[Chem. Pharm. Bull.
31(12)4391—4400(1983)]

Fischer Indolization and Its Related Compounds. XVIII.[1) Formation of Four Unexpected Angular Benz[*e*]indoles on Fischer Indolization of Ethyl Phenylpyruvate 2-[(1,4-Dimethoxy-2-naphthyl)hydrazone]

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(Received May 11, 1983)

The Fischer indolization of ethyl phenylpyruvate 2-[(1,4-dimethoxy-2-naphthyl)hydrazone] (**2**) with ethanolic hydrogen chloride gave four angular benz[*e*]indole products (ethyl 4-chloro-5-ethoxy- (**14a**), ethyl 4-chloro-5-methoxy- (**14b**), ethyl 5-ethoxy- (**14c**), and ethyl 5-methoxy- (**14d**) -1-phenyl-3*H*-benz[*e*]indole-2-carboxylates), instead of the anticipated linear benz[*f*]indole, ethyl 4,9-dimethoxy-3-phenyl-1*H*-benz[*f*]indole-2-carboxylate (**3**).

Oxidation of these benz[*e*]indole derivatives (**14b** and **14d**) with chromic acid in acetic acid provided an *o*-quinone derivative (**15**) which showed anti-viral activity in a preliminary biological test.

Keywords——Fischer indolization; ethanolic hydrogen chloride; 1,4-dimethoxy-2-naphthylhydrazone; benz[*e*]indole; oxidation with chromic acid; formation of *o*-quinone; anti-viral activity

In connection with studies[2) on the biological activities of 1,4-naphthoquinone derivatives, three[3) of us (N. I., H. M., and S. T.), reported the preparation of a 1,4-naphthoquinone derivative (**1**) by Fischer indolization of ethyl phenylpyruvate 2-[(1,4-dimethoxy-2-naphthyl)hydrazone] (**2**) with ethanolic hydrogen chloride followed by oxidation of the resulting reaction mixture with chromic acid without demethylation. In this reaction sequence, they claimed the formation of the 4,9-dimethoxybenz[*f*]indole (**3**) by the Fischer indolization of the starting 1,4-dimethoxy-2-naphthylhydrazone derivative (**2**). Moreover, Goldsmith *et al.*[4) reported the formation of 9-methoxy-1*H*-benz[*f*]indole (**4**), a linear type of benzindole product, by the Fischer indolization of ethyl pyruvate 2-[(1-methoxy-2-naphthyl)hydrazone] (**5**) in 1953.

On the other hand, we[1a,5) have studied the Fischer indolization of ethyl pyruvate 2-[(2-methoxyphenyl)hydrazone] (**6**) with ethanolic hydrogen chloride in detail, and found that the cyclization took place at the *ortho*-position, occupied already by a methoxy group, to give ethyl 6-chloroindole-2-carboxylate (**8**) as the main product. From the viewpoint of Fischer indolization, it seems that the reaction mode of naphthylhydrazone derivatives is different from that of phenylhydrazone derivatives. This consideration led us to investigate the Fischer indolization of 1-methoxy-2-naphthylhydrazone derivatives.

We began with a re-examination of the Fischer indolization of ethyl phenylpyruvate 2-[(1,4-dimethoxy-2-naphthyl)hydrazone] (**2**). The starting 2-amino-1,4-dimethoxynaphthalene (**9**) was prepared from 1,4-naphthoquinone (**10**) according to the reported method.[6) Japp–Klingemann reaction[7) of the aminonaphthalene (**9**) using ethyl α-benzylacetoacetate[8) (**13**)

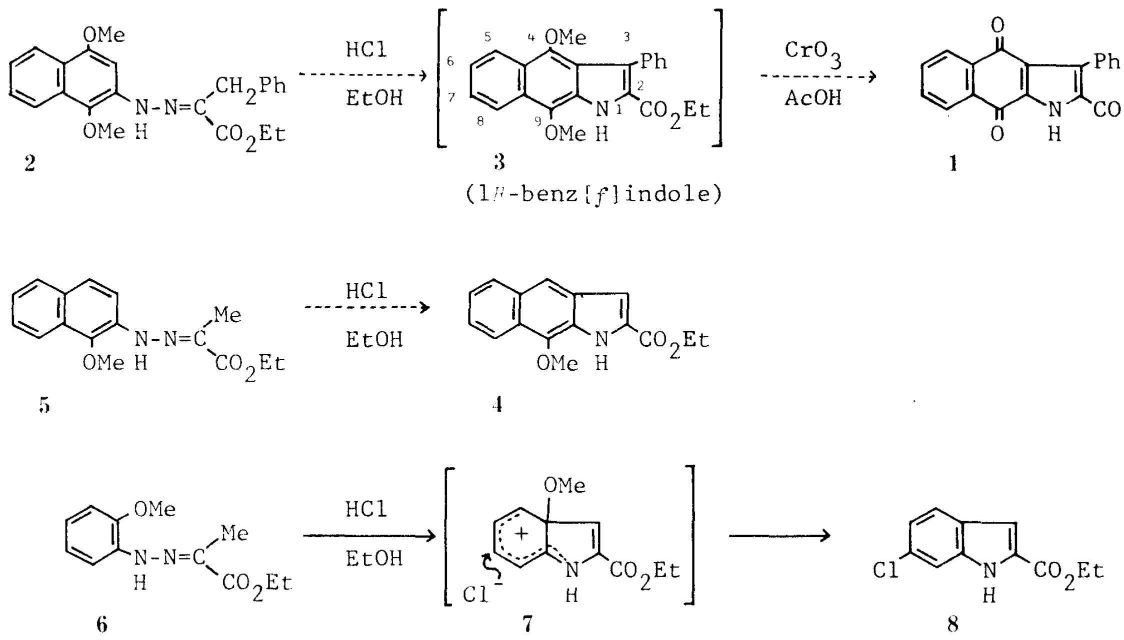


Chart 1

gave a mixture of geometrical isomers of the desired naphthylhydrazones [(*Z*)- and (*E*)-**2**] in which the assignment of geometrical structures was made by comparison[5b)] of their spectral data, especially the chemical shifts of their imino protons. Treatment of the geometrical mixture of the hydrazones (**2**) with ethanolic hydrogen chloride gave a mixture (**14**) of several products. According to a previous report,[3)] direct oxidation of the mixture (**14**) with chromic acid in acetic acid without any separation work gave orange leaflets (**15**) as a sole product, which shows the same melting point, mp 265—268 °C, as reported (lit.[3)] mp 267.5—269.5 °C), in 16.8% yield calculated from the starting naphthylhydrazone (**2**). The quinone structure of this material was supported by the spectral data and elemental analysis.

