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Fischer Indolization and Its Related Compounds. V.[1] Indolization of Ethyl Pyruvate 2-Methoxyphenylhydrazone and Its N-Methyl Derivative with Protic Acids. Unpredictable Products and the Mechanism

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Fischer indolization of ethyl pyruvate 2-methoxyphenylhydrazone (**1**) and its N-methyl derivative with protic acids give a variety of unpresumable indole products. Main products have been found to be 6-substituted indole derivatives formed by substitution of the methoxy group of the starting phenylhydrazone (**1**) with nucleophiles in the reaction medium. The tentative mechanism including an important key intermediate cation (**15**) is presented for the formation of the unexpected indole products.

In a preliminary communication,[3] we reported that ethyl pyruvate 2-methoxyphenylhydrazone (**1**) on treatment with ethanolic hydrogen chloride gave ethyl 6-chloro- (**2**) and 6-ethoxy- (**3**) indole-2-carboxylates as main products rather than a normally expected ethyl 7-methoxyindole-2-carboxylate (**4**). In the present paper, we wish to present a detail of the experiments on cyclization of several 2-substituted phenylhydrazone derivatives with protic acids and a full account of the mechanism which can uniformly interpret the complicated formation of the unexpected indole products.

In the course of a study of syntheses of indoloquinones, we have occasionally found that treatment of some dimethoxyphenylhydrazone derivatives under a condition of Fischer indolization results in several modes of abnormal transformation. These unpresumable transformations involve a formation of a *p*-phenylenediamine derivative by an N-substituted aniline type rearrangement,[4a)] an abnormal indolization accompanying elimination and/or migration of a methoxy group situated at ortho position of a starting phenylhydrazone,[5] a cleavage of the linkage between a phenyl group and an N_A nitrogen atom[5] and others.[5] On the other hand, in 1958, Pappalardo, *et al.*,[6] reported that treatment of ethyl pyruvate 2-methoxyphenylhydrazone (**1**) with ethanolic hydrogen chloride gave an unidentified indole product, mp 168°, instead of the expected ethyl 7-methoxyindole-2-carboxylate (**4**) which was obtained by cyclization of the same hydrazone (**1**) in mixed sulfuric and acetic acids. This description prompted us to reinvestigate their experiments as a clue of establishment of the mechanism for the formation of unpresumable indole products in our study of Fischer indolization of 2-methoxyphenylhydrazone derivatives.

Ethyl pyruvate phenylhydrazone derivatives used as the starting material in a series of our studies were prepared by Japp-Klingemann reaction,[7] in which coupling reaction of

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[1] Part IV: H. Ishii, Y. Murakami, K. Hosoya, T. Furuse, H. Takeda, and N. Ikeda, *Chem. Pharm. Bull.* (Tokyo), **20**, 1088 (1972).

[2] Location: *1-33, Yayoi-cho, Chiba.*

[3] H. Ishii, Y. Murakami, Y. Suzuki, and N. Ikeda, *Tetrahedron Letters*, **1970**, 1181.

[4] *a*) H. Ishii, Y. Murakami, S. Tani, K. Abe, and N. Ikeda, *Yakugaku Zasshi*, **90**, 724 (1970); *b*) J. Elguero, R. Jacquier, and G. Tarrago, *Bull. Soc. Chim. France*, **1966**, 2981.

[5] H. Ishii, Y. Murakami, and N. Ikeda, unpublished results.

[6] G. Pappalardo and T. Vitali, *Gazz. Chim. Ital.*, **88**, 574 (1958) [*C.A.*, **53**, 20030a (1959)].

[7] R.R. Phillips, "Organic Reaction", Vol. **10**, ed. by R. Adams, John Wiley and Sons, Inc., N.Y., 1959, p. 143.

Table I. Spectra of Geometrical Isomers of Ethyl Pyruvate Phenylhydrazone Derivatives

Substituents on a benzene ring	Form	IR (Nujol) NH (cm^{-1})	IR (Nujol) CO (cm^{-1})	NMR (τ) (CCl$_4$) NH	UV (95%EtOH) mμ (log ε)	Reference
2-Methoxy-	Z	3271$^{a)}$	1681$^{a)}$	−2.08	360 (4.24)	this paper
	E	3368$^{a)}$	1703$^{a)}$	2.08	331.5(4.29)	
2-Chloro-	Z	3212	1679	−2.30	343 (4.23)	18a
	E	3350	1694	2.02	316 (4.29)	
2,5-Dimethoxy-	Z	3269$^{a)}$	1674$^{a)}$	−2.06$^{b)}$	367 (4.22)	4
	E	3365$^{a)}$	1698$^{a)}$	2.08$^{b)}$	340.5(4.26)	
2-Methoxy-	Z	3258	1682	−2.03	357.5(4.25)	18b
5-Chloro-	E	3370	1705	2.16	333 (4.29)	
3,4-Dichloro-	Z	3250$^{c)}$	1679$^{c)}$	−1.98	343.5(4.30)	18b
	E	3350$^{c)}$	1704$^{c)}$	2.32$^{b)}$	328 (4.36)	
2,6-Dichloro-	Z	3210	1670	−1.94	322 (4.14)	18a
	E	3350	1685	2.50	289 (4.23)	

a) measured in CCl$_4$ *b)* measured in CDCl$_3$ *c)* measured in CHCl$_3$

the diazonium compound and ethyl α-methylacetoacetate[8] gave a mixture of geometrical isomers of the ethyl pyruvate phenylhydrazone derivative. Column chromatography of the mixture of such isomers on silicic acid gave two each component, (Z)- and (E)-isomer. The geometrical assignment of each isomer was easily carried out by comparison of the spectral evidences of them.[4] Since (Z)-isomer has an intramolecular hydrogen bonding between a carbonyl group and imino hydrogen in its molecule, the signal due to imino hydrogen of (Z)-isomer appears in lower field than that of (E)-isomer in the nuclear magnetic resonance (NMR) spectrum and both the carbonyl and the NH band of (Z)-isomer shift to lower frequency region in the infrared (IR) spectrum (Table I). Practically, (Z)-isomer is obtained as a quick eluent on column chromatography and shows a spot having a larger *Rf* value on thin-layer chromatography (TLC).[4] Generally speaking, such an isolation work is unnecessary for a study of Fischer indolization, because both isomers would change each other and give a mixture of the same products under an acid condition. Actually, we confirmed the presumption was correct on our both isomers. But, in order to give a guarantee for purity of the starting material, the sole isomer showing a single spot on TLC was used for the experiments in a series of our studies.

Treatment of (Z)-ethyl pyruvate 2-methoxyphenylhydrazone (1a) with 3N ethanolic hydrogen chloride gave a mixture of various indolic products. Careful isolation work on the reaction mixture using column chromatography gave three known indole compounds, ethyl 7-methoxy[6,9] (**4**), 6-chloro-[10] (**2**) and 4-methoxy-[6,9] (**5**) indole-2-carboxylates, and two new ones, ethyl 6-ethoxy- (**3**) and 7-ethoxy- (**6**) indole-2-carboxylates. Their structures were anticipated by diagnostic inspection of their NMR spectra, mass spectra and other physical properties, and confirmed by direct comparison with the samples prepared from corresponding o-nitrotoluene derivatives by Reissert's method[11] for 4-, 6- and 7-substituted indole products. In addition to these compounds, we obtained an indolic mixture which showed a single spot on TLC in various solvent systems. All efforts to separate the mixture to individual components failed, but its gas chromatography (VPC) showed three peaks corresponding to ethyl

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[8] A. Michael, *Ber.*, 38, 2083 (1905).

[9] K.G. Blaikie and W.H. Perkin, Jr., *J. Chem. Soc.*, **125**, 296 (1924).

[10] G. Pappalardo and T. Vitali, *Gazz. Chim. Ital.*, **88**, 1147 (1958) [*C.A.*, 53, 21876g (1959)].

[11] P.L. Julian, E.W. Meyer, and H.C. Printy, "Heterocyclic Compounds," Vol. 3, ed. by R.C. Elderfield, John Wiley and Sons, Inc., N.Y., 1952, p. 18.; W.E. Noland and F.J. Baude, *Org. Synth.*, 43, 40 (1963).

