vacuo*, and the residue dissolved in water. The aqueous soln was washed with ether, made acidic with 10% HCl aq, then extracted with ether. The ethereal soln was dried over $MgSO_4$ and evaporated to dryness *in vacuo*. Sublimation of the residue (160–180° at 2 mmHg) gave 143 mg of colourless needles, m.p. 182–183·5°; IR ν_{max}^{Nujol} cm^{-1}: 3443 (NH), 3313 (enolic OH), 1698, 1671 (C=O); NMR (acetone-d_6) δ: 2·10 (3H, s, $COCH_3$), 3·78 (2H, s, $COCH_2Ph$), 6·97 (1H, q, J = 2·0 Hz, J = 8·0 Hz, C_5—H), 7·17 (1H, d, J = 2·5 Hz, C_3—H), 7·41 (1H, d, J = 2·0 Hz, C_7—H), 7·63 (1H, d, J = 8·0 Hz, C_4—H), 10·69 (1H, br s, NH). Mass spectrum *m/e*: 217 (M^+). (Found: C, 65·97; H, 5·03; N, 6·64. $C_{12}H_{11}O_3N$ requires: C, 66·35; H, 5·10; N, 6·45%).

6-(2,2-Ethylenedithiopropyl)indole-2-carboxylic acid (**13**)

To a soln of **12** (220 mg) in 2 ml AcOH was added 0·22 ml BF_3·Et_2O and 0·22 ml ethanedithiol. The mixture was allowed to stand at room temp overnight then diluted with a large excess of water. The ppt was filtered off and recrystallized from EtOH to give 175 mg of colourless needles, m.p. 236–238°; IR ν_{max}^{Nujol} cm^{-1}: 3330 (NH), 1670 (C=O); NMR (acetone-d_6) δ: 1·69 (3H, s, CCH_3), 3·29 (4H, s, SCH_2CH_2S), 3·33 (2H, s, $PhCH_2$), 7·15 (1H, q, J = 7·5 Hz, 2·0 Hz, C_5—H), 7·16 (1H, d, J = 2·5 Hz, C_3—H), 7·54 (1H, d, J = 2·0 Hz, C_7—H), 7·58 (1H, d, J = 7·5 Hz, C_4—H), 10·67 (1H, br, s, NH). Mass spectrum *m/e*: 293 (M^+). (Found: C, 57·45; H, 5·10; N, 4·73. $C_{14}H_{15}O_2NS_2$ requires: C, 57·33; H, 5·16; N, 4·78%).

Ethyl 6-n-propylindole-2-carboxylate (**14**)

To a soln of **13** (175 mg) in 25 ml EtOH was added Raney Ni prepared from 9 g of the alloy and the mixture was refluxed for 3·5 hr. After the mixture had cooled, Raney Ni was removed by filtration and washed thoroughly with 5% NaOH aq. The filtrate was evaporated to dryness *in vacuo*. The residue was dissolved into 5% NaOH aq and combined with the washings. The alkaline soln was washed with ether, made acidic with conc HCl, and extracted with ether. The extract was dried over $MgSO_4$ and evaporated to dryness *in vacuo*. A soln of the residue (46 mg) in 20 ml of EtOH was treated with dry HCl, refluxed for 1·5 hr, then evaporated to dryness *in vacuo*. The residue was taken up in ether, washed with 5% $NaHCO_3$ aq, dried over $MgSO_4$, and evaporated to dryness *in vacuo*. The residue was dissolved in benzene and chromatographed on silicic acid. Elution with benzene gave 19 mg of colourless needles, m.p. 77–79°, which were recrystallized from pentane. The product was identical with authentic **14** prepared from **15**[4] by Reissert's method.[3]

Authentic ethyl 6-n-propylindole-2-carboxylate (**14**)