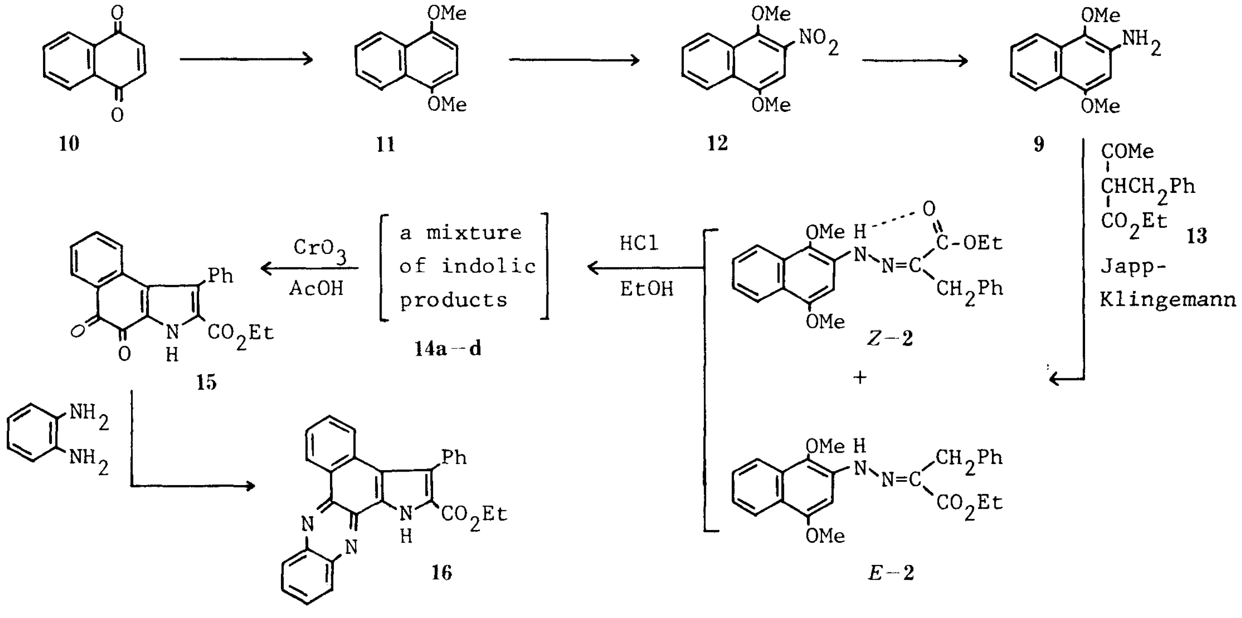


Chart 2

TABLE I. Data for Characterization of the Fischer Products (**14a**—**d**)

Compound		**14a**	**14b**	**14c**	**14d**
Molecular formula		$C_{23}H_{20}ClNO_3$	$C_{22}H_{18}ClNO_3$	$C_{23}H_{21}NO_3$	$C_{22}H_{19}NO_3$
mp		147.5—149 °C	182—183.5 °C	251—252 °C	234—236.5 °C
IR (cm^{-1})	NH	3295	3240	3295	3305
	C=O	1685	1675	1660	1655
^1H-NMR (δ) Common signal	$CH_2C\underline{H}_3$	1.07 (3H, t, $J=7.2$ Hz)	1.08 (3H, t, $J=7.3$ Hz)	1.00 (3H, t, $J=7.2$ Hz)	1.00 (3H, t, $J=7.0$ Hz)
	$OC\underline{H}_2CH_3$	4.16 or 4.23 (2H, q, $J=7.2$ Hz)	4.17 (2H, q, $J=7.3$ Hz)	4.06 or 4.24 (2H, q, $J=7.2$ Hz)	4.05 (2H, q, $J=7.0$ Hz)
	C_6-H (Hα)	8.12 (1H, dd, $J=7.5$ and 2.0 Hz)	8.13 (1H, dif d, $J=7.5$ Hz)	8.18 (1H, dif d, $J=7.5$ Hz)	8.14 (1H, dif d, $J=7.0$ Hz)
	NH	9.38 (1H, br s)	9.43 (1H, br s)	11.02 (1H, br s)	12.06 (1H, br s)
Characteristic signal	$CH_2C\underline{H}_3$	1.56 (3H, t, $J=7.2$ Hz)	—	1.52 (3H, t, $J=7.2$ Hz)	—
	$OC\underline{H}_2CH_3$	4.23 or 4.16 (2H, q, $J=7.2$ Hz)	—	4.24 or 4.06 (2H, q, $J=7.2$ Hz)	—
	OCH_3	—	4.05 (3H, s)	—	3.99 (3H, s)
	C_4-H	—	—	7.00 (1H, s)	7.00 (1H, s)
	Other arom. H	7.12—7.64 (8H, m)	7.20—7.68 (8H, m)	7.08—7.60 (8H, m)	7.07—7.60 (8H, m)

However, treatment of the resulting quinone (**15**) with *o*-phenylenediamine gave yellow needles in 94.2% yield. The elemental analysis of this material was consistent with the molecular formula, $C_{27}H_{19}N_3O_2$, expected for a quinoxaline derivative (**16**). In the infra red (IR) spectrum, this material shows no carbonyl group absorption band other than that of an ester carbonyl. This experiment indicated that the quinone should be an *o*-quinone (**15**), indicating that the Fischer indolization of the naphthylhydrazone (**2**) did not take place at the C_3-position, a vacant *ortho*-position, but at the C_1-position, the *ortho*-position occupied by a methoxy group.

Subsequently, we undertook to establish the structures of the products in Fischer indolization of the 1,4-dimethoxy-2-naphthylhydrazone (**2**). Column chromatography of the reaction mixture (**14**) on silica gel gave four pure indolic products, the chloro-ethoxy- (**14a**), the chloro-methoxy- (**14b**), the ethoxy- (**14c**), and the methoxy- (**14d**)-benzindoles in 16.0, 5.3, 14.5, and 1.1% yields, respectively. These products were characterized (Table I).

The diagnostic inspection of these data (Table I) suggested that the first compound (**14a**) and the third (**14c**) have an ethoxy group in their molecules and the former (**14a**) bears a chlorine atom on the aromatic skeleton instead of an aromatic proton of the latter (**14c**). Furthermore, the other two methoxy derivatives (**14b** and **14d**) have a similar structural relationship except for bearing a methoxy group instead of an ethoxy group. These assumptions were supported by the following experiments. Catalytic hydrogenation of the chloro-ethoxy- (**14a**) and the chloro-methoxy- (**14b**) benzindoles over palladium–carbon in the presence of calcium oxide gave the corresponding dehalogenated products, the ethoxy- (**14c**) and the methoxy- (**14d**)-benzindoles, respectively. Conversely, treatment of the methoxy-benzindole (**14d**) with *N*-chlorosuccinimide (NCS) provided the chloro-methoxy-benzindole (**14b**). The structural interrelationship between the ethoxy-benzindole (**14c**) and the methoxy-benzindole (**14d**) was clarified by conversion of the latter (**14d**) into the former (**14c**) on treatment with ethanolic hydrogen chloride, the condition for Fischer indolization in our studies, in 98.0% yield.