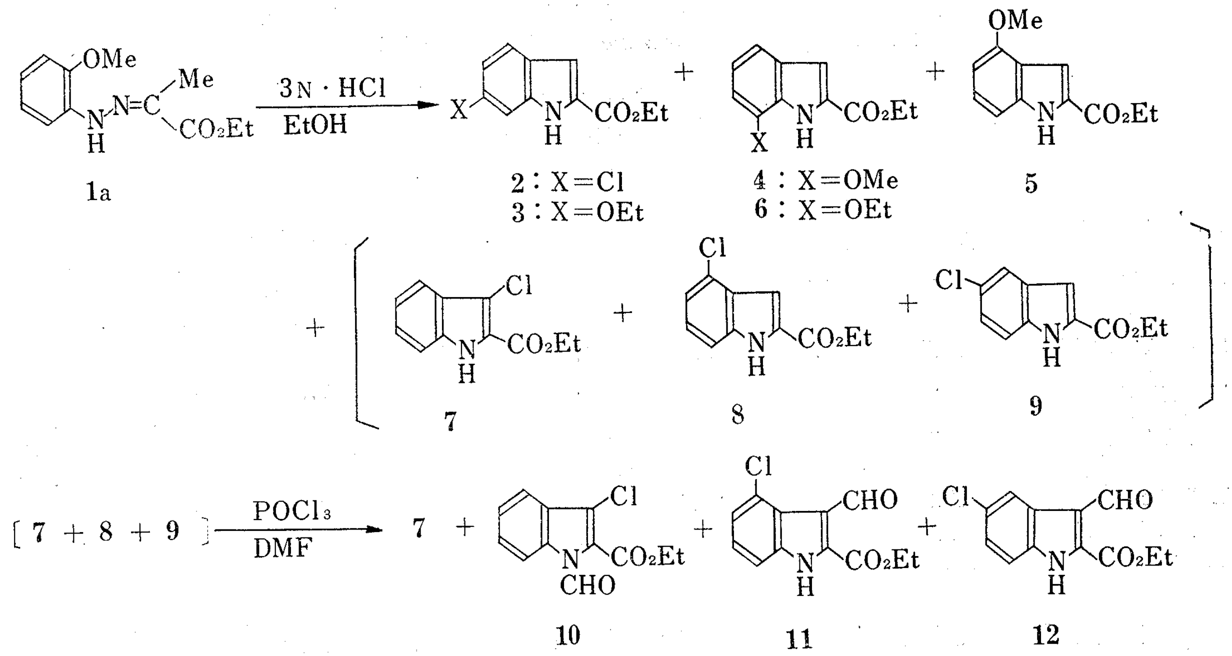

Chart 1

3-[10,12] (**7**), 4-[10,13] (**8**) and 5-[10,14] (**9**) chloroindole-2-carboxylates. Formylation[15] of the mixture with Vilsmeier reagent (DMF+$POCl_3$) followed by column chromatography gave one unformylated and three formylated products, which were identified with authentic samples of ethyl 3-chloroindole-2-carboxylate (**7**) and its 1-formyl derivative (**10**), ethyl 4- (**11**) and 5- (**12**) chloro-3-formylindole-2-carboxylates. These authentic samples were obtained by formylation of the corresponding indolic compounds with Vilsmeier reagent, respectively. During the syntheses of the authentic formylated compounds, it was recognized that formylation at the indolic nitrogen atom of ethyl 3-chloroindole-2-carboxylate (**7**) is more difficult than those at the C_3 carbon atom of other C_3-free indole derivatives. These results indicate that cyclization of ethyl pyruvate 2-methoxyphenylhydrazone (**1**) with ethanolic hydrogen chloride results in formation of one expected and seven unpresumable indole products. In order to decide the step of the transformation, we treated ethyl 7-methoxyindole-2-carboxylate (**4**), which is the expected product, with 3N ethanolic hydrogen chloride and recovered it unchanged. This observation implies that the transformation has taken place before indole formation and allows us to expect that similar reaction may happen with another protic acid. Therefore, we have examined the cyclization of the same hydrazone (**1**) with sulfuric acid in ethanol, and with hydrogen chloride in acetic acid, respectively. The results shown in Table II demonstrate that the abnormal transformation of ethyl pyruvate 2-methoxyphenylhydrazone (**1**) is not restricted to ethanolic hydrogen chloride but seemed to be fairly common phenomenon with a protic acid in protic solvent.

Independently, Gannon, *et al.*[16] reported cyclization of the same hydrazone (**1**) with saturated ethanolic hydrogen chloride instead of 3N one in the large scale of the starting material (50 g) and isolated two indolic compounds, ethyl 6- (**2**) and 3- (**7**) chloroindole-2-carboxylates. And also they claimed the presence of ethyl 7-methoxy- (**4**) and 6-ethoxy- (**3**) indole-2-car-

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12) *a*) S. Gabriel, W. Gerhard, and R. Wolter, *Ber.*, **56**, 1024 (1923); *b*) M. Kunori, *Nippon Kagaku Zasshi*, **81**, 1431 (1960) [*C.A.*, **56**, 3441i (1962)].

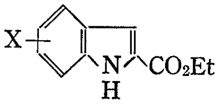
13) A. Romeo, H. Corrodi, and E. Hardegger, *Helv. Chim. Acta*, **38**, 463 (1955).

14) H.N. Rydon and J.C. Tweddle, *J. Chem. Soc.*, **1955**, 3499; B.H. Brown and P.G. Philpott, *J. Chem. Soc.*, **1965**, 7185.

15) R.J. Sundberg, "The Chemistry of Indoles," Academic Press, New York and London, P. 35.

16) W.F. Gannon, J.D. Benigni, D.E. Dickson, and R.L. Minnis, *J. Org. Chem.*, **34**, 3002 (1969).

Table II. Abnormal Fischer Indolization Products of Ethyl 2-Methoxyphenylhydrazone (1) with Protic Acids (%)



Products (X=) / Reagents	7-OMe (4)	7-OEt (6)	6-Cl (2)	6-OEt (3)	4-OMe (5)	3-, 4-, 5-Cl mixture (7)+(8)+(9)	H	Dimer
3N·HCl–EtOH	15.5	1.1	9.9	4.8	0.7	11.6	—	—
sat. HCl–EtOH (ours)	4.2	1.8	34.7	0.26	—	7.7	—	Cl-(+) 0.55
sat. HCl–EtOH (Gannon's)	(+) TLC	—	36.1	(+) mass spectrum	—	3-Cl(7) 0.89	—	MeO-(+) 0.093
HCl–AcOH	17.2		20.5		—	6.1	—	—
H_2SO_4–EtOH	12.8	—		2.0	—		0.2	—

boxylates in the reaction mixture from the evidences that the solid mass obtained from the mother liquor of recrystallization of ethyl 3-chloroindole-2-carboxylate (**7**) showed a spot corresponding to the former indolic compound on TLC and an additional peak at *m/e* 233 corresponding to a parent peak of the latter (**3**) in the mass spectrum. At first sight their result is slightly different from ours, particularly on the yields of 6-substituted indolic products. Therefore, we have repeated the same cyclization under their condition and found that ratio of yields of ethyl 6-chloro- (**2**) and 6-ethoxy (**3**) indole-2-carboxylates depended upon the concentration of hydrogen chloride in ethanol. Robinson's mechanism[17] widely accepted for the standard Fischer indolization can be expanded to interprete such a complicated formation of a variety of unpresumable indolic products as follows. Carbon-carbon bond for-

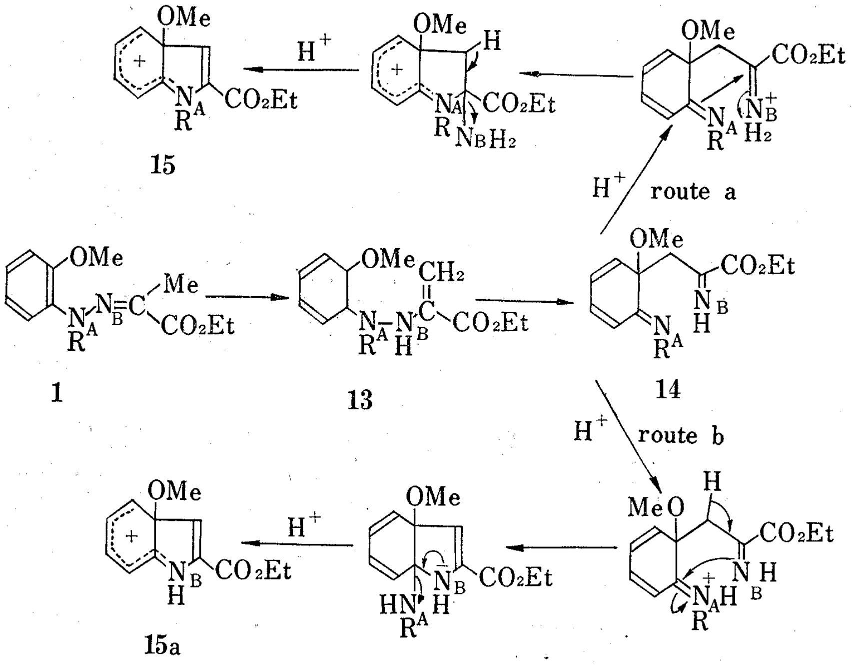


Chart 2

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[17] G.M. Robinson and R. Robinson, *J. Chem. Soc.*, **113**, 639 (1918); *idem, ibid* **125**, 827 (1924); R.B. Carlin and E.E. Fisher, *J. Am. Chem. Soc.*, **70**, 3421 (1948).

mation of an ene-hydrazine intermediate (**13**) at the ortho position occupied by a methoxy group gives an intermediate (**14**) which by protonation of N_B nitrogen, attack of the ring imino nitrogen to the immonium carbon and elimination of ammonia molecule leads to a key intermediate cation (**15**) (Chart 2: route a). The key intermediate (**15**) plays dramatic acts in various manners. We can summarized the complicated following steps to the three representative categories, addition of a nucleophile present in the reaction mixture to C_6 or C_4 position (Chart 3), 1,2-migration of the methoxy group for intramolecular stabilization (Chart 3), and substitution of the methoxy group with nucleophile at C_3 position (Chart 7).