(a) *4-(1,1-Ethylenedithiopropyl)-2-nitrotoluene* (**16**). A mixture of **15**[4] (5·00 g), 5·4 ml ethanedithiol, and 5·4 ml BF_3·Et_2O in 21·5 ml AcOH was allowed to stand at room temp overnight. The mixture was poured into ice water and extracted with ether. The extract in ether was washed with 10% NaOH aq, dried over K_2CO_3, and evaporated to dryness *in vacuo*. The residue was dissolved in benzene and chromatographed on Al_2O_3 (Woelm, basic, grade I). Elution with benzene gave 6·00 g of yellow pillars, m.p. 33·5°, which were purified by distillation under reduced pressure (b.p. 160–178° at 2 mmHg); IR ν_{max}^{Film} cm^{-1}: 1520, 1350 (NO_2); NMR (CCl_4) δ: 0·90 (3H, t, J = 7·5 Hz, CH_2CH_3), 2·32 (2H, q, J = 7·5 Hz, CH_2CH_3), 2·55 (3H, s, aryl CH_3), 3·05–3·47 (4H, m, SCH_2CH_2S), 7·21 (1H, d, J = 8·0 Hz, C_5—H), 7·73 (1H, q, J = 8·0 Hz, J = 2·5 Hz, C_6—H), 8·24 (1H, d, J = 2·5 Hz, C_2—H). Mass spectrum *m/e*: 269 (M^+). (Found: C, 52·99; H, 5·82; N, 5·17. $C_{12}H_{15}O_2NS_2$ requires: C, 53·50; H, 5·61; N, 5·20%).

(b) *Ethyl 4-(1,1-ethylenedithiopropyl)-2-nitrophenylpyruvate* (**17**). To a soln of t-BuOK (1·59 g) and 1·92 ml diethyl oxalate in 7·5 ml abs benzene was added a soln of **16** (1·40 g) in 11·8 ml abs benzene. The mixture was refluxed for 17·5 hr. The mixture was cooled, and the ppt was collected by filtration, decomposed by addition of 1·62 ml AcOH in a large amount of water, and extracted with ether. The ethereal soln was washed with 5% $NaHCO_3$ aq, dried over $MgSO_4$, and evaporated to dryness *in vacuo*. The residue was dissolved in benzene and chromatographed on silicic acid to give 1·13 g of yellow oil; IR ν_{max}^{Film} cm^{-1}: 1720 (C=O); mass spectrum *m/e*: 369 (M^+).

(c) *Ethyl 6-n-propylindole-2-carboxylate* (**14**). A mixture of **17** (570 mg) and Raney Ni, prepared from 22·5 g of the alloy, in 20 ml abs EtOH was refluxed for 2 hr. After the mixture had cooled, Raney Ni was removed by filtration and washed thoroughly with EtOH. The filtrate and washing were combined and evaporated to dryness *in vacuo*. The residue dissolved in a mixture of benzene and hexane (1:1) was chromatographed on silicic acid. Elution with the mixed solvents gave 165 mg of colourless needles, m.p. 79–81°, which were recrystallized from pentane; IR ν_{max}^{Nujol} cm^{-1}: 3319 (NH), 1698 (C=O); NMR (CCl_4) δ: 0·93 (3H, t, J = 7·5 Hz, CH_2CH_3), 1·41 (3H, t, J = 7·5 Hz, CH_2CH_3), 1·67 (2H, m, $CH_2CH_2CH_3$), 2·65 (2H, t, J = 7·5 Hz, $PhCH_2CH_2$), 4·39 (2H, q, J = 7·5 Hz, OCH_2CH_3), 6·87 (1H, q, J = 8·0 Hz, J = 1·0 Hz, C_5—H), 7·05 (1H, d, J = 1·0 Hz, C_3—H), 7·10 (1H, d, J = 1·0 Hz, C_7—H), 7·47 (1H, d, J = 8·0 Hz, C_4—H), 9·27 (1H, br, s, NH); mass spectrum *m/e*: 231 (M^+). (Found: C, 72·93; H, 7·46; N, 6·12. $C_{14}H_{17}O_2N$ requires: C, 72·70; H, 7·41; N, 6·06%).