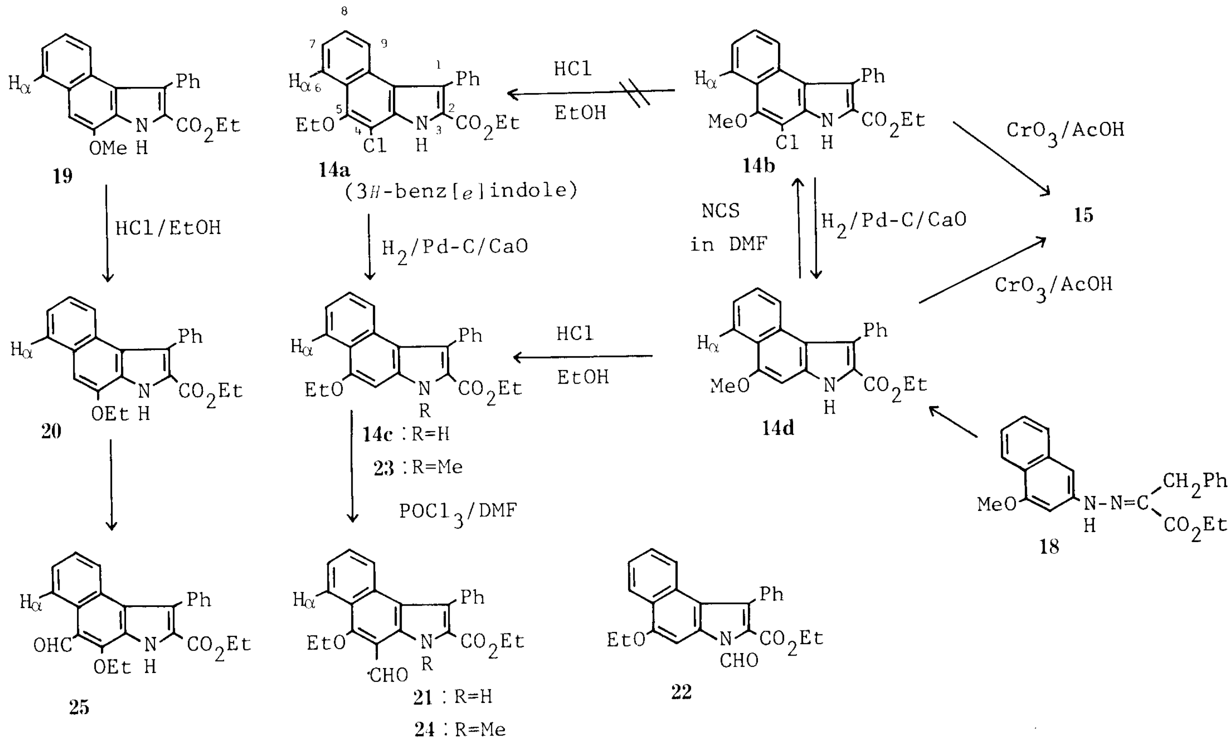
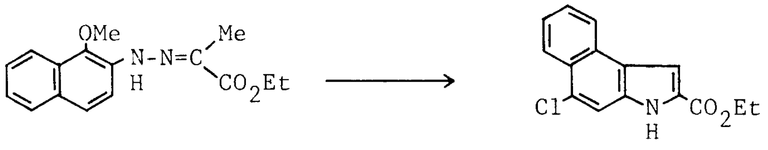


Chart 3

On the other hand, oxidation of the methoxy-benzindoles (**14b** and **14d**) with chromic acid in acetic acid gave the same *o*-quinone (**15**). This experimental result established rigidly the mother skeleton of the four benzindolic products (**14a**—**d**) as an angular benz[*e*]indole. Loss of a chlorine atom from the chloro-methoxy-benz[*e*]indole (**14b**) restricted the locations of its chlorine atom and its methoxy group to the C_4- and C_5-positions of a benz[*e*]indole nucleus. Moreover, the methoxy group situated at the C_1-position of the starting 1,4-dimethoxy-2-naphthylhydrazone (**2**) was involved in this abnormal Fischer indolization, indicating that cyclization took place at the *ortho*-position occupied by a methoxy group, the C_1-position. These considerations suggest that the methoxy-benz[*e*]indoles (**14b** and **14d**) are 5-methoxybenz[*e*]indole derivatives because it may be easily supposed that the methoxy group of these methoxy-benz[*e*]indoles (**14b** and **14d**) originated from one of the two methoxy groups of the starting 1,4-dimethoxy-2-naphthylhydrazone (**2**), indicating that the C_4-methoxy group should remain unchanged. We, however, were initially reluctant to accept this conclusion since we[4)] knew that Fischer indolization of ethyl pyruvate 2-[(1-methoxy-2-naphthyl)-hydrazone] (**5**) with ethanolic hydrogen chloride gave ethyl 5-chloro-3*H*-benz[*e*]indole-2-carboxylate (**17**) bearing a chlorine atom at a different position from that of the chloro-methoxy-benz[*e*]indole product (**14b**) and, in addition, a methoxy group situated at an *ortho*-position of some phenylhydrazones rearranged to the C_5-position of the indolic product[1a,5b)] during Fischer indolization. Therefore, the methoxy-benz[*e*]indole product was identified by direct comparison with a sample of ethyl 5-methoxy-3*H*-benz[*e*]indole-2-carboxylate[9)] (**14d**) which was prepared by Fischer indolization of ethyl phenylpyruvate 2-[(4-methoxy-2-naphthyl)hydrazone] (**18**).

Although the experimental data described so far indicate that these four compounds



5 17

Chart 4

(**14a**—**d**) are all benz[*e*]indole derivatives, there was no unequivocal proof of the location of the introduced ethoxy group of the ethoxy derivatives (**14a** and **14c**), because an attempt to convert the chloro-methoxy-benz[*e*]indole (**14b**) into the corresponding chloro-ethoxy-benz[*e*]indole (**14a**) by treatment with ethanolic hydrogen chloride failed. Consideration of the mechanism of formation of an ethoxy-benz[*e*]indole from a methoxy-benz[*e*]indole did not allow us to exclude absolutely the possibility that mutual positional interconversion of these groups might take place during the reaction, for example, from the 5-methoxybenz[*e*]indole (**14d**) to the 4-ethoxybenz[*e*]indole (**20**) and so on. In order to obtain conclusive proof of the positions of the ethoxy group in these ethoxy-benz[*e*]indoles (**14a** and **14c**), ethyl 4-methoxy-1-phenyl-3*H*-benz[*e*]indole-2-carboxylate (**19**), mp 211.5—214 °C, was prepared *via* an unequivocal pathway.9) The methoxy group of the 4-methoxybenz[*e*]indole9) (**19**) could also be converted into an ethoxy group by treatment with ethanolic hydrogen chloride to give the 4-ethoxybenz[*e*]indole (**20**), mp 167—168.5 °C, which was different from the 5-ethoxy-benz[*e*]indole (**14c**), mp 251—252 °C, derived from the 5-methoxybenz[*e*]indole (**14d**), mp 234—236.5 °C, described above.