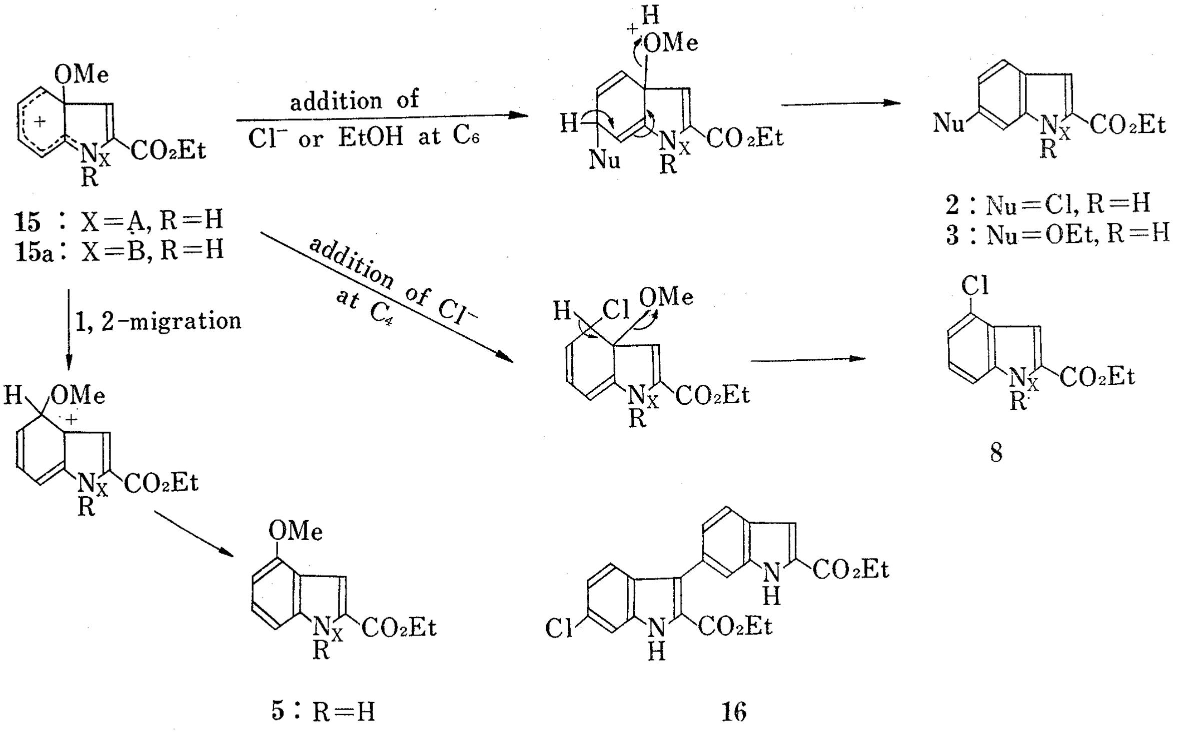

Chart 3

First, addition of the chloride anion or ethanol molecule to the C_6 position of the carbonium ion (**15**) followed by elimination of methanol molecule results in formation of ethyl 6-chloro- (**2**) and 6-ethoxy- (**3**) indole-2-carboxylates. And also similar attack of the chloride anion at C_4 position of the key intermediate (**15**) rationalized the formation of ethyl 4-chloroindole-2-carboxylate (**8**) (Chart 3). Therefore, it is not difficult to understand that the variation of the yields of the 6-substituted indole derivatives is concerned with the concentration of each nucleophiles in the reaction mixture. In addition, we obtained an indolic dimer having a chlorine atom in its molecule from the reaction mixture with saturated ethanolic hydrogen chloride. Since ethyl 6-chloroindole-2-carboxylate (**2**) produced by the above abnormal Fischer indolization as a main product may still behave as a nucleophile possessing a reaction site at C_3 position of the indole nucleus, our dimer is supposed to be diethyl 6-chloro-3,6′-biindole-2,2′-dicarboxylate (**16**). Furthermore, Gannon, *et al.*,[16] reported the isolation of another indolic dimer (**17**) not having a chlorine atom but a methoxy group in its molecule. This compound could be also supposed to be a product by the abnormal indole

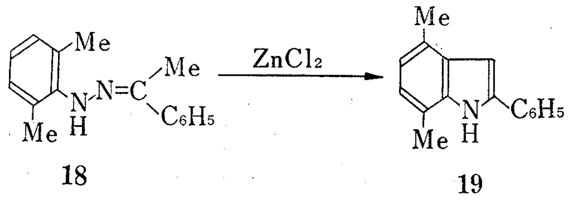

Chart 4

formation. Certification of the correctness of this assumption will be published in another paper.[18a]

The intramolecular stabilization of the key intermediate cation (**15**) by 1,2-migration of a methoxy group rationalized the formation of ethyl 4-methoxyindole-2-carboxylate (**5**). About ten years ago, Carlin, *et al.*,[19] examined the cyclization of acetophenone 2,6-dimethylphenylhydrazone (**18**) with zinc chloride and obtained a 1,2-migration product of a methyl group, 4,7-dimethyl-2-phenylindole (**19**) (Chart 4). However, such a 1,2-migration of a methoxy group is still remained unknown up to the present.

On the formation of ethyl 3-chloroindole-2-carboxylate (**7**), Gannon, *et al.*,[16] proposed an attractive mechanism which contained an alternative protonation on NA nitrogen of an intermediate (**14**) in the Fischer sense[20] (Chart 5). In spite of a lack of experimental foundation, it sounds quite reasonable because the presence of a carbethoxy group at the α-position of the N_B nitrogen results in a lowering of the basicity of the N_B imino group. In order

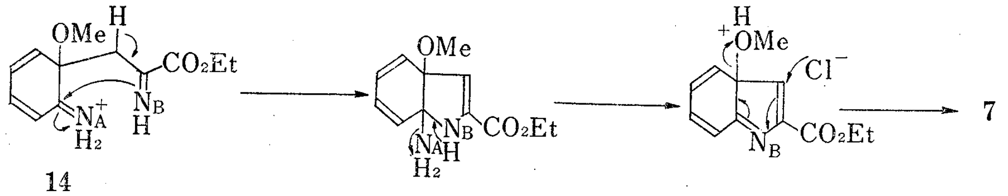

Chart 5

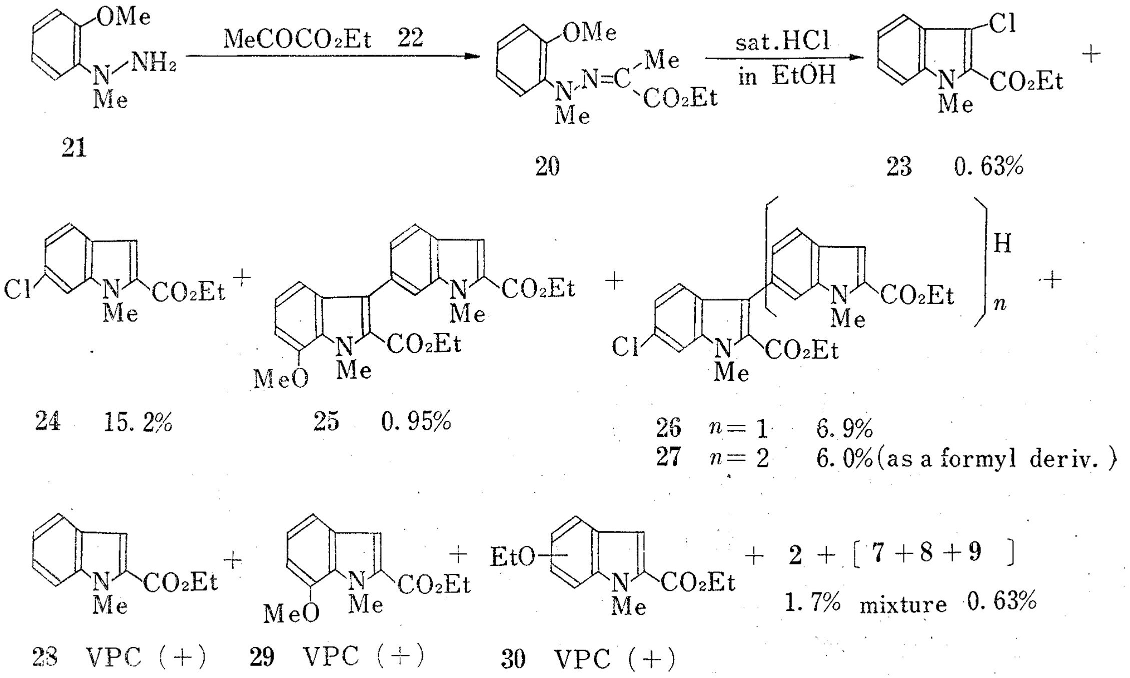

Chart 6

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18) *a*) H. Ishii, Y. Murakami, T. Furuse, K. Hosoya, and N. Ikeda, *Chem. Pharm. Bull.* (Tokyo), **21**, 1495 (1973); *b*) H. Ishii, Y. Murakami, H. Takeda, and T. Furuse, unpublished result.

19) R.B. Carlin and D.P. Carlson, *J. Am. Chem. Soc.*, **81**, 4673 (1959); R.B. Carlin, A.J. Magistro, and G.J. Mains, *J. Am. Chem. Soc.*, **86**, 5300 (1964).

20) For a review of the Fischer indolization, see B. Robinson, *Chem. Rev.*, **63**, 373 (1963); *idem*, *ibid.*, **69**, 227 (1969).

to give an additional evidence to their mechanism, cyclization of ethyl pyruvate N_A-methyl-2-methoxyphenylhydrazone (**20**) prepared by condensation of 1-(2-methoxyphenyl)-1-methylhydrazine[21] (**21**) with ethyl pyruvate[22] (**22**) was undertaken. The Gannon's mechanism predicts formation of ethyl 3-chloroindole-2-carboxylate (**7**) in place of its N-methyl derivative (**23**) by treating of the above N_A-methylphenylhydrazone (**20**) with ethanolic hydrogen chloride. Actually, treatment of the hydrazone (**20**) under the above condition gave a mixture of eight N-methyl and four NH indolic products as shown in Chart 6. Among them, five N-methyl (**23**—**27**) and one NH (**2**) indole derivatives were isolated as crystalline forms. The structures of these N-methylindoles were confirmed by direct comparison with the sample prepared from the corresponding NH specimen, except the trimer (**27**). The other NH indole products were obtained as an inseparable mixture of three chloroindoles, whose VPC showed three peaks corresponding to ethyl 3- (**7**), 4- (**8**) and 5- (**9**) chloroindole-2-carboxylates. Other than above indole products, we obtained a mixture of N-methylindole derivatives which showed four peaks in its VPC but could not separate into individual components due to the scarce amount of it. The mass spectrum of the mixture showed four characteristic peaks at *m/e* 247, 237, 233 and 203 which corresponded to the parent peaks of ethyl 1-methylindole-2-carboxylate bearing ethoxy- ($C_{14}H_{17}O_3N$), chloro- ($C_{12}H_{12}O_2NCl$), methoxy- ($C_{13}H_{15}O_3N$) and no other ($C_{12}H_{13}O_2N$) substituents in their molecules, respectively. In its VPC, retention times of the first, second and third peaks were identical with those of authentic samples of ethyl unsubstituted- (**28**), 3-chloro- (**23**) and 7-methoxy- (**29**) 1-methylindole-2-carboxylates, respectively. It should be noted that the second component (**23**) has been isolated as a crystalline form from the other fraction of the reaction mixture and the third component (**29**) is a normally expected indole in Fischer sense. Moreover, it is easily supposed from the results obtained on the abnormal cyclization of the corresponding NH-phenylhydrazone (**1**) under the same condition that the fourth ethoxyindole component (**30**) may be ethyl 6-ethoxy-1-methylindole-2-carboxylate (**31**). However, an authentic sample prepared by methylation of ethyl 6-ethoxyindole-2-carboxylate (**3**) shows different retention time from that of the fourth peak of the mixture on VPC. Therefore, the position of the ethoxy group of the minor product (**30**) was remained undefined.