Ethyl α-acetyl-2-ethoxycarbonylindole-6-acetate (**11**)

A mixture of **1**[2] (3·54 g), ethyl acetoacetate (19·5 g), and anhyd TsOH (7·69 g) in 70 ml of abs benzene was refluxed for 30 min. After it had cooled, the mixture was poured into ice-water and extracted with ether. The ethereal soln was washed with 5% $NaHCO_3$ aq, dried over $MgSO_4$, and evaporated to dryness *in vacuo*. The excess ethyl acetoacetate was removed by distillation under reduced pressure. The residue in benzene was chromatographed on Al_2O_3 (Woelm, acidic grade II). Elution with benzene gave 438 mg of colourless needles, m.p. 116–117°, which were recrystallized from benzene–hexane and identified with an authentic sample of **4**.[2]

Elution with chloroform gave a mixture of **4** and another indolic compound. The mixture was dissolved in

benzene and was chromatographed on silicic acid. After first eluting with benzene, elution with chloroform gave 943 mg of colourless needles, m.p. 116–118°, which were recrystallized from benzene–hexane; IR ν_{max}^{Nujol} cm^{-1}: 3295 (NH), 1726, 1719, 1698 (C=O); NMR ($CDCl_3$) δ: 1·26 (3H, t, J = 7·0 Hz, $CH_2\underline{CH_3}$), 1·41 (3H, t, J = 7·0 Hz, $CH_2\underline{CH_3}$), 2·18 (3H, s, $COCH_3$), 4·22 (2H, q, J = 7·0 Hz, $OC\underline{H_2}CH_3$), 4·42 (2H, q, J = 7·0 Hz, $OC\underline{H_2}CH_3$), 4·78 (1H, s, $PhC\underline{H}(CO_2Et)(CO)$), 7·12 (1H, q, J = 8·0 Hz, J = 2·0 Hz, C_5—H), 7·22 (1H, d, J = 2·0 Hz, C_3—H), 7·51 (1H, d, J = 2·0 Hz, C_7—H), 7·70 (1H, d, J = 8·0 Hz, C_4—H), 9·17 (1H, br s, NH), mass spectrum *m/e* 317 (M^+). (Found: C, 64·13; H, 5·86; N, 4·47. $C_{17}H_{19}O_5N$ requires: C, 64·34; H, 6·04; N, 4·41%).

Ethyl 2-ethoxycarbonylindole-6-acetate (**18**)

To a soln of **11** (190 mg) in 3 ml abs EtOH was added gradually 3 ml EtOH containing KOH (40 mg). The mixture was allowed to stand at room temp for 1·5 hr, poured into ice-water, and extracted with ether. The ethereal soln was dried over $MgSO_4$ and evaporated to dryness *in vacuo*. The residue (118 mg) was dissolved in chloroform and chromatographed on silicic acid. Elution with chloroform gave 80 mg of colourless needles, m.p. 93–94°, which were recrystallized from benzene–hexane; IR ν_{max}^{Nujol} cm^{-1}: 3308 (NH), 1734, 1688 (C=O); NMR ($CDCl_3$) δ: 1·24 (3H, t, J = 7·0 Hz, $CH_2\underline{CH_3}$), 1·40 (3H, t, J = 7·0 Hz, $CH_2\underline{CH_3}$), 3·69 (2H, s, $PhC\underline{H_2}CO$), 4·15 (2H, q, J = 7·0 Hz, $OC\underline{H_2}CH_3$), 4·38 (2H, q, J = 7·0 Hz, $OC\underline{H_2}CH_3$), 7·06 (1H, q, J = 8·0 Hz, J = 2·0 Hz, C_5—H), 7·17 (1H, d, J = 2·0 Hz, C_3—H), 7·32 (1H, d, J = 2·0 Hz, C_7—H), 7·61 (1H, d, J = 8·0 Hz, C_4—H), 9·06 (1H, br, s, NH); mass spectrum *m/e*: 275 (M^+). (Found: C, 65·50; H, 6·33; N, 5·22. $C_{15}H_{17}O_4N$ requires: C, 65·44; H, 6·22; N, 5·09%).