In the proton nuclear magnetic resonance (^{1}H-NMR) spectrum, these two new benz[*e*]indole products (**19** and **20**) show no aromatic signal at lower field than δ 7.80, but all of the benz[*e*]indole products (**14a**—**d**) which were derived from the 1,4-dimethoxy-2-naphthylhydrazone (**2**) commonly show one 1H signal due to an aromatic proton at around δ 8.15. Such a downfield shift of a 1H aromatic signal in the ^{1}H-NMR spectrum of these benz[*e*]indole products could be explained by supposing that they had an alkoxy group at the C_5-position of the benz[*e*]indole nucleus and the signals of their C_6-protons were subject to an anisotropic effect of the C_5-alkoxy group. In order to provide unequivocal evidence, we carried out Vilsmeier reaction5a,9) of the 5-ethoxy-benz[*e*]indole (**14c**), because it is well known that introduction of a formyl group at the nitrogen atom of C_3-substituted indole derivatives induces a fairly big downfield shift of the C_7-proton signal of indole derivatives due to an anisotropic effect of the inserted carbonyl group. However, treatment of the ethoxy-benz[*e*]indole (**14c**) with phosphorus oxychloride in dimethylformamide (DMF) gave the C-formylated product (**21**) in place of the desired N-formyl compound (**22**). In the ^{1}H-NMR spectrum, the formylated product (**21**) still showed an NH signal at δ 10.95. The location of the formyl group of the C-formyl derivative (**21**) was restricted to the C_4- or C_5-position of the benz[*e*]indole nucleus, because the 1H aromatic singlet which could be observed in the starting material (**14c**) had disappeared. The abnormality of the Vilsmeier reaction of the ethoxy-benz[*e*]indole (**14c**) was confirmed by the finding that a similar reaction took place with the *N*-methyl-ethoxy-benz[*e*]indole (**23**) to give a C-formyl derivative (**24**). In the ^{1}H-NMR spectrum, these two C-formyl indolic products (**21** and **24**) still show an aromatic signal at δ 8.23 and δ 8.12, respectively. On the other hand, Vilsmeier reaction of the 4-ethoxybenz[*e*]indole (**20**) also gave a C-formyl derivative (**25**). In the ^{1}H-NMR spectrum, this material (**25**) shows one 1H aromatic signal at δ 9.25 in the lower field region. Such a big downfield shift can be ascribed to the anisotropic effect of the formyl group introduced at a *peri*-position, indicating introduction of the formyl group at the C_5-position of the benz[*e*]indole skeleton. Therefore, we may evidently conclude that Fischer indolization of the 1,4-

dimethoxy-2-naphthylhydrazone (**2**) produced a mixture of the 5-methoxy- and 5-ethoxybenz[*e*]indole derivatives (**14**).

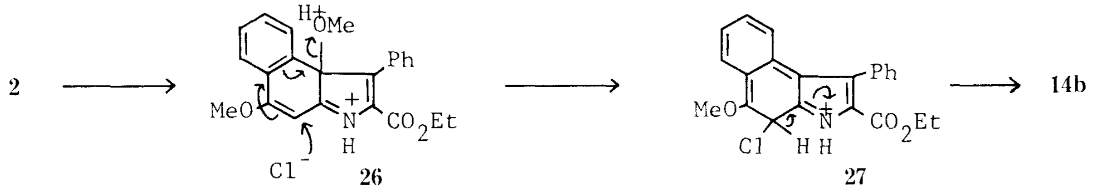


Chart 5

The mechanism of formation of these 5-alkoxybenz[*e*]indoles (**14**) may be explained as follows. i) In the case of the 5-methoxybenz[*e*]indole (**14d**), we may say that formation of such a product, which was derived by the reductive cleavage of an *ortho*-substituted group through an undefined pathway, is fairly common in the Fischer indolization of *ortho*-substituted phenylhydrazone derivatives.[1a)] ii) The 5-ethoxybenz[*e*]indole (**14c**) was formed from the 5-methoxybenz[*e*]indole (**14d**) during Fischer indolization as a by-product. iii) The 4-chloro-5-methoxybenz[*e*]indole (**14b**) is a real product formed by the abnormal Fischer indolization[1b)] which was a major subject of our research. The mechanism of formation of such an abnormal product (**14b**) may be as illustrated in Chart 5. In this mechanism, the cyclization took place at the C_1-position of the starting 1,4-dimethoxy-2-naphthylhydrazone (**2**) to give a key intermediate cation (**26**) as in the case[5)] of ethyl pyruvate 2-[(2-methoxyphenyl)hydrazone] (**6**). The *tertiary* methoxy group of the key intermediate cation (**26**) was subject to substitution with a chloride anion at the C_4-position in the mode of an S_N1' type reaction to give the 4-chloro-5-methoxybenz[*e*]indole (**14b**). As described in the previous papers,[1a,5b,5c)] we had classified the abnormal Fischer indolization of an *ortho*-methoxyphenylhydrazone into two categories, a) addition of a nucleophile at the C_6-position of an indole nucleus (*ortho*-C_6 abnormal Fischer indolization) and b) S_N1' type substitution of the *tertiary* methoxy group of the key intermediate cation (*ortho*-C_5 abnormal Fischer indolization). We can consider the result of the present work as a vinylogy of *ortho*-C_5 abnormal Fischer indolization. iv) Although the 4-chloro-5-ethoxybenz[*e*]indole (**14a**) was also suspected to be a by-product formed from the 4-chloro-5-methoxybenz[*e*]indole (**14b**), this possibility was ruled out by the fact that treatment of the 4-chloro-5-methoxybenz[*e*]indole (**14b**) with ethanolic hydrogen chloride resulted in recovery of the starting benz[*e*]indole (**14b**) as described above. Therefore, for the formation of the 4-chloro-5-ethoxybenz[*e*]indole (**14a**), we postulated that addition of an ethanol molecule to the key intermediate (**26**) took place in preference to the substitution of the *tertiary* methoxy group with chloride anion at the C_4-position as shown in Chart 6.

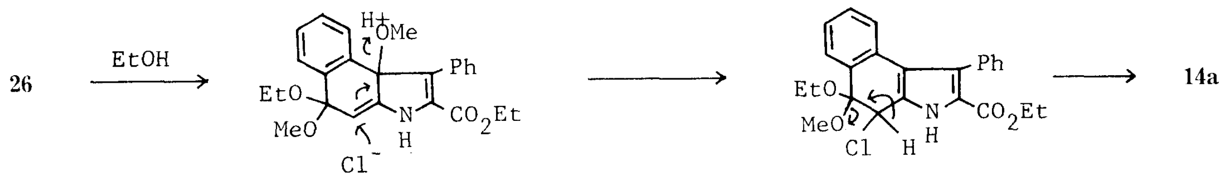


Chart 6

In conclusion, it should be emphasized here that we could find no evidence for formation of a benz[*f*]indole derivative, which would be derived by cyclization at the vacant *ortho*-position of the starting ethyl phenylpyruvate 2-[(1,4-dimethoxy-2-naphthyl)hydrazone] (**2**), the C_3-position, in the reaction mixture. In other words, 9-methoxybenz[*f*]indole derivatives [*e.g.* (**3**)], a linear type of benzindole, could not be prepared by Fischer indolization of 1-methoxy-2-naphthylhydrazone derivatives.

Finally, we would like to add here that the *o*-quinone (**15**) showed anti-viral activity in a preliminary biological test.