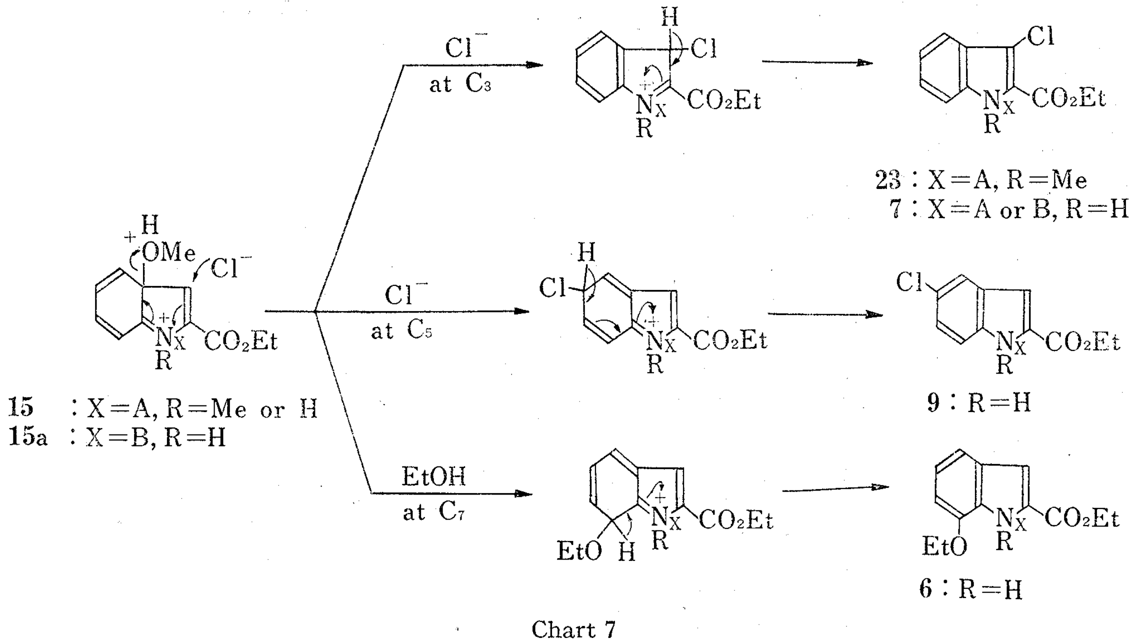

Chart 7

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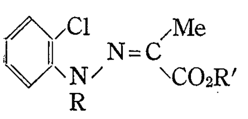
[21] H-H. Stroh and G. Westphal, *Chem. Ber.*, 97, 83 (1964).
[22] J.W. Cornforth, *Org. Synth. Coll. Vol.*, 4, 467 (1963).

The results mentioned above were entirely unexpected. The formation of ethyl 3-chloro-1-methylindole-2-carboxylate (**23**) cannot be explained by Gannon's mechanism and strongly indicates that abnormal cyclization mainly proceed by an alternative process even in the formation of 3-chloroindole derivatives. Further protonation at a tertiary methoxy group of the key intermediate cation (15: $R=CH_3$ in Chart 2) could be happened under the rather stronger acidic condition like Fischer indolization and followed by elimination of methanol molecule with introduction of a chloride anion at C_3 position to give ethyl 3-chloro-1-methylindole-2-carboxylate (**23**). In the strict sence of the term, we are not in a position to discuss both cyclization of an NH-phenylhydrazone and its N-methyl derivative in the same category, but, at least we may assume that protonation on N_A nitrogen is more unfavorable in the case of an NH-phenylhydrazone than its N_A-methyl derivative, because the N_A nitrogen of the latter should be more basic due to the electronic effect of the methyl group than that of the corresponding NH-phenylhydrazone. These consideration allows us to suppose that ethyl 3-chloroindole-2-carboxylate (**7**) containing N_A nitrogen has been also formed by protonation at the N_B nitrogen of the starting ethyl pyruvate 2-methoxyphenylhydrazone (**1**).

It is conceivable that similar substitution of a methoxy group of the key intermediate cation (**15**) with ethanol molecule at C_7 or with chloride anion at C_5 on cyclization of the NH-phenylhydrazone (**1a**) give rise to ethyl 7-ethoxy- (**6**) and 5-chloro- (**9**) indole-2-carboxylates, respectively.

It is important to note that the presence of several NH-indole derivatives in some extent, particularly ethyl 6-chloroindole-2-carboxylate (**2**), in the reaction mixture obtained by cyclization of N_A-methylphenylhydrazone (**20**), although the yields of them have been much lower than those of N-methylindole derivatives. This evidence demonstrates that there exists a side cyclization process of a pyrrole ring system (Chart 2: route b) other than the main pathway (Chart 2: route a) which was confirmed by Allen's labelling experiments.[23] Although there is no criterion of the contribution of the side process to the indolic products when the NH-phenylhydrazone derivative are used for cyclization, we assume that it could not be excluded from the full account of the mechanism of the abnormal Fischer indolization. In other words, it is very interesting that the process through protonation on an N_B-imino group and attack of a ring imino nitrogen to the immonium carbon still remains as a main pathway even in the Fischer indolization of ethyl pyruvate phenylhydrazone which has an N_A nitrogen whose basicity is strengthened by N_A-methylation and an N_B nitrogen whose basicity is weakened by the presence of the carbonyl group on the α position, since the total yield of N-methylindole products is absolutely higher on the cyclization of ethyl pyruvate N_A-methylphenylhydrazone (**20**) than that of NH-indolic products.

Finally, in the course of the study on the cyclization of N_A-methylphenylhydrazone derivatives, we have observed that the introduction of a methyl group on N_A nitrogen of phenylhydrazones tremendously accelerates their cyclization. For instance, esterification of pyruvic acid 2-chlorophenylhydrazone (**32**) was performed by refluxing with saturated ethanolic hydrogen chloride to give ethyl pyruvate 2-chlorophenylhydrazone (**33**) in good yield as described in literature,[24] but ethyl ester of its N_A-methyl derivative (**34**) smoothly gives the products of Fischer indolization by dissolving it in the same reagent at room temperature. This indolization product also contained an abnormal 6-chloroindole derivative. However, since it gives a lot of other curious abnormal products, we would like to discuss these transformation together with the results of further experiments elsewhere.



32: R=H, R'=H
33: R=H, R'=Et
34: R=Me, R'=Et

Chart 8

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[23] C.F.H. Allen and C.V. Wilson, *J. Am. Chem. Soc.*, **65**, 611 (1943).

[24] J.T. Hewitt, *J. Chem. Soc.*, **59**, 209 (1881); H.N. Rydon and J. Tweddle, *J. Chem. Soc.*, **1955**, 3499.

Experimental[25]

Japp-Klingemann Reaction of *o*-Anisidine and Ethyl α-Methyl Acetoacetate——To a suspension of 24.7 g of *o*-anisidine hydrochloride in 300 ml of EtOH was added dropwise 23.4 g of isoamylnitrite under cooling. A solution of 22.2 g of ethyl α-methyl acetoacetate in 300 ml of abs. EtOH containing 7.2 g of metal sodium was added to the above mixture with stirring under cooling. After addition, the mixture was further stirred for 2 hr, poured into water and extracted with benzene. The benzene extract was dried over $MgSO_4$ and evaporated to dryness *in vacuo*. The residue (27.3 g) was dissolved in benzene and chromatographed on silicic acid.

(Z)-Ethyl Pyruvate 2-Methoxyphenylhydrazone (1a)——Elution with benzene gave 10.9 g of yellow plates, mp 90—90.5°, which were recrystallized from hexane. *Anal.* Calcd. for $C_{12}H_{16}O_3N_2$: C, 61.00; H, 6.83; N, 11.86. Found: C, 61.01; H, 6.83; N, 11.68. IR $\nu_{max}^{CCl_4}$ cm^{-1}: 3271 (NH), 1681 (C=O). NMR (CCl_4) τ: 8.65 (3H, t, J=7.0 Hz, $CH_2C\underline{H}_3$), 7.87 (3H, s, vinyl CH_3), 6.11 (3H, s, OCH_3), 5.77 (2H, q, J=7.0 Hz, $OC\underline{H}_2CH_3$), 3.25 (3H, m, aromatic protons), 2.55 (1H, m, aromatic proton), −2.08 (1H, br. s, NH). Mass Spectrum *m/e*: 236 (M^+).

(E)-Ethyl Pyruvate 2-Methoxyphenylhydrazone (1b)——Continued elution with benzene afforded 9.22 g of yellow plates, mp 74.5—76°, which were recrystallized from hexane. *Anal.* Calcd. for $C_{12}H_{16}O_3N_2$: C, 61.00; H, 6.83; N, 11.86. Found: C, 60.64; H, 6.92; N, 11.62. IR $\nu_{max}^{CCl_4}$ cm^{-1}: 3368 (NH), 1703 (C=O). NMR (CCl_4) τ: 8.66 (3H, t, J=7.0 Hz, $CH_2C\underline{H}_3$), 7.97 (3H, s, vinyl CH_3), 6.15 (3H, s, OCH_3), 5.80 (2H, q, J=7.0 Hz, $OC\underline{H}_2CH_3$), 3.20 (3H, m, aromatic protons), 2.46 (1H, m, aromatic proton), 2.08 (1H, br. s, NH). Mass Spectrum *m/e*: 236 (M^+).

Fischer Indolization of (Z)-Ethyl Pyruvate 2-Methoxyphenylhydrazone (1a) with 3N Ethanolic Hydrogen Chloride——A solution of 5.00 g of (Z)-ethyl pyruvate 2-methoxyphenylhydrazone (1a) in 150 ml of 3N ethanolic hydrogen chloride was refluxed for 2 hr, concentrated *in vacuo* and poured into cold water. The product was extracted with ether. The ethereal solution was washed with 5% $NaHCO_3$ aq. dried over $MgSO_4$ and evaporated to dryness. The oily residue (3.391 g) in benzene was chromatographed on Al_2O_3. Elution with benzene gave 2.63 g of solid mass showing four spots on TLC. The solid mass in benzene was rechromatographed on silicic acid. Elution with benzene followed by TLC was fractionated to four fractions (fraction A, B, C and D in the order of elution) corresponded to each spots on TLC. Fraction A and D showed a single spot on TLC in various solvent systems. Fraction B showed a single spot on TLC in several solvent systems, but three peaks on VPC. Fraction C showed a single spot on TLC in benzene but three in chloroform. Elution with EtOH (fraction E) gave no indolic compound on this trial.