(Z)-Ethyl pyruvate 4-ethoxycarbonylmethylphenylhydrazone (**21**)

To a mixture of a soln of **20**[5] (5·38 g) in 20 ml water and 2·85 g conc HCl, cooled to 0°, was added $NaNO_2$ (1·90 g). This diazonium soln was added dropwise at 0–4° with stirring to a mixture of ethyl α-methylacetoacetate (4·0 g) dissolved in 30 ml EtOH, KOH (1·82 g), and 1·82 ml water. The mixture was stirred for 30 min, poured into water, and extracted with ether. The ethereal soln was dried over $MgSO_4$ and evaporated to dryness *in vacuo*. A mixture of the residue (8·34 g), 8 ml 85% H_3PO_4, and 40 ml EtOH was refluxed for 15 min, poured into water, and extracted with ether. The extract in ether was dried over $MgSO_4$ and the solvent was distilled off. The residue (7·39 g) was dissolved in benzene and chromatographed on silicic acid. Elution with benzene gave 1·595 g yellow needles, m.p. 64–65°, which were recrystallized from hexane; IR ν_{max}^{Nujol} cm^{-1}: 3245 (NH), 1734, 1662 (C=O); NMR (CCl_4) δ: 1·21 (3H, t, J = 7·5 Hz, $CH_2\underline{CH_3}$), 1·33 (3H, t, J = 7·5 Hz, $CH_2\underline{CH_3}$), 2·09 (3H, s, N=CCH_3), 3·40 (2H, s, $PhC\underline{H_2}CO$), 4·04 (2H, q, J = 7·5 Hz, $OC\underline{H_2}CH_3$), 4·22 (2H, q, J = 7·5 Hz, $OC\underline{H_2}CH_3$), 7·06 (4H, s, aromatic protons), 12·02 (1H, br, s, NH); mass spectrum *m/e*: 292 (M^+). (Found: C, 61·54; H, 6·87; N, 9·88. $C_{15}H_{20}O_4N_2$ requires: C, 61·63; H, 6·90; N, 9·58%).

Further elution with benzene and chloroform gave 2·883 g of a mixture of (E)- and (Z)-forms of the phenylhydrazone (**21**).

Ethyl 2-ethoxycarbonylindole-5-acetate (**19**)

A soln of **21** (700 mg) in 20 ml EtOH was refluxed with bubbling of HCl gas for 4 hr. After it had cooled, the mixture was poured into water and extracted with ether. The organic layer was washed with 5% $NaHCO_3$ aq, dried over $MgSO_4$, and evaporated to dryness *in vacuo*. The residue (442 mg) was dissolved in chloroform and chromatographed on silicic acid. First elution with chloroform gave a mixture of (Z)- and (E)-forms of the starting phenylhydrazone. Second elution with chloroform gave 88 mg of colourless needles, m.p. 118·5–120°, which were recrystallized from benzene–hexane; IR ν_{max}^{Nujol} cm^{-1}: 3305 (NH), 1735, 1690 (C=O); NMR (CCl_4) δ: 1·21 (3H, t, J = 7·5 Hz, $CH_2\underline{CH_3}$), 1·40 (3H, t, J = 7·5 Hz, $CH_2\underline{CH_3}$), 3·55 (2H, s, $PhC\underline{H_2}CO$), 4·07 (2H, q, J = 7·5 Hz, $OC\underline{H_2}CH_3$), 4·36 (2H, q, J = 7·5 Hz, $OC\underline{H_2}CH_3$), 7·04 (1H, d, J = 2·0 Hz, C_3—H), 7·12 (1H, q, J = 7·5 Hz, J = 1·5 Hz, C_6—H), 7·28 (1H, d, J = 7·5 Hz, C_7—H), 7·46 (1H, d, J = 1·5 Hz, C_4—H), 9·37 (1H, br, s, NH); mass spectrum *m/e*: 275 (M^+). (Found: C, 65·35; H, 6·16; N, 5·11. $C_{15}H_{17}O_4N$ requires: C, 65·44; H, 6·22; N, 5·09%).

Diethyl 6-chloro-3,6′-biindole-2,2′-dicarboxylate (**22**)

A mixture of **2**[2] (4·47 g), **1**[2] (4·73 g), and anhydrous TsOH (10·3 g) in 200 ml abs benzene was refluxed for 30 min. After it had cooled, the benzene soln was washed with dil $NaHCO_3$ aq, dried over $MgSO_4$, and evaporated to dryness *in vacuo*. The residue was dissolved in benzene, chromatographed on Al_2O_3 (grade I) and eluted in two fractions, fraction A (eluant with benzene) and fraction B (eluant with chloroform).