Experimental

All melting points were measured on a micro melting point hot stage apparatus (Yanagimoto) and are uncorrected. IR and ultraviolet (UV) spectra were recorded on a Hitachi EPI-G3 spectrometer (in Nujol) and on a Hitachi 340 spectrophotometer (as solutions in 95% ethanol), respectively. ^{1}H-NMR spectra were recorded on a JEOL JNM-4H-100 spectrometer in deuteriochloroform, with tetramethylsilane as an internal reference. Mass spectra (MS) were measured on a Hitachi RMU-6E spectrometer at 70 eV chamber voltage with a direct inlet system. For chromatography (column), silicic acid (100 mesh), Mallinckrodt Chemical Works, Silica gel 60 (70—230 mesh ASTM), Merck, and aluminium oxide (neutral, grade I), Woelm, were used, and for preparative thin layer chromatography (TLC), Silica gel GF_{254}, Merck. All identification of products was done by IR and TLC comparisons, and by mixed melting point determination. The abbreviations used are as follows: s, singlet; d, doublet; dd, double doublet; t, triplet; m, multiplet; br, broad; dif, diffused; sh, shoulder. The assignment of NH or OH signals was confirmed by disappearance of the signals after addition of deuterium oxide.

2-Amino-1,4-dimethoxynaphthalene (9)——Prepared starting from 1,4-naphthoquinone (**10**) according to the reported method,[6)] pale brown needles, mp 104—105 °C (lit.,[6)] mp 100—101 °C). IR $\nu_{\max}$ cm^{-1}: 3500, 3400 (NH).

(*Z*)-Ethyl Phenylpyruvate 2-[(1,4-Dimethoxy-2-naphthyl)hydrazone] [(*Z*)-2]——A solution of 2-amino-1,4-dimethoxynaphthalene (**9**) (13.0 g) in H_2O (120 ml) containing conc. HCl (13.5 g) and EtOH (40 ml) was diazotized by treatment with a solution of $NaNO_2$ (4.64 g) in H_2O (20 ml) under ice-cooling. The diazonium solution was added dropwise to an ice-cooled solution of ethyl α-benzylacetoacetate[8)] (14.1 g) in EtOH (240 ml) containing 50% KOH aq. (7.17 g). The mixture was stirred at room temperature for 1 h and poured into H_2O. The precipitates were collected by filtration and dissolved in EtOH (60 ml) containing 85% H_3PO_4 (10 ml). Then the solution was refluxed for 30 min. The reaction mixture was poured into a large amount of H_2O and extracted with Et_2O. The ethereal solution was washed with 5% $NaHCO_3$, dried over $MgSO_4$, and evaporated to dryness *in vacuo*. Recrystallization of the residue (21.5 g) from EtOH gave yellow needles (8.78 g), mp 132.5—133 °C. *Anal.* Calcd for $C_{23}H_{24}N_2O_4$: C, 70.39; H, 6.16; N, 7.14. Found: C, 70.27; H, 6.17; N, 7.12. IR $\nu_{\max}$ cm^{-1}: 3237 (NH), 1673 (CO). ^{1}H-NMR δ: 1.27 (3H, t, J=7.2 Hz, $CH_2C\underline{H}_3$), 3.89 and 3.94 (each 3H, s, OCH_3), 3.91 (2H, s, $C\underline{H}_2Ph$), 4.23 (2H, q, J=7.2Hz, $OC\underline{H}_2CH_3$), 7.12 (1H, s, C_3-H), 7.10—7.56 (7H, m, arom. H), 7.90 and 8.13 (each 1H, dd, J=8.1 and 1.5 Hz, C_5- and C_8-H), 12.48 (1H, s, NH).

As described in the following item, an additional amount (0.74 g) (total yield, 9.52 g) of this material [(*Z*)-**2**] was obtained from the first eluate of the column chromatography of the crude material obtained from the mother liquor of recrystallization of this (*Z*)-isomer.

(*E*)-Ethyl Phenylpyruvate 2-[(1,4-Dimethoxy-2-naphthyl)hydrazone] [(*E*)-2)]——The material obtained from the mother liquor of recrystallization of the above (*Z*)-isomer [(*Z*)-**2**]) was chromatographed on silica gel with benzene to give two eluates. The first eluate gave the (*Z*)-hydrazone [(*Z*)-**2**]) (0.74 g).

The second eluate gave pale yellow needles (2.50 g), mp 103—104.5 °C, which were recrystallized from EtOH. *Anal.* Calcd for $C_{23}H_{24}N_2O_4$: C, 70.39; H, 6.16; N, 7.14. Found: C, 70.29; H, 6.18; N, 7.15. IR $\nu_{\max}$ cm^{-1}: 3333 (NH), 1720 (CO). ^{1}H-NMR δ: 1.41 (3H, t, J=7.2 Hz, $CH_2C\underline{H}_3$), 3.31 and 4.01 (each 3H, s, OCH_3), 4.09 (2H, s, $C\underline{H}_2Ph$), 4.38 (2H, q, J=7.2 Hz, $OC\underline{H}_2CH_3$), 7.20 (1H, s, C_3-H), 7.56—7.18 (7H, m, arom. H), 7.76 and 8.12 (each 1H, dd, J=8.1 and 1.5 Hz, C_5- and C_8-H), 8.52 (1H, s, NH).

Ethyl 4,5-Dihydro-4,5-dioxo-1-phenyl-3*H*-benz[*e*]indole-2-carboxylate (the *o*-Quinone) (15)——i) Indolic Mixture Obtained from Fischer Indolization of (*Z*)- and (*E*)-Ethyl Phenylpyruvate 2-[(1,4-Dimethoxy-2-naphthyl)hydrazone] (**2**): A mixture of (*Z*)- and (*E*)-ethyl phenylpyruvate 2-[(1,4-dimethoxy-2-naphthyl)hydrazone] (**2**) (10.0 g) was dissolved in saturated ethanolic hydrogen chloride (60 ml). The solution was refluxed for 5 h, poured into a large amount of H_2O, and extracted with $CHCl_3$. The chloroform solution was washed with saturated $NaHCO_3$ aq., dried over $MgSO_4$, and evaporated to dryness *in vacuo*.

ii) Ethyl 4,5-Dihydro-4,5-dioxo-1-phenyl-3*H*-benz[*e*]indole-2-carboxylate (the *o*-Quinone) (**15**): A solution of CrO_3 (6.5 g) in 80% AcOH (32.5 ml) was added dropwise to a solution of the residue (10.1 g) in AcOH (12.5 ml) at room temperature during 2.5 h. The reaction mixture was poured into a large amount of H_2O and extracted with AcOEt. The organic layer was washed with saturated $NaHCO_3$ aq., dried over $MgSO_4$, and evaporated to dryness *in vacuo*. The residue was chromatographed on silica gel with $CHCl_3$ to give orange leaflets (1.48 g), mp 265—268 °C, which were recrystallized from $CHCl_3$–hexane. *Anal.* Calcd for $C_{21}H_{15}NO_4$: C, 73.03; H, 4.38; N, 4.06. Found: C, 72.84; H, 4.43; N, 4.05. IR $\nu_{\max}$ cm^{-1}: 3200 (NH), 1695, 1675 (CO). ^{1}H-NMR δ: 1.08 (3H, t, J=7.0 Hz, $CH_2C\underline{H}_3$), 4.21 (2H, q, J=7.0 Hz, $OC\underline{H}_2CH_3$), 6.92 (1H, m, arom. H), 7.14—7.58 (7H, m, arom. H), 8.05 (1H, dd, J=6.0 and 3.5 Hz, C_6-H), 10.20 (1H, br s, NH). MS m/z: 345 (M^+, 49.6%), 271 (base peak).