Ethyl 6-Chloroindole-2-carboxylate (2)——Fraction A gave 468 mg of colourless needles, mp 182—184°, which were recrystallized from benzene·hexane. Beilstein's test was positive. *Anal.* Calcd. for $C_{11}H_{10}O_2NCl$: C, 59.07; H, 4.51; N, 6.26. Found: C, 59.05; H, 4.35; N, 6.41. IR ν_{max}^{KBr} cm^{-1}: 3326 (NH), 1695 (C=O). NMR ($CDCl_3$) τ: 8.58 (3H, t, J=7.5 Hz, $CH_2C\underline{H}_3$), 5.58 (2H, q, J=7.5 Hz, $OC\underline{H}_2CH_3$), 2.88 (1H, q, J=9.5 Hz, J=2.0 Hz, C_5-H), 2.80 (1H, d, J=2.5 Hz, C_3-H), 2.57 (1H, d, J=2.0 Hz, C_7-H), 2.40 (1H, d, J=9.5 Hz, C_4-H), 0.94 (1H, br. s, NH). Mass Spectrum *m/e*: 225 (M^++2, 34% intensity of M^+), 223 (M^+). It was identical with authentic ethyl 6-chloroindole-2-carboxylate[10] (2) prepared from 4-chloro-2-nitrotoluene by Reissert's method (yield 12.5%).

Formylation of Fraction B (A Mixture of Ethyl 3- (7), 4- (8) and 5- (9) Chloroindole-2-carboxylates) with Vilsmeier Reagent——Fraction B showed three peaks corresponding to those of authentic ethyl 3-(**7**), 4-(**8**), and 5-(**9**) chloroindole-2-carboxylates on VPC. All efforts to isolate to each component failed as a state of free compound. Thus, a solution of 3.0 g of $POCl_3$ in 10 ml of DMF was stirred for 30 min with cooling and a solution of fraction B (550 mg) in 2 ml of DMF was added . After the mixture was heated at 115° for 4 hr, it was poured onto ice water, basified with 10% Na_2CO_3 aq and extracted with ether. The ethereal solution was dried over $MgSO_4$ and evaporated to dryness. The residue (458 mg) in chloroform was chromatographed on silicic acid. Elution with chloroform gave fraction F and G in the order of elution.

Ethyl 3-Chloro-1-formylindole-2-carboxylate (10)——Fraction F in benzene was chromatographed on silicic acid. Elution with benzene gave 86 mg of colourless needles, mp 125—127°, which were recrystallized

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25) All melting points were measured on micro melting point hot stage (Yanagimoto) and uncorrected. IR, NMR and Mass spectra were obtained with Hitachi EPI-G3, JEOL JMN-4H-100 and Hitachi RMU-6E spectrometer. In the NMR spectrum, the assignments of all NH and C_3-H signals of indolic derivatives were confirmed by disappearance of NH signal and changing of the shape of C_3-H signal from doublet to singlet after addition of D_2O. Gas chromatography was done with Hitachi Gas chromatograph-063 equipped with a stainless steel column (100 cm × 3 mm) packed with 15% diethylene glycol succinate on shimalite 60—80 mesh. Condition: column temperature, 200°; injection temperature, 260°; detection (FID) temperature, 260°; Carrier gas, N_2 (30 ml/min). For column chromatography, SILICIC ACID, 100 mesh Mallinckrodt Chemical Works and Aluminium Oxide, Neutral, M. Woelm, were used. All identification of the compound has been done with respect to IR spectra, mixed melting point and TLC.

from cyclohexane. *Anal.* Calcd. for $C_{12}H_{10}O_3NCl$: C, 57.27; H, 4.01; N, 5.57. Found: C, 57.56; H, 3.94; N, 5.53. IR ν_{max}^{Nujol} cm^{-1}: NH (nil), 1706, 1693 (C=O). NMR ($CDCl_3$) τ: 8.53 (3H, t, $J=7.3$ Hz, $CH_2C\underline{H}_3$), 5.51 (2H, q, $J=7.3$ Hz, $OC\underline{H}_2CH_3$), 2.37 (3H, m, aromatic protons), 1.40 (1H, m, C_7-H), -0.04 (1H, s, CHO). UV λ_{max}^{EtOH} mμ (log ε): 241 (4.15), 283 (4.20) sh, 292.5 (4.26), 311 (4.00) sh. Mass Spectrum *m/e*: 253 ($M^+ +2$, 37% intensity of M^+), 251 (M^+). It was identical with authentic ethyl 3-chloro-1-formylindole-2-carboxylate (**10**) prepared from ethyl 3-chloroindole-2-carboxylate (**7**) by Vilsmeier reaction (yield 29%).

Ethyl 3-Chloroindole-2-carboxylate (**7**)——Further elution with benzene on the above column chromatography gave 176 mg of colourless needles, mp 158—160°, which were recrystallized from benzene–hexane. *Anal.* Calcd. for $C_{11}H_{10}O_2NCl$: C, 59.07; H, 4.51; N, 6.26. Found: C, 59.23; H, 4.57; N, 6.25. IR ν_{max}^{Nujol} cm^{-1}: 3275 (NH), 1679 (C=O). NMR ($CDCl_3$) τ: 8.57 (3H, t, $J=7.0$ Hz, $CH_2C\underline{H}_3$), 5.57 (2H, q, $J=7.0$ Hz, $OC\underline{H}_2CH_3$), 2.60—2.90 (3H, m, aromatic protons), 2.29 (1H, d, $J=8.3$ Hz, C_4-H), 1.13 (1H, br. s, NH). Mass Spectrum *m/e*: 225 ($M^+ +2$, 34.4% intensity of M^+), 223 (M^+). It was identical with an authentic sample of ethyl 3-chloroindole-2-carboxylate (**7**) which was prepared by the method of chlorination of ethyl indole-2-carboxylate[26] with sulfuryl chloride in the literature[12b] (yield quantitatively).

Ethyl 5-Chloro-3-formylindole-2-carboxylate (**12**)——Fraction G in chloroform was rechromatographed on silicic acid. First elution with chloroform gave 107.5 mg of colourless leaflets, mp 240—241°, which were recrystallized from EtOH. *Anal.* Calcd. for $C_{12}H_{10}O_3NCl$: C, 57.27; H, 4.01; N, 5.57. Found: C, 57.77, H, 4.09; N, 5.57. IR ν_{max}^{Nujol} cm^{-1}: 3125 (NH), 1725 (ester), 1635 (CHO). NMR (DMSO-d_6) τ: 8.59 (3H, t, $J=7.5$ Hz, $CH_2C\underline{H}_3$), 5.53 (2H, q, $J=7.5$ Hz, $OC\underline{H}_2CH_3$), 2.60 (1H, q, $J=8.2$ Hz, $J=2.5$ Hz, C_6-H),, 2.38 (1H d, $J=8.2$ Hz, C_7-H), 1.76 (1H, d, $J=2.5$ Hz, C_4-H), -0.58 (1H, s, CHO), -2.91 (1H, br. s, NH). Mass Spectrum *m/e*: 253 ($M^+ +2$, 34.3% intensity of M^+), 251 (M^+). It was identical with authentic ethyl 5-chloro-3-formylindole-2-carboxylate (**12**) which was prepared from ethyl 5-chloroindole-2-carboxylate[9,13] (**9**) by Vilsmeier reagent (Yield 75%).

Ethyl 4-Chloro-3-formylindole-2-carboxylate (**11**)——Second elution with chloroform of column chromatography of fraction G gave 83 mg of colourless leaflets, mp 212—213°, which were recrystallized from EtOH. *Anal.* Calcd. for $C_{12}H_{10}O_3NCl$: C, 57.27; H, 4.01; N, 5.57. Found: C, 57.24; H, 3.87; N, 5.64. IR ν_{max}^{Nujol} cm^{-1}: 3155 (NH), 1724 (ester), 1658 (CHO). NMR (DMSO-d_6) τ: 8.61 (3H, t, $J=7.5$ Hz, $CH_2C\underline{H}_3$), 5.55 (2H, q, $J=7.5$ Hz, $OC\underline{H}_2CH_3$), 2.48 (3H, m, aromatic protons), -0.65 (1H, s, CHO), -2.98 (1H, br. s, NH). Mass Spectrum *m/e*: 253 ($M^+ +2$, 34.2% intensity of M^+), 251 (M^+). It was identical with authentic ethyl 4-chloro-3-formylindole-2-carboxylate (**11**) prepared from ethyl 4-chloroindole-2-carboxylate[10,13] (**8**) with Vilsmeier reagent (yield 38%).

Ethyl 7-Methoxyindole-2-carboxylate (**4**)——Recrystallization of fraction C from benzene–hexane gave 415 mg of colourless needles, mp 115—117°. *Anal.* Calcd. for $C_{12}H_{13}O_3N$: C, 65.74; H, 5.98; N, 6.39. Found: C, 66.00; H, 6.05; N, 6.38. IR ν_{max}^{KBr} cm^{-1}: 3336 (NH), 1705 (C=O). NMR (CCl_4) τ: 8.54 (3H, t, $J=7.0$ Hz, $CH_2C\underline{H}_3$), 6.03 (3H, s, OCH_3), 5.61 (2H, q, $J=7.0$ Hz, $OC\underline{H}_2CH_3$), 3.88 (1H, d, $J=7.5$ Hz, C_6-H), 3.05 (1H, t, $J=7.5$ Hz, C_5-H), 2.91 (1H, d, $J=2.0$ Hz, C_3-H), 2.81 (1H, d, $J=7.5$ Hz, C_4-H), 1.00 (1H, br. s, NH). Mass Spectrum *m/e*: 219 (M^+). It was identified with an authentic sample of ethyl 7-methoxyindole-2-carboxylate[6,9] (**4**) prepared from 3-methyl-2-nitroanisole by Reissert's method (yield 20.6%).

The mother liquor of recrystallization was evaporated to dryness *in vacuo*. The residue (fraction H: 414 mg) in chloroform was chromatographed on silicic acid and fractionated to three fractions (fraction I, J and K in the order of elution). Fraction J gave additional 306 mg of ethyl 7-methoxyindole-2-carboxylate (**4**) (total yield 721 mg).