Recrystallization of fraction A from cyclohexane–benzene gave 2·95 g colourless needles, m.p. 184–185°, which were identified with an authentic sample of **2**. The mother liquor of the recrystallization was evaporated to dryness and the residue was taken up in benzene and chromatographed on silicic acid. First elution with benzene gave a further 0·88 g of **2**. Second elution with benzene gave 0·51 g colourless needles, m.p. 112–114°, which were recrystallized from benzene–hexane and identified with an authentic sample of **4**.[2]

Recrystallization of fraction B gave 308 mg of colourless pillars, m.p. 243–244°, which were recrystallized from acetone; IR ν_{max}^{Nujol} cm^{-1}: 3315, 3300 (NH), 1683, 1668 (C=O); UV λ_{max}^{EtOH} mμ (log ε): 236 (4·62), 306 (4·50); NMR (DMSO—d_6) δ: 1·16 (3H, t, J = 7·0 Hz, $CH_2\underline{CH_3}$), 1·35 (3H, t, J = 7·0 Hz, $CH_2\underline{CH_3}$), 4·20 (2H, q, J = 7·0 Hz, $OC\underline{H_2}CH_3$), 4·34 (2H, q, J = 7·0 Hz, $OC\underline{H_2}CH_3$), 7·70–7·00 (6H, m, aromatic protons), 7·16 (1H, d, J = 2·0 Hz, C_3—H), 11·82 (1H, br, s, NH), 11·95 (1H, br, s, NH); mass spectrum *m/e*: 412 (M^+ + 2 39% intensity of M^+), 410 (M^+). (Found: C, 64·16; H, 4·58; N, 6·79. $C_{22}H_{19}O_4N_2Cl$ requires: C, 64·31; H, 4·66; N, 6·82%). This material was identical with **22**[2] isolated from the reaction mixture of **1** on the cyclization with ethanolic HCl.[2]

The mother liquor of the recrystallization of the above biindole (**22**) was evaporated to dryness *in vacuo*. The residue was dissolved in chloroform and chromatographed on silicic acid. First elution with chloroform gave 15 mg of colourless pillars, m.p. 154–158°, which were recrystallized from benzene–cyclohexane and identified with an authentic sample of **10**.[1]

Ethyl 5-p-tosyloxyindole-2-carboxylate (**23**)

Second elution with chloroform in the above experiment gave 88 mg colourless needles, m.p. 158–159°, which were recrystallized from benzene–cyclo-

hexane; IR ν_{max}^{Nujol} cm^{-1}: 3324 (NH), 1690 (C=O), 1377, 1189, 1181, 1170 (OSO_2); NMR ($CDCl_3$) δ: 1·40 (3H, t, J = 7·5 Hz, $CH_2\underline{CH_3}$), 2·42 (3H, s, aryl CH_3), 4·40 (2H, q, J = 7·5 Hz, $OC\underline{H_2}CH_3$), 6·95 (1H, q, J = 9·5 Hz, J = 2·0 Hz, C_6—H), 7·13 (1H, d, J = 2·0 Hz, C_3—H), 7·37–7·22 (4H, m, aromatic protons), 7·71 (2H, d, J = 8·0 Hz, $C_{2'}$—H and $C_{6'}$—H), 9·11 (1H, br, s, NH); mass spectrum *m/e*: 359 (M^+). (Found: C, 60·30; H, 4·87; N, 4·26. $C_{18}H_{17}O_5NS$ requires: C, 60·15; H, 4·77; N, 3·90%). The product was identified with an authentic sample of **23** prepared by tosylation of **25**.[7]

Authentic ethyl 5-p-*tosyloxyindole-2-carboxylate* (**23**)

A soln of **25**[7] (100 mg) and tosyl chloride (100 mg) in 1 ml pyridine was allowed to stand at room temp for 9 hr. The mixture was poured into water and extracted with ether. The ethereal soln was washed with dil HCl, dried over $MgSO_4$, and evaporated to dryness *in vacuo*. The residue was dissolved in benzene and chromatographed on silicic acid. Elution with benzene gave 52 mg of colourless needles, m.p. 161–163°, which were recrystallized from benzene–hexane.