Ethyl 1-Phenyl-quinoxalino[2,3-*q*]-3*H*-benz[*e*]indole-2-carboxylate (16)——A mixture of the *o*-quinone (**15**) (0.050 g) and *o*-phenylenediamine (freshly sublimed, *ca.* 120 °C at 6 mmHg) (0.017 g) in AcOH (0.5 ml) was refluxed for 45 min. The reaction mixture was diluted with a large amount of H_2O and extracted with AcOEt. The organic layer was washed with saturated $NaHCO_3$ aq., dried over $MgSO_4$, and evaporated to dryness *in vacuo*. Recrystallization of the residue from EtOH gave yellow needles (0.059 g), mp 92—95 °C. *Anal.* Calcd for $C_{27}H_{19}N_3O_2$: C, 77.68; H, 4.59; N, 10.07. Found: C, 77.27; H, 4.60; N, 9.82. IR ν_{max} cm^{-1}: 3466 (NH), 1718 (CO). ^{1}H-NMR δ: 1.12 (3H, t, $J=7.5$ Hz, $CH_2C\underline{H}_3$), 4.22 (2H, q, $J=7.5$ Hz, $OC\underline{H}_2CH_3$), 7.20—8.34 (12H, m, arom. H), 9.22 (1H, dif d, $J=7.5$ Hz, arom. H), 10.48 (1H, br s, NH). MS *m/z*: 417 (M^+, 25%), 149 (base peak).

Fischer Indolization of the 1,4-Dimethoxy-2-naphthylhydrazone [(*Z*)-2]——The (*Z*)-naphthylhydrazone [(*Z*)-**2**] (5.30 g) was treated with ethanolic hydrogen chloride in the same manner as described above. The crude reaction mixture (5.03 g) was fractionated into two fractions by column chromatography on silica gel with benzene. Each fraction was rechromatographed on silica gel with Et_2O–hexane to give two compounds, providing four compounds in all.

i) Ethyl 4-Chloro-5-ethoxy-1-phenyl-3*H*-benz[*e*]indole-2-carboxylate (**14a**): The first nonpolar product was obtained as colorless prisms (0.853 g), mp 147.5—149 °C, which were recrystallized from AcOEt–EtOH. *Anal.* Calcd for $C_{23}H_{20}ClNO_3$: C, 70.13; H, 5.12; N, 3.56. Found: C, 70.12; H, 4.99; N, 3.70. MS *m/z*: 395 ($M^+ + 2$, 39%), 393 (M^+, base peak).

ii) Ethyl 4-Chloro-5-methoxy-1-phenyl-3*H*-benz[*e*]indole-2-carboxylate (**14b**): The second nonpolar product was obtained as colorless prisms (0.273 g), mp 182—183.5 °C, which were recrystallized from AcOEt–EtOH. *Anal.* Calcd for $C_{22}H_{18}ClNO_3$: C, 69.56; H, 4.78; N, 3.69. Found: C, 69.72; H, 4.73; N, 3.65. MS *m/z*: 381 ($M^+ + 2$, 36%), 379 (M^+, base peak).

iii) Ethyl 5-Ethoxy-1-phenyl-3*H*-benz[*e*]indole-2-carboxylate (**14c**): The third nonpolar product was obtained as colorless prisms (0.702 g), mp 251—252 °C, which were recrystallized from $CHCl_3$–EtOH. *Anal.* Calcd for $C_{23}H_{21}NO_3$: C, 76.86; H, 5.89; N, 3.90. Found: C, 76.78; H, 5.82; N, 4.01. MS *m/z*: 359 (M^+, base peak).

iv) Ethyl 5-Methoxy-1-phenyl-3*H*-benz[*e*]indole-2-carboxylate (**14d**): The most polar product was obtained as colorless needles (0.050 g), mp 234—236.5 °C, which were recrystallized from $CHCl_3$–EtOH. *Anal.* Calcd for $C_{22}H_{19}NO_3$: C, 76.50; H, 5.55; N, 4.06. Found: C, 76.26; H, 5.53; N, 3.97. MS *m/z*: 345 (M^+, base peak).

Dechlorination of Ethyl 4-Chloro-5-ethoxy-1-phenyl-3*H*-benz[*e*]indole-2-carboxylate (14a) [Ethyl 5-Ethoxy-1-phenyl-3*H*-benz[*e*]indole-2-carboxylate (14c)]——A solution of the 4-chloro-5-ethoxybenz[*e*]indole (**14a**) (0.100 g) in EtOH (100 ml) was hydrogenated over 10% Pd-C (80 mg) and CaO (200 mg) at 60—70 °C under atmospheric pressure. After the catalyst had been removed by filtration, the filtrate was evaporated to dryness *in vacuo*. Preparative TLC of the residue on silica gel with $CHCl_3$ gave colorless prisms (30 mg), mp 253 °C, which were recrystallized from $CHCl_3$–EtOH. *Anal.* Calcd for $C_{23}H_{21}NO_3$: C, 76.86; H, 5.89; N, 3.90. Found: C, 76.66; H, 5,89; N, 3.88. IR ν_{max} cm^{-1}: 3300 (NH), 1660 (CO). This compound was identical with the third Fischer product (**14c**).

Dechlorination of Ethyl 4-chloro-5-methoxy-1-phenyl-3*H*-benz[*e*]indole-2-carboxylate (14b) [Ethyl 5-Methoxy-1-phenyl-3*H*-benz[*e*]indole-2-carboxylate (14d)]——A solution of the 4-chloro-5-methoxybenz[*e*]indole (**14b**) (0.049 g) in EtOH (20 ml) was hydrogenated over 10% Pd-C (0.052 g) and CaO (0.097 g) at 60—70 °C under atmospheric pressure. Work-up as described in the case of the 4-chloro-5-ethoxybenz[*e*]indole (**14a**) gave a crude mixture which was chromatographed on silica gel with Et_2O–hexane (2 : 1, v/v). The first eluate (0.014 g) was found to be the starting material (**14b**).

The second eluate gave colorless needles (0.020 g), mp 234—237 °C, which were recrystallized from $CHCl_3$–EtOH. IR ν_{max} cm^{-1}: 3310 (NH), 1660 (CO). This compound was identical with the fourth Fischer product (**14d**).

Chlorination of Ethyl 5-Methoxy-1-phenyl-3*H*-benz[*e*]indole-2-carboxylate (14d) [Ethyl 4-Chloro-5-methoxy-1-phenyl-3*H*-benz[*e*]indole-2-carboxylate (14b)]——A solution of *N*-chlorosuccinimide (0.147 g) in dimethylformamide (DMF) (5.0 ml) was added dropwise to a solution of the 5-methoxybenz[*e*]indole (**14d**) (0.345 g) in dry DMF (8 ml) at room temperature over 5 min and the whole was stirred at room temperature for 23 h. The reaction mixture was poured into a large amount of H_2O and extracted with $CHCl_3$. The chloroform solution was washed with 5% citric acid aqueous solution followed by H_2O, then dried over $MgSO_4$, and evaporated to dryness *in vacuo*. The residue was chromatographed on silica gel with Et_2O–hexane (1 : 4, v/v) to give colorless needles (0.310 g), mp 181—183.5 °C, which were recrystallized from AcOEt–EtOH. *Anal.* Calcd for $C_{22}H_{18}ClNO_3$; C, 69.57; H, 4.78; N, 3.69. Found: C, 69.63; H, 4.74; N, 3.59. IR ν_{max} cm^{-1}: 3250 (NH), 1677 (CO). This compound was identical with the second Fischer product (**14b**).