Ethyl 7-Ethoxyindole-2-carboxylate (**6**)——Fraction I gave 56 mg of colourless needles, mp 69—70°, which were recrystallized from hexane. *Anal.* Calcd. for $C_{13}H_{15}O_3N$: C, 66.93; H, 6.48; N, 6.01. Found: C, 66.51; H, 6.50; N, 6.13. IR ν_{max}^{Nujol} cm^{-1}: 3375, 3335 (NH), 1687 (C=O). NMR (CCl_4) τ: 8.59 (3H, t, $J=7.0$ Hz, $CH_2C\underline{H}_3$), 8.49 (3H, t, $J=7.0$ Hz, $CH_2C\underline{H}_3$), 5.81 (2H, q, $J=7.0$ Hz, $OC\underline{H}_2CH_3$), 5.62 (2H, q, $J=7.0$ Hz, $OC\underline{H}_2CH_3$), 3.39 (1H, d, $J=7.5$ Hz, C_6-H), 3.07 (1H, t, $J=7.5$ Hz, C_5-H), 2.90 (1H, d, $J=2.5$ Hz, C_3-H), 2.81 (1H, d, $J=7.5$ Hz, C_4-H), 1.08 (1H, br. s, NH). Mass Spectrum *m/e*: 233 (M^+). It was identical with an authentic sample of ethyl 7-ethoxyindole-2-carboxylate (**6**) prepared from 3-methyl-2-nitrophenetole by Reissert's method (yield 5.5%).

Ethyl 4-Methoxyindole-2-carboxylate (**5**)——Fraction K gave 33 mg of colourless pillars, mp 177—180°, which were recrystallized from benzene–hexane. *Anal.* Calcd. for $C_{12}H_{13}O_3N$: C, 65.74; H, 5.98; N, 6.39. Found: C, 65.83; H, 6.04; N, 6.51. IR ν_{max}^{Nujol} cm^{-1}: 3323 (NH), 1687 (C=O). NMR ($CDCl_3$) τ: 8.63 (3H, t, $J=7.5$ Hz, $CH_2C\underline{H}_3$), 6.09 (3H, s, OCH_3), 5.63 (2H, q, $J=7.5$ Hz, $OC\underline{H}_2CH_3$), 3.54 (1H, d, $J=8.0$ Hz, C_5-H), 3.03 (1H, d, $J=8.0$ Hz, C_7-H), 2.80 (1H, t, $J=8.0$ Hz, C_6-H), 2.68 (1H, d, $J=2.5$ Hz, C_3-H), 0.89 (1H, br. s, NH). Mass spectrum *m/e*: 219 (M^+). It was identical with an authentic sample of ethyl 4-methoxyindole-2-carboxylate[6,9] (**5**) which was prepared from ethyl pyruvate 3-methoxyphenylhydrazone by Fischer indolization as follows.

Preparation of Authentic Ethyl 4-Methoxyindole-2-carboxylate (**5**)——a) (Z)-Ethyl Pyruvate 3-Methoxyphenylhydrazone: To an ice cooled solution of 14.4 g of ethyl α-methylacetoacetate in 100 ml of EtOH

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26) W.E. Noland and F.J. Baude, *Org. Synth.*, 43, 40 (1963).

was added a solution of 6.75 g of KOH in 7 ml of water. The cold solution of 3-methoxybenzene diazonium chloride prepared from 12.3 g of *m*-anisidine, 21.0 g of conc. HCl and 7.25 g of $NaNO_2$ in 80 ml of water was added to the first solution with stirring below 10° and continued cooling in ice for 1 hr. The mixture was diluted with 300 ml of water and extracted with benzene. The organic layer was dried over $MgSO_4$ and evaporated to dryness *in vacuo*. The residue (27.5 g) was dissolved in a mixed solution of 60 ml of EtOH and 10 ml of 85% H_3PO_4, and refluxing for 15 min. After cooling it was poured into water and then extracted with benzene. The benzene extract was washed with 5% $NaHCO_3$ aq., dried over $MgSO_4$ and evaporated to dryness *in vacuo*. The residue (21.7 g) in benzene was chromatographed on silicic acid. Benzene elution gave 2.40 g of yellow needles, mp 59—60°, which were recrystallized from pentane. *Anal.* Calcd. for $C_{12}H_{16}O_3N_2$: C, 61.00; H, 6.83; N, 11.86. Found: C, 61.29; H, 6.85; N, 11.67. IR ν_{max}^{Nujol} cm^{-1}: 3250 (NH), 1670 (C=O). NMR (CCl_4) τ: 8.66 (3H, t, $J=7.5$ Hz, $CH_2C\underline{H}_3$), 7.88 (3H, s, vinyl CH_3), 6.24 (3H, s, OCH_3), 5.78 (2H, q, $J=7.5$ Hz, $OC\underline{H}_2CH_3$), 2.87—3.72 (4H, m, aromatic protons), −1.99 (1H, br. s, NH). Mass Spectrum *m/e*: 236 (M^+).

b) Authentic Ethyl 4-Methoxyindole-2-carboxylate (5): A mixture of 1.30 g of (Z)-ethyl pyruvate 3-methoxyphenylhydrazone and 4.00 g of anhydrous $ZnCl_2$ in 12 ml of AcOH was refluxed for 1 hr. After cooling the reaction mixture was poured into 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*. The residue (1.116 g) in chloroform was chromatographed on silicic acid. Elution with chloroform gave 110 mg of ethyl 4-methoxyindole-2-carboxylate (5) as colourless fine needles, mp 177.5—178°, which were recrystallized from benzene–hexane.

Further elution with chloroform gave 535 mg of ethyl 6-methoxyindole-2-carboxylate as colourless needles, mp 140—141.5°, which were recrystallized from benzene–hexane. *Anal.* Calcd. for $C_{12}H_{13}O_3N$: C, 65.74; H, 5.98; N, 6.39. Found: C, 65.57; H, 5.81; N, 6.49. IR ν_{max}^{Nujol} cm^{-1}: 3330 (NH), 1681 (C=O). NMR ($CDCl_3$) τ: 8.61 (3H, t, $J=7.3$ Hz, $CH_2C\underline{H}_3$), 6.16 (3H, s, OCH_3), 5.60 (2H, q, $J=7.3$ Hz, $OC\underline{H}_2CH_3$), 3.20 (1H, q, $J=9.7$ Hz, $J=2.5$ Hz, C_5-H), 3.16 (1H, d, $J=2.5$ Hz, C_7-H), 2.84 (1H, d, $J=2.5$ Hz, C_3-H), 2.45 (1H, d, $J=9.7$ Hz, C_4-H), 1.06 (1H, br. s, NH). Mass Spectrum *m/e*: 219 (M^+). It was identified with an authentic sample of ethyl 6-methoxyindole-2-carboxylate prepared from 4-methyl-3-nitro-anisole by Reissert's method (yield 3.4%).

Ethyl 6-Ethoxyindole-2-carboxylate (3)——Fraction D gave 237 mg of colourless prisms, mp 118—120°, which were recrystallized from benzene–hexane. *Anal.* Calcd. for $C_{13}H_{15}O_3N$: C, 66.93; H, 6.48; N, 6.01. Found: C, 67.08; H, 6.30; N, 6.15. IR ν_{max}^{KBr} cm^{-1}: 3340 (NH), 1670 (C=O). NMR ($CDCl_3$) τ: 8.61 (3H, t, $J=7.5$ Hz, $CH_2C\underline{H}_3$), 8.56 (3H, t, $J=7.5$ Hz, $CH_2C\underline{H}_3$), 5.95 (2H, q, $J=7.5$ Hz, $OC\underline{H}_2CH_3$), 5.63 (2H, q, $J=7.5$ Hz, $OC\underline{H}_2CH_3$), 3.22 (1H, q, $J=10.0$ Hz and $J=2.0$ Hz, C_5-H), 3.19 (1H, d, $J=2.0$ Hz, C_7-H), 2.86 (1H, d, $J=2.5$ Hz, C_3-H), 2.48 (1H, d, $J=10.0$ Hz, C_4-H), 1.20 (1H, br. s, NH). Mass Spectrum *m/e*: 233 (M^+). It was identified with an authentic sample of ethyl 6-ethoxyindole-2-carboxylate (3) prepared from 4-methyl-3-nitrophenetole by Reissert's method (yield 7.7%).

General Procedure of Preparation of Authentic Samples of Ethyl Indole-2-carboxylate Derivatives by Reissert's Method——a) Ethyl 2-Nitrophenylpyruvate Derivatives: To a solution of 49 mmole of *t*-BuOK and 51 mmole of diethyl oxalate in 43 ml of abs. benzene was added a solution of 29 mmole of 2-nitrotoluene derivative in 65 ml of abs. benzene. The mixture was stirred with refluxing for 10 hr. The red precipitate was collected by filtration, dissolved in an aqueous solution containing 98 mmole of AcOH and extracted with ether. The ethereal solution was washed with 5% $NaHCO_3$ aq., and dried over $MgSO_4$. Evaporation of the above solution gave crude ethyl 2-nitrophenylpyruvate derivative which was used for further transformation without purification.

b) Ethyl Indole-2-carboxylate Derivatives: A solution of 3.8 mmole of the above ethyl 2-nitrophenylpyruvate derivative in 50 ml of EtOH was hydrogenated over 1 g of 5% palladium charcoal at atmospheric pressure and room temperature until absorption of hydrogen ceased. The filtered solution was evaporated to dryness *in vacuo*. Recrystallization of the residue from appropriate solvent gave a pure sample of ethyl indole-2-carboxylate derivative.

General Procedure of Preparation of Authentic Samples of Ethyl 3-Formylindole-2-carboxylate Derivatives with Vilsmeier Reagent——A solution of 13.5 mmole of $POCl_3$ in 10 ml of DMF was stirred for 20 min at room temperature. After addition of a solution of 1.5 mmole of ethyl indole-2-carboxylate derivative, the mixture was heated at 100—110° for 2hr. After cooling, it was poured into water, made alkaline with 10% Na_2CO_3 aq., and extracted with ether. The ethereal solution was dried over $MgSO_4$ and evaporated. The residue usually obtained as a crystalline was purified by column chromatography on silicic acid and recrystallization to give an authentic sample.

Fischer Indolization of (Z)-Ethyl Pyruvate 2-Methoxyphenylhydrazone (1a) with Saturated Ethanolic Hydrogen Chloride——A suspended solution of 10 g of (Z)-ethyl pyruvate 2-methoxyphenylhydrazone (1a) in 200 ml of EtOH was saturated with dry hydrogen chloride and refluxed for 25 min. The reaction mixture was treated by the same procedure described for the reaction with 3N ethanolic hydrogen chloride to give each corresponding fraction. In this case, fraction E (elution with EtOH in the first column chromatography on Al_2O_3) gave a dimeric indole compound.