Diethyl 6-*chloro*-3'-*formyl*-3,6'-*biindole*-2,2'-*dicarboxylate* (**24**)

A soln of 500 mg $POCl_3$ in 4 ml freshly distilled DMF was cooled to 0°. To this soln was added a soln of **22** (100 mg) in 1 ml DMF. The mixture was then heated at 100° for 1·5 hr, cooled, and poured into water. The mixture was made alkaline with 10% Na_2CO_3 aq and extracted with ether. The ethereal soln was dried over $MgSO_4$ and evaporated to dryness *in vacuo*. The residue (85 mg) was chromatographed on Al_2O_3 (grade Super I). Elution with chloroform gave 72 mg of pale yellow leaflets, m.p. 290–293°, which were recrystallized from dioxane–EtOH; IR ν_{max}^{Nujol} cm^{-1}: 3287 (NH), 3160 (br) (NH), 1722, 1689, 1639 (C=O), NMR (DMSO—d_6) δ: 1·15 (3H, t, J = 7·2 Hz, $C\underline{H_2}CH_3$), 1·41 (3H, t, J = 7·2 Hz, $CH_2C\underline{H_3}$), 4·19 (2H, q J = 7·2 Hz, $OC\underline{H_2}CH_3$), 4·46 (2H, q, J = 7·2 Hz, $OCH_2C\underline{H_3}$), 7·07 (1H, q, J = 8·5 Hz, J = 2·0 Hz, C_5—H), 7·43 (1H, q, J = 8·5 Hz, J = 2·0 Hz, $C_{5'}$—H), 7·47 (1H, d, J = 8·5 Hz, C_4—H), 7·52 (1H, d, J = 2·0 Hz, C_7— or $C_{7'}$—H), 7·63 (1H, d, J = 2·0 Hz, C_7—H or $C_{7'}$—H), 8·27 (1H, d, J = 8·5 Hz, $C_{4'}$—H), 10·64 (1H, s, CHO), 11·98 (1H, br, s, NH), 12·72 (1H, br, s, NH); mass spectrum *m/e*: 440 (M^+ +2, 37·4% intensity of M^+), 438 (M^+). (Found: C, 62·72; H, 4·22; N, 6·43. $C_{23}H_{19}O_5N_2Cl$ requires: C, 62·94; H, 4·36; N, 6·38%).

Fischer indolization of ethyl pyruvate 2-*methoxyphenylhydrazone* (**1**) *in the presence of ethyl* 7-*methoxyindole*-2-*carboxylate* (**4**)

A mixture of **1**[2] (3·54 g), **4**[2] (3·30 g), and anhydrous TsOH (7·75 g) was refluxed for 30 min, poured into water, and extracted with ether. The ethereal soln was washed with 10% $NaHCO_3$ aq, dried over $MgSO_4$, and evaporated to dryness *in vacuo*. The residue (6·523 g) was dissolved in benzene and chromatographed on Al_2O_3 (Woelm, acidic, grade II). First elution with benzene gave 2·041 g of **4**, m.p. 116–117°. Second elution with benzene and chloroform gave 2·10 g of a mixture of two indolic derivatives which were separated by preparative TLC using silicic acid and a mixed solvent (AcOH : chloroform : benzene = 1 : 20 : 10 v/v).

(a) *Diethyl* 7-*methoxy*-4,6'-*biindole*-2,2'-*dicarboxylate* (*Dimer I*) (**26**). The first component (661 mg), showing a larger R_f value (*ca* 0·21) on TLC, was obtained as colourless prisms, m.p. 234–236°, which were recrystallized from benzene; IR ν_{max}^{Nujol} cm^{-1}: 3315 (NH), 1695, 1680 (C=O); UV λ_{max}^{EtOH} mμ (log ε): 223·5 (4·54), 247 (4·64), 297 (4·34), 342 (4·39); mass spectrum *m/e*: 406 (M^+). (Found: C, 68·14; H, 5·39; N, 6·88. $C_{23}H_{22}O_5N_2$ requires: C, 67·96; H, 5·46; N, 6·89%).