The Conversion of Ethyl 5-Methoxy-1-phenyl-3*H*-benz[*e*]indole-2-carboxylate (14d) into Ethyl 5-Ethoxy-1-phenyl-3*H*-benz[*e*]indole-2-carboxylate (14c)——A solution of the methoxy-benz[*e*]indole (**14d**) (0.100 g) in saturated ethanolic hydrogen chloride (35 ml) was stirred at room temperature for 30 h until the starting material (**14d**) could not be detected on TLC. The reaction mixture was evaporated to dryness *in vacuo*. A large amount of H_2O was added to the residue and the suspension was extracted with Et_2O. The ethereal solution was washed with H_2O, dried over $MgSO_4$, and evaporated to dryness *in vacuo*. The residue was chromatographed on silica gel with Et_2O–hexane (1 : 1, v/v) to give colorless prisms (0.102 g), mp 247.5—249 °C, which were recrystallized from $CHCl_3$–EtOH. This compound was identical with the second Fischer product (**14c**).

Oxidation of Ethyl 5-Methoxy-1-phenyl-3*H*-benz[*e*]indole-2-carboxylate (14d) and Ethyl 4-Chloro-5-methoxy-1-phenyl-3*H*-benz[*e*]indole-2-carboxylate (14b) [the *o*-Quinone (15)]——i) From Ethyl 5-Methoxy-1-phenyl-3*H*-benz[*e*]indole-2-carboxylate (**14d**): A solution of CrO_3 (0.073 g) in 80% AcOH (0.5 ml) was added dropwise to a solution of the 5-methoxybenz[*e*]indole (**14d**) (0.100 g) in AcOH (1.0 ml) at room temperature. The mixture was stirred at the same temperature for 30 min and then heated at 100 °C for 30 min. The same work-up as described above gave a crude product. Recrystallization of this from $CHCl_3$–hexane gave orange prisms (0.016 g), mp 261—262 °C. This compound was identical with the *o*-quinone (**15**) obtained by direct oxidation of the mixture of indole products (**14**).

ii) From Ethyl 4-Chloro-5-methoxy-1-phenyl-3*H*-benz[*e*]indole-2-carboxylate (**14b**): A solution of CrO_3 (0.073 g) in 80% AcOH (0.5 ml) was added dropwise to a solution of the 4-chloro-5-methoxybenz[*e*]indole (**14b**) (0.110 g) in AcOH (3.5 ml) at room temperature. The mixture was stirred at room temperature for 3 h. The reaction mixture was worked up as described in the case of the direct oxidation of the mixture of benz[*e*]indole products. The crude product was recrystallized from $CHCl_3$–hexane to give orange prisms (0.035 g), mp 262.5—265 °C. This compound was identical with the *o*-quinone (**15**) obtained by direct oxidation of the mixture of benz[*e*]indole products.

The Conversion of Ethyl 4-Methoxy-1-phenyl-3*H*-benz[*e*]indole-2-carboxylate (19) into Ethyl 4-Ethoxy-1-phenyl-3*H*-benz[*e*]indole-2-carboxylate (20)——A solution of the 4-methoxybenz[*e*]indole[9] (**19**) (0.100 g), mp 211.5—214 °C, in saturated ethanolic hydrogen chloride (35 ml) was stirred at room temperature for 23 h until the starting material (**19**) could not be detected on TLC. After being concentrated under reduced pressure, the reaction mixture was poured into H_2O and extracted with Et_2O. The ethereal solution was washed with H_2O, dried over $MgSO_4$, and evaporated to dryness *in vacuo*. The residue was chromatographed on silica gel with Et_2O–hexane (1 : 2, v/v) to give colorless prisms (0.087 g), mp 167—168.5 °C, which were recrystallized from $CHCl_3$–EtOH. *Anal.* Calcd for $C_{23}H_{21}NO_3$: C, 76.86; H, 5.89; N, 3.90. Found: C, 77.00; H, 5.90; N, 3.84. IR $\nu_{\max}$ cm^{-1}: 3475 (NH), 1710 (CO). ^{1}H-NMR δ: 1.07 (3H, t, $J=7.0$ Hz, $CH_2C\underline{H}_3$), 1.56 (3H, t, $J=7.0$ Hz, $CH_2C\underline{H}_3$), 4.15 (2H, q, $J=7.0$ Hz, $OC\underline{H}_2CH_3$), 4.30 (2H, q, $J=7.0$ Hz, $OC\underline{H}_2CH_3$), 6.89 (1H, s, C_5–H), 7.41 (5H, s, arom. H), 6.98—7.77 (4H, m, arom. H), 9.40 (1H, br s, NH). MS *m/z*: 359 (M^+, base peak).

Ethyl 5-Ethoxy-4-formyl-1-phenyl-3*H*-benz[*e*]indole-2-carboxylate (21)——The 5-ethoxybenz[*e*]indole (**14c**) (0.100 g) was added to a solution of $POCl_3$ (0.426 g) in anhydrous DMF (1.5 ml). The mixture was heated at 100—110 °C with stirring for 6 h. After the reaction had been quenched by addition of H_2O, the reaction mixture was extracted with Et_2O. The ethereal solution was washed with H_2O, dried over $MgSO_4$, and evaporated to dryness *in vacuo*. The residue was purified by preparative TLC on silica gel with $CHCl_3$ to give pale yellow needles (0.035 g), mp 154.5—156 °C, which were recrystallized from EtOH. *Anal.* Calcd for $C_{24}H_{21}NO_4$: C, 74.40; H, 5.46; N, 3.62. Found: C, 74.15; H, 5.46; N, 3.52. IR $\nu_{\max}$ cm^{-1}: 3413 (NH), 1692, 1664 (CO). ^{1}H-NMR (DMSO-d_6) δ: 1.04 and 1.53 (each 3H, t, $J=7.2$ Hz, $CH_2C\underline{H}_3$), 4.11 and 4.34 (each 2H, q, $J=7.2$ Hz, $OC\underline{H}_2CH_3$), 7.30—7.60 (8H, m, arom. H), 8.23 (1H, dif d, $J=7.5$ Hz, C_6–H), 10.57 (1H, s, CHO), 10.95 (1H, s, NH). MS *m/z*: 387 (m^+, base peak).