Fraction A gave 3.277 g of ethyl 6-chloroindole-2-carboxylate (**2**) as colourless needles, mp 180—182°.

Recrystallization of fraction B (729 mg) gave 75 mg of ethyl 3-chloroindole-2-carboxylate (**7**) as colourless needles, mp 158.5—160°. Mother liquor was evaporated to dryness *in vacuo*. The residue (526 mg) was treated with Vilsmeier reagent. Fraction F gave 80 mg of ethyl 3-chloro-1-formylindole-2-carboxylate (**10**) as colourless prisms, mp 127—131°, and 120.5 mg of ethyl 3-chloroindole-2-carboxylate (**7**) as colourless needles, mp 159—161°. Fraction G gave 122 mg of ethyl 5-chloro-3-formylindole-2-carboxylate (**12**) as colourless needles, mp 238—239°, and 44 mg of ethyl 4-chloro-3-formylindole-2-carboxylate (**11**) as colourless prisms, mp 211—212.5°.

Diethyl 6-Chloro-3,6′-biindole-2,2′-dicarboxylate (16)——Fraction E in benzene was chromatographed on silicic acid. Elution with benzene gave 47 mg of colourless pillars, mp 233—240°, which was recrystallized from benzene–hexane. *Anal.* Calcd. for $C_{22}H_{19}O_4N_2Cl$: C, 64.31; H, 4.66; N, 6.82. Found: C, 64.16; H, 4.58; N, 6.79. 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) τ: 8.84 (3H, t, J=7.0 Hz, $CH_2C\underline{H}_3$), 8.65 (3H, t, J=7.0 Hz, $CH_2C\underline{H}_3$), 5.80 (2H, q, J=7.0 Hz, $OC\underline{H}_2CH_3$), 5.66 (2H, q, J=7.0 Hz, $OC\underline{H}_2CH_3$), 2.3—3.0 (6H, m, aromatic protons), 2.84 (1H, d, J=2.0 Hz, C_3-H), −1.82 (1H, br. s, NH), −1.95 (1H, br. s, NH). Mass Spectrum m/e: 412 (M$^+$+2, 39% intensity of M$^+$), 410 (M$^+$).

Fischer Indolization of (E)-Ethyl Pyruvate 2-Methoxyphenylhydrazone (1b) with Hydrogen Chloride in Acetic Acid——A solution of 5.00 g of (E)-ethyl pyruvate 2-methoxyphenylhydrazone (**1b**) was refluxed for 20 min. During the reaction, dry hydrogen chloride gas was bubbled through the solution. The reaction mixture was treated by the same procedure for the reaction with 3N ethanolic hydrogen chloride to give each corresponding fractions.

Fraction A gave 970 mg of ethyl 6-chloroindole-2-carboxylate (**2**) as colourless needles, mp 182—183°.

Fraction B gave 290 mg of a mixture of indoles whose VPC showed three peaks corresponding to ethyl 3-chloro-(**7**), 4-chloro-(**8**) and 5-chloro-(**9**) indole-2-carboxylates. Fraction C gave 800 mg of ethyl 7-methoxyindole-2-carboxylate (**4**), as colourless needles, mp 111—113°.

Fischer Indolization of (Z)-Ethyl 2-Methoxyphenylhydrazone (1a) with Sulfuric Acid in Ethanol——A mixture of 1.00 g of (Z)-ethyl pyruvate 2-methoxyphenylhydrazone (**1a**) and 2.00 g of sulfuric acid in 10 ml of EtOH was refluxed for 5 hr. The mixture was poured into water and extracted with benzene. The organic layer was washed with dil. $NaHCO_3$aq., dried over $MgSO_4$ and evaporated to dryness. The residue (866 mg) in benzene was chromatographed on silicic acid.

Ethyl Indole-2-carboxylate (17)——First elution with benzene gave 1.5 mg of colourless needles, mp 123—124°, which were recrystallized from benzene·hexane. *Anal.* Calcd. for $C_{11}H_{11}O_2N$: C, 69.82; H, 5.86; N, 7.40. Found: C, 69.76; H, 5.73; N, 7.43. IR ν_{max}^{KBr} cm^{-1}: 3321 (NH), 1690 (C=O). NMR (CCl_4) τ: 8.57 (3H, t, J=7.5 Hz, $CH_2C\underline{H}_3$), 5.60 (2H, q, J=7.5 Hz, $OC\underline{H}_2CH_3$), 2.33—3.07 (5H, m, aromatic protons and C_3-H), 0.50 (1H, br. s, NH). Mass Spectrum m/e: 189 (M$^+$). It was identified with a sample of ethyl indole-2-carboxylate[26] (**17**) prepared from 2-nitrotoluene by Reissert's method (yield 46.4%).

Second and third elution with benzene gave 119 mg of ethyl 7-methoxyindole-2-carboxylate (**4**) as colourless needles, mp 112—114°, and 15 mg of ethyl 6-ethoxyindole-2-carboxylate (**3**) as colourless prisms, mp 118—120°, respectively.

Ethyl Pyruvate N$_A$-Methyl-2-methoxyphenylhydrazone (20)——A mixture of 647 mg of 1-(2-methoxyphenyl)-1-methylhydrazine[21] (**21**) and 518 mg of ethyl pyruvate[22] (**22**) in 15 ml of abs. benzene was refluxed for 40 min. After cooling, it was washed with dil. HCl aq., and water, dried over $MgSO_4$ and evaporated to dryness *in vacuo*. Recrystallization of the residue from hexane gave pale yellow prisms, mp 80—81°. *Anal.* Calcd. for $C_{13}H_{18}O_3N_2$: C, 62.38; H, 7.25; N, 11.19. Found: C, 62.13; H, 7.19; N, 11.18. IR ν_{max}^{Nujol} cm^{-1}: NH (nil), 1690 (C=O). NMR (CCl_4) τ: 8.67 (3H, t, J=7.3 Hz, $CH_2C\underline{H}_3$), 8.53 (3H s, vinyl CH_3), 6.71 (3H, s, NCH_3), 6.16 (3H, s, OCH_3), 5.83 (2H, q, J=7.3 Hz, $OC\underline{H}_2CH_3$), 3.33—2.83 (4H, m, aromatic protons). Mass Spectrum m/e: 250 (M$^+$).

Fischer Indolization of Ethyl Pyruvate N$_A$-Methyl-2-methoxyphenylhydrazone (20) with Saturated Ethanolic Hydrogen Chloride——To 200 ml of saturated ethanolic hydrogen chloride was added 10.00 g of ethyl pyruvate N$_A$-methyl-2-methoxyphenylhydrazone (**20**). The mixture was refluxed for 15 min. The mixture was concentrated on a steam bath to 80 ml under reduced pressure, poured into 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*. The residue (8.345 g) in benzene was chromatographed on Al_2O_3 (grade: Super I) and fractionated into three portions, elution with benzene (fraction A: 0.863 g), with chloroform (fraction B: 5.539 g) and with EtOH (fraction C: 0.183 g).

Ethyl 6-Chloro-1-methylindole-2-carboxylate (24)——Fraction A in benzene was rechromatographed on silicic acid. First elution with benzene gave 702 mg of colourless needles, mp 76.5—77°, which were recrystallized from aqueous EtOH. And an additional amount of this material was obtained from the following separation work on the fraction B. Total yield 1.446 g. *Anal.* Calcd. for $C_{12}H_{12}O_2NCl$: C, 60.64; H, 5.09; N, 5.89. Found: C, 60.79; H, 4.91; N, 5.83. IR ν_{max}^{Nujol} cm^{-1}: NH (nil), 1713 (C=O). NMR (CCl_4) τ: 8.63 (3H, t, J=7.5 Hz, $CH_2C\underline{H}_3$), 5.99 (3H, s, NCH_3), 5.72 (2H, q, J=7.5 Hz, $OC\underline{H}_2CH_3$), 3.01 (1H, q, J=8.8 Hz, J=2.0 Hz, C_5-H), 2.89 (1H, s, C_3-H), 2.73 (1H, d, J=2.0 Hz, C_7-H), 2.54 (1H, d, J=8.8 Hz, C_4-H).

Mass Spectrum *m/e*: 239 ($M^+ + 2$, 34.8% of intensity of M^+), 237 (M^+). It was identified with an authentic sample of ethyl 6-chloro-1-methylindole-2-carboxylate (24) prepared by methylation of ethyl 6-chloroindole-2-carboxylate (2) (yield 48%).

Ethyl 3-Chloro-1-methylindole-2-carboxylate (23)——Further elution with benzene gave 60 mg of colourless needles, mp 70.5—71.5°, which were recrystallized from hexane. *Anal.* Calcd. for $C_{12}H_{12}O_2NCl$: C, 60.64; H, 5.09; N, 5.89. Found: C, 60.44; H, 5.02; N, 5.85. IR $\nu_{\max}^{\text{Nujol}}$ cm^{-1}: NH (nil), 1699 (C=O). NMR (CCl_4) τ: 8.57 (3H, t, $J=7.5$ Hz, $CH_2C\underline{H}_3$), 6.00 (3H, s, NCH_3), 5.63 (2H, q, $J=7.5$ Hz, $OC\underline{H}_2CH_3$), 3.00—2.65 (3H, m, aromatic protons), 2.37 (1H, d, $J=8.0$ Hz, C_4-H). Mass Spectrum *m/e*: 239 ($M^+ + 2$, 32.8% of intensity of M^+), 237 (M^+). It was identified with a sample of ethyl 3-chloro-1-methylindole-2-carboxylate (23) prepared by methylation of ethyl 3-chloroindole-2-carboxylate (7) (yield 67%).