(b) *Diethyl* 7-*methoxy*-3,6'-*biindole*-2,2'-*dicarboxylate* (*Dimer II*) (**27**). The second component (996 mg), showing a smaller R_f value (*ca* 0·19) on TLC, was obtained as colourless prisms, m.p. 205–207°, which were recrystallized from benzene; IR ν_{max}^{Nujol} cm^{-1}: 3325, 3300 (NH), 1670 (C=O); UV λ_{max}^{EtOH} mμ (log ε): 225 sh (4·53), 238 (4·61), 292 (4·37), 314 sh (4·28), 330 sh (4·26); mass spectrum *m/e*: 406 (M^+). (Found: C, 68·29; H, 5·36; N, 6·83. $C_{23}H_{22}O_5N_2$ requires: C, 67·96; H, 5·46; N, 6·89%).

Diethyl 3,3'-*diformyl*-7-*methoxy*-4,6'-*biindole*-2,2'-*dicarboxylate* (**28**)

A soln of $POCl_3$ (192 mg) in 2·0 ml DMF was cooled to 0°. To this soln was added a soln of **26** (41 mg) in 0·5 ml DMF. The mixture was then heated at 100° for 1 hr, cooled and poured into ice-water. The mixture was made alkaline with 10% $NaHCO_3$ aq and extracted with EtOAc. The organic layer was dried over $MgSO_4$ and evaporated to dryness *in vacuo*. Recrystallization of the residue (28 mg) from DMSO–EtOH gave 12 mg of yellow needles, m.p. 271–272·5°; IR ν_{max}^{Nujol} cm^{-1}: 3250, 3160 (NH), 1720 sh, 1710, 1675, 1638 (C=O); UV λ_{max}^{EtOH} mμ (log ε): 224 (4·65), 249 sh (4·44), 251 (4·45), 259 sh (4·44), 324 sh (4·23), 341 (4·34); mass spectrum *m/e*: 462 (M^+). (Found: C, 60·27; H, 5·09; N, 5·20; S, 5·74. $C_{25}H_{22}O_7N_2 \cdot (CH_3)_2SO$ requires: C, 60·00; H, 5·22; N, 5·18; S, 5·93%).

Diethyl 3',4-*diformyl*-7-*methoxy*-3,6'-*biindole*-2,2'-*dicarboxylate* (**29**)

A soln of $POCl_3$ (231 mg) in 2·4 ml DMF was cooled to 0°. To this soln was added a soln of **27** (60 mg) in 0·6 ml DMF. The mixture was heated at 100° for 1 hr, cooled, and poured onto ice water. The aqueous mixture was made alkaline with 10% $NaHCO_3$ aq and extracted with EtOAc. The organic layer was dried over $MgSO_4$ and evaporated to dryness *in vacuo*. The residue was dissolved in chloroform and chromatographed on silicic acid. First elution with chloroform gave 7 mg of colourless needles, m.p. 262–266°, which seemed to be a monoformyl derivative because of the presence of the parent peak at *m/e* 434 in the mass spectrum; IR ν_{max}^{Nujol} cm^{-1}: 3325, 3160 (NH), 1728, 1700, 1638 (C=O).

Second elution with chloroform gave 23 mg of colourless needles, m.p. >280°, which were recrystallized from DMSO–H_2O; IR ν_{max}^{Nujol} cm^{-1}: 3320, 3130 (NH), 1705, 1660, 1655 (C=O); UV λ_{max}^{EtOH} mμ (log ε): 221 (4·66), 248 (4·57), 253 (4·58), 257 (4·58), 328 (4·43), 340 sh (4·42); mass spectrum *m/e*: 462 (M^+). (Found: C, 64·58; H, 4·68; N, 6·08. $C_{25}H_{22}O_7N_2$ requires: C, 64·93; H, 4·80; N, 6·06%).

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