Ethyl 5-Ethoxy-3-methyl-1-phenyl-3*H*-benz[*e*]indole-2-carboxylate (23)——A suspension of the 5-ethoxybenz[*e*]indole (**14c**) (0.170 g) in acetone (5 ml) containing 10% KOH aq. (0.8 ml) and Me_2SO_4 (0.07 ml) was stirred at room temperature for 1 h. The reaction mixture was poured into a large amount of H_2O, extracted with Et_2O, dried over $MgSO_4$, and evaporated to dryness *in vacuo*. The residue was chromatographed on silica gel with benzene to give colorless needles (0.150 g), mp 126—127.5 °C, which were recrystallized from benzene–hexane. *Anal.* Calcd for $C_{24}H_{23}NO_3$: C, 77.19; H, 6.21; N, 3.75. Found: C, 77.29; H, 6.20; N, 3.69. IR $\nu_{\max}$ cm^{-1}: 1690 (CO), no NH. ^{1}H-NMR δ: 0.94 and 1.58 (each 3H, t, $J=7.2$ Hz, $CH_2C\underline{H}_3$), 4.00 and 4.26 (each 2H, q, $J=7.2$ Hz, $OC\underline{H}_2CH_3$), 4.12 (3H, s, NCH_3), 6.74 (1H, s, C_4–H), 7.14—7.52 (8H, m, arom. H), 8.27 (1H, dif d, $J=7.5$ Hz, C_6–H). MS *m/z*: 373 (M^+, base peak).

Ethyl 5-Ethoxy-4-formyl-3-methyl-1-phenyl-3*H*-benz[*e*]indole-2-carboxylate (24)——A solution of the 5-ethoxy-*N*-methylbenz[*e*]indole (**23**) (0.070 g) in DMF (1 ml) containing $POCl_3$ (0.290 g) was heated at 100 °C with stirring for 8 h. The reaction mixture was poured into a large amount of H_2O, and the solution was basified with Na_2CO_3, then extracted with Et_2O. The ethereal solution was washed with H_2O, dried over $MgSO_4$, and evaporated to dryness *in vacuo*. The residue (0.060 g) was purified by preparative TLC on silica gel with hexane–Et_2O (4 : 1, v/v) to give pale yellow prisms (0.015 g), mp 116—118 °C, which were recrystallized from hexane. *Anal.* Calcd for $C_{25}H_{23}NO_4$: C, 74.79; H, 5.78; N, 3.49. Found: C, 74.86; H, 5.83; N, 3.39. IR $\nu_{\max}$ cm^{-1}: no NH, 1706, 1678 (CO). ^{1}H-NMR δ: 0.95 and 1.55 (each, 3H, t, $J=7.2$ Hz, $CH_2C\underline{H}_3$), 4.00 (3H, s, NCH_3), 4.01 and 4.24 (each 2H, q, $J=7.2$ Hz, $OC\underline{H}_2CH_3$), 7.16—7.50 (8H, m, arom. H), 8.12 (1H, dif d, $J=7.5$ Hz, C_6–H), 10.73 (1H, s, CHO). MS *m/z*: 401 (M^+, 12.8%), 149 (base peak).

Ethyl 4-Ethoxy-5-formyl-1-phenyl-3*H*-benz[*e*]indole-2-carboxylate (25)——The 4-ethoxybenz[*e*]indole[9] (**20**) (0.100 g) was added to a solution of $POCl_3$ (0.26 ml) in anhydrous DMF (1.5 ml) and the resulting solution was heated at 100—110 °C with stirring for 20 min. After the reaction had been quenched by addition of H_2O, the reaction mixture was basified with $NaHCO_3$, and extracted with Et_2O. The ethereal solution was washed with saturated NaCl aq., dried over $MgSO_4$, and evaporated to dryness *in vacuo*. The residue was chromatographed on silica gel with hexane–AcOEt (10 : 1, v/v) to give colorless needles (0.069 g), mp 188—190 °C, which were recrystallized from

EtOH. *Anal.* Calcd for $C_{24}H_{21}NO_4$: C, 74.40; H, 5.46; N, 3.62. Found: C, 74.37; H, 5.41; N, 3.70. IR ν_{max} cm^{-1}: 3180 (NH), 1705, 1640 (CO). ^1H-NMR (DMSO-d_6) δ: 0.95 and 1.51 (each 3H, t, $J=8.0$ Hz, $CH_2C\underline{H}_3$), 4.12 and 4.42 (each 2H, q, $J=8.0$ Hz, $OC\underline{H}_2CH_3$), 7.10—7.70 (8H, m, arom. H), 9.25 (1H, dd, $J=7.5$ and 2.0 Hz, C_6-H), 10.67 (1H, s, CHO), 12.88 (1H, s, NH). MS *m/z*: 387 (M^+, base peak).

References and Notes

1) *a)* Part XVII: H. Ishii, *Acc. Chem. Res.*, **14**, 275 (1981); *b)* Part XVI: Y. Murakami and H. Ishii, *Chem. Pharm. Bull.*, **29**, 711 (1981).
2) K. Miyaki, N. Ikeda, Y. Ito, and D. Mizuno, *Yakugaku Zasshi*, **71**, 643 (1951); K. Miyaki, N. Ikeda, and D. Mizuno, *ibid.*, **73**, 961 (1953); K. Miyaki and N. Ikeda, *ibid.*, **73**, 964 (1953); K. Miyaki and N. Ikeda, *ibid.*, **74**, 655 (1954); N. Ikeda, *ibid.*, **75**, 645, 649, and 1073 (1955); K. Miyaki, S. Ugami, N. Ikeda, and K. Kuretani, *Pharm. Bull.* (Japan), **4**, 417 (1956); K. Takano, M.-S. Yamada, Y. Hirokawa, D. Mizuno, M. Abe, K. Miyaki, and N. Ikeda, *Jpn. J. Med. Sci. Biol.*, **12**, 473 (1959).
3) N. Ikeda, H. Mitsui, and S. Tani, Abstracts of Papers, the 87th Annual Meeting of the Pharmaceutical Society of Japan, Kyoto, April 1967, p. 363.
4) E. A. Goldsmith and H. G. Lindwall, *J. Org. Chem.*, **18**, 507 (1953); Recently, we reexamined of their work and found that their product also has an angular structure. The results will be published shortly.
5) *a)* H. Ishii, Y. Murakami, Y. Suzuki, and N. Ikeda, *Tetrahedron Lett.*, **1970**, 1181; *b)* H. Ishii, Y. Murakami, K. Hosoya, H. Takeda, Y. Suzuki, and N. Ikeda, *Chem. Pharm. Bull.*, **21**, 1481 (1973); *c)* H. Ishii, Y. Murakami, T. Furuse, K. Hosoya, and N. Ikeda, *Chem. Pharm. Bull.*, **21**, 1495 (1973).
6) A. Inoue, K. Nakano, N. Kuroki, and K. Konishi, *Yuki Gosei Kagaku Kyokai Shi*, **14**, 513 (1956) [*Chem. Abstr.*, **51**, 4713*h* (1957)].
7) R. R. Phillips, "Organic Reactions," Vol. 10, ed. by R. Adams, John Wiley and Sons, Inc., New York, 1959, p. 143.
8) F. L. Ehrlich, *Justus Liebigs Ann. Chem.*, **187**, 11 (1877).
9) H. Ishii, Y. Murakami, T. Watanabe, H. Suzuki, and H. Maejima, *Chem. Pharm. Bull.* **31**, 4401 (1983).
10) H. Ishii, Y. Murakami, T. Furuse, K. Hosoya, H. Takeda, and N. Ikeda, *Tetrahedron*, **29**, 1991 (1977).