Diethyl 6-Chloro-1,1′-dimethyl-3,6′-biindole-2,2′-dicarboxylate (26)——Final elution with benzene gave 70 mg of colourless prisms, mp 141.5—143°, which were recrystallized from cyclohexane. An additional amount of this material was obtained by the following separation work on fraction B. Total yield 607 mg. *Anal.* Calcd. for $C_{24}H_{23}O_4N_2Cl$: C, 65.67; H, 5.28; N, 6.38. Found: C, 65.99; H, 4.97; N, 6.22. IR $\nu_{\max}^{\text{Nujol}}$ cm^{-1}: NH (nil), 1704 (C=O). NMR (CCl_4) τ: 9.08 (3H, t, $J=7.3$ Hz, $CH_2C\underline{H}_3$), 8.60 (3H, t, $J=7.3$ Hz, $CH_2C\underline{H}_3$), 5.96 (3H, s, NCH_3), 5.95 (2H, q, $J=7.3$ Hz, $OC\underline{H}_2CH_3$), 5.93 (3H, s, NCH_3), 5.69 (2H, q, $J=7.3$ Hz, $OC\underline{H}_2CH_3$), 3.08—2.37 (7H, m, aromatic protons and $C_3'H$). Mass Spectrum *m/e*: 440 ($M^+ + 2$, 37.0% intensity of M^+), 438 (M^+). Beilstein test is positive. It was identified with an authentic sample of diethyl 6-chloro-1,1′-dimethyl-3,6′-biindole-2,2′-dicarboxylate (26) prepared by methylation of diethyl 6-chloro-3,6′-biindole-2,2′-dicarboxylate18) (yield 11.0%).

Presence of Ethyl Unsubstituted- (28), 7-Methoxy- (29) and Undefined Ethoxy- (30) 1-methylindole-2-carboxylates——Fraction B in benzene was chromatographed on silicic acid. First elution with benzene gave an additional ethyl 6-chloro-1-methylindole-2-carboxylate (24). Second elution with benzene gave 65 mg of a mixture of indolic products whose VPC showed four peaks. Mass Spectrum of the mixture also showed four characteristic peaks at *m/e* 247, 237, 233 and 203. In its VPC (column: 10% SE-30 on chromosorb W), the retention time of the first peak of the mixture was identical with that of authentic ethyl 1-methylindole-2-carboxylate27) (28), M^+ ($C_{12}H_{13}O_2N$) at *m/e* 247. The second peak did not coincide in retention time with that of ethyl 6-chloro-1-methylindole-2-carboxylate (24) which was a main component of the fraction B, but that of ethyl 3-chloro-1-methylindole-2-carboxylate (23), M^+ ($C_{12}H_{12}O_2NCl$) at *m/e* 237. The retention time of the third peak was compatible with that of authentic ethyl 7-methoxy-1-methylindole-2-carboxylate (29), M^+ ($C_{13}H_{15}O_3N$) at *m/e* 233. The retention time of the last peak due to undefined ethyl ethoxy-1-methylindole-2-carboxylate (30) was confirmed to be not identical with that of authentic ethyl 6-ethoxy-1-methyl-2-carboxylate (31), M^+ ($C_{12}H_{13}O_2N$) at *m/e* 247.

Authentic Ethyl 7-Methoxy-1-methylindole-2-carboxylate (29)——N-Methylation of 219 mg of ethyl 7-methoxyindole-2-carboxylate (4) by general procedure (vide infra) gave 216 mg of ethyl 7-methoxy-1-methylindole-2-carboxylate (29), mp 47.5—48.5°, as colourless needles which were purified by recrystallization from aqueous EtOH. *Anal.* Calcd. for $C_{13}H_{15}O_3N$: C, 66.93; H, 6.48; N, 6.01. Found: C, 67.07; H, 6.22; N, 6.00. IR $\nu_{\max}^{\text{Nujol}}$ cm^{-1}: NH (nil), 1710 (C=O). NMR (CCl_4) τ: 8.64 (3H, t, $J=7.5$ Hz, $CH_2C\underline{H}_3$), 6.13 (3H, s, OCH_3), 5.76 (2H, q, $J=7.5$ Hz, $OC\underline{H}_2CH_3$), 5.68 (3H, s, NCH_3), 3.49 (1H, d, $J=7.5$ Hz, C_6-H), 3.18 (1H, t, $J=7.5$ Hz, C_5-H), 2.93 (1H, d, $J=7.5$ Hz, C_4-H), 2.92 (1H, s, C_3-H). Mass Spectrum *m/e*: 233 (M^+).

Authentic Ethyl 6-Ethoxy-1-methylindole-2-carboxylate (31)——N-Methylation of 117 mg of ethyl 6-chloroindole-2-carboxylate (2) by general procedure (vide infra) gave 85 mg of ethyl 6-ethoxy-1-methylindole-2-carboxylate (31), mp 81—82.5°, as colourless needles which were recrystallized from aqueous EtOH. *Anal.* Calcd. for $C_{14}H_{17}O_3N$: C, 67.99; H, 6.93; N, 5.66. Found: C, 68.11; H, 6.61; N, 5.56. IR $\nu_{\max}^{\text{Nujol}}$ cm^{-1}: NH (nil), 1703 (C=O). NMR (CCl_4) τ: 8.67 (3H, t, $J=7.5$ Hz, $CH_2C\underline{H}_3$), 8.58 (3H, t, $J=7.5$ Hz, $CH_2C\underline{H}_3$), 6.04 (3H, s, NCH_3), 6.00 (2H, q, $J=7.5$ Hz, $OC\underline{H}_2CH_3$), 5.76 (2H, q, $J=7.5$ Hz, $OC\underline{H}_2CH_3$), 3.42 (1H, d, $J=2.0$ Hz, C_7-H), 3.37 (1H, q, $J=8.7$ Hz, J=2.0 Hz, C_5-H), 2.93 (1H, s, C_3-H), 2.63 (1H, d, $J=8.7$ Hz, C_4-H). Mass Spectrum *m/e*: 247 (M^+).

Ethyl 6-Chloroindole-2-carboxylate (2)——Third elution with benzene gave 201 mg of crude ethyl 6-chloroindole-2-carboxylate (2) whose TLC revealed the presence of a scarce amount of several other indole derivatives. Purification of the above material by rechromatography on silicic acid gave 145 mg of pure ethyl 6-chloroindole-2-carboxylate (2) as colourless needles, mp 181—182.5°, which was identified with an authentic sample of it.

A Mixture of Ethyl 3- (7), 4- (8) and 5- (9) Chloroindole-2-carboxylates——Fourth elution with benzene gave 615 mg of a mixture of indolic derivatives. The mixture in chloroform was rechromatographed on silicic acid. The first elution with chloroform gave 537 mg of diethyl 6-chloro-1,1′-dimethyl-3,6′-biindole-2,2′-dicarboxylate (26). Second elution with chloroform afforded 56 mg of an inseparable mixture of indolic derivatives whose VPC showed three peaks corresponding to ethyl 3- (7), 4- (8) and 5- (9) chloroindole-2-carboxylates.

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Diethyl 1,1′-Dimethyl-7-methoxy-3,6′-biindole-2,2′-dicarboxylate (25)——Fifth elution with benzene on column chromatography of fraction B gave 232 mg of an oily mixture. Rechromatography of the mixture in benzene on silicic acid gave 83 mg of colourless needles, mp 97—100°, which were repeatedly recrystallized from EtOH and/or hexane. *Anal.* Calcd. for $C_{25}H_{26}O_5N_2$: C, 69.11; H, 6.03; N, 6.45. Found: C, 69.48; H, 6.45; N, 6.10. IR $\nu_{max}^{CHCl_3}$ cm^{-1}: NH (nil), 1700 (C=O). NMR (CCl_4) τ: 9.10 (3H, t, $J=7.5$ Hz, $CH_2C\underline{H}_3$), 8.60 (3H, t, $J=7.5$ Hz, $CH_2C\underline{H}_3$), 6.07 (3H, s, OCH_3), 5.92 (3H, s, NCH_3), 5.69 (3H, s, NCH_3), 6.15—5.58 (4H, m, $2\times OC\underline{H}_2CH_3$), 3.47—2.40 (6H, m, aromatic protons), 2.81 (1H, s, C_3-H). Mass Spectrum *m/e*: 434 (M^+). It was identified with an authentic sample of diethyl 1,1′-dimethyl-7-methoxy-3,6′-biindole-2,2′-dicarboxylate (25) prepared by N-methylation of diethyl 7-methoxy-3,6′-biindole-2,2′-dicarboxylate[18] (yield 88%).

Formyl Derivative of Trimer (27)——After removal of fifth elution with benzene on chromatography of fraction B, the solvent was changed from benzene to chloroform. Elution with chloroform gave 400 mg of oily product. All efforts of crystallization of it failed. To a solution of 300 mg of $POCl_3$ in 2 ml of DMF was added 100 mg of the above oily product in 1 ml of DMF. The mixture was heated at 100—110° for 1 hr, poured into water, made alkaline with 10% Na_2CO_3aq. and extracted with ether. The ethereal solution was dried over $MgSO_4$ and the solvent was distilled off. Purification of the residue by column chromatography gave 80 mg of colourless fine prisms, mp 211—213.5°, which were recrystallized from benzene–EtOH. *Anal.* Calcd. for $C_{37}H_{34}O_7N_3Cl$: C, 66.51; H, 5.13; N, 6.29. Found: C, 66.50; H 5.06; N, 6.40. IR ν_{max}^{Nujol} cm^{-1}: NH (nil), 1715, 1700, 1650 (C=O). NMR (DMSO-d_6) τ: 9.02 (3H, t, $J=7.5$ Hz, $CH_2C\underline{H}_3$), 8.98 (3H, t, $J=7.5$ Hz, $CH_2C\underline{H}_3$), 8.56 (3H, t, $J=7.5$ Hz, $CH_2C\underline{H}_3$), 6.00 (3H, s, NCH_3), 5.96 (3H, s, NCH_3), 5.93 (3H, s, NCH_3), 6.07—5.65 (4H, m, $2\times OC\underline{H}_2CH_3$), 5.51 (2H, q, $J=7.5$ Hz, $OC\underline{H}_2CH_3$), 3.00—2.20 (8H, m, aromatic protons), 1.64 (1H, d, $J=9.0$ Hz, C_4-H), −0.45 (1H, s, CHO).

General Procedure of N-Methylation of Ethyl Indole-2-carboxylate Derivatives——To a solution of 1.00 mmole of ethyl indole-2-carboxylate in 5 ml of acetone was added 1.5 ml of 10% KOH aq. and 0.13 ml of dimethyl sulfate. The mixture was stirred for 1 hr at room temperature, poured into water, and extracted with ether. The ethereal solution was dried over anhydrous K_2CO_3 and evaporated to dryness *in vacuo*. Chromatography of the residue in benzene on silicic acid gave the pure sample.

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