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Fischer Indolization and Its Related Compounds. VI.[1] Effect of Reagents and Substituent of the *ortho*-Substituted Phenylhydrazone on Abnormal Fischer Indolization

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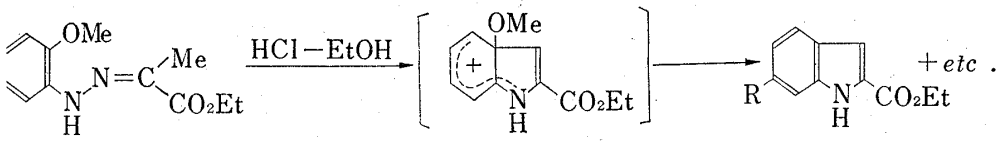
Treatment of ethyl pyruvate 2-methoxyphenylhydrazone (**1**) with Lewis acid gave 5-substituted and/or 5-methoxy- indole products with ethyl 7-methoxyindole-2-carboxylate (**2**) as a main product. It contrasts strikingly with the results reported in the previous paper[1] on a reaction center of the abnormal Fischer indolization. It was also found that differences of the acid strength of the reagent and of the electron density on a benzene ring due to introduction of some other additional substituents could be the determinant for the direction of the abnormal transformation.

In the preceding paper[1] of this series, we have showed that treatment of ethyl pyruvate 2-methoxyphenylhydrazone (**1**) with ethanolic hydrogen chloride or other protic acid in protic solvent gave a large variety of unexpected indolic products and that total amount of such abnormal products was superior to that of the expected ethyl 7-methoxyindole-2-carboxylate (**2**), in general. And we also proposed a plausible mechanism for these transformation which contained an important step of a useful key intermediate cation (**3**). The most preferable process under the condition using a protic acid as a catalyst seems to be an addition of nucleophiles on C_6 position of the indole nucleus.



1 3 4 : R=Cl 5 : R=OEt

Chart 1

In 1948, Carlin, *et al.*[3] reported that treatment of acetophenone 2,6-dichlorophenylhydrazone (**6**) with anhydrous zinc chloride in the absence of solvent or in the presence of phenol, nitrobenzene or other aprotic solvents gave only one migration product of chlorine atom, 5,7-dichloro-2-phenylindole (**7**), in generally low yield. In their subsequent papers,[4] they also showed that treatment of the above phenylhydrazone (**6**) with anhydrous zinc bromide in refluxing nitrobenzene afforded a mixture of 5,7-dichloro- (**7**) and 5-bromo-7-chloro- (**8**) 2-phenylindoles and similar treatment of acetophenone 2,6-dibromophenylhydrazone (**9**) with anhydrous zinc chloride gave a mixture of 7-bromo- (**10**), 5,7-dibromo- (**11**) and 7-bromo-5-chloro- (**12**) 2-phenylindoles. These evidences show that not only migration but

1) Part V: H. Ishii, Y. Murakami, K. Hosoya, H. Takeda, Y. Suzuki and N. Ikeda, *Chem. Pharm. Bull.* (Tokyo), **21**, 1481 (1973).
2) Location: *1-33, Yayoi-cho, Chiba.*
3) R.B. Carlin and E.E. Fisher, *J. Am. Chem. Soc.*, **70**, 3421 (1948); R.B. Carlin, J.G. Wallace and E.E. Fisher, *ibid.*, **74**, 990 (1952).
4) R.B. Carlin and G.W. Larson, *J. Am. Chem. Soc.*, **79**, 934 (1957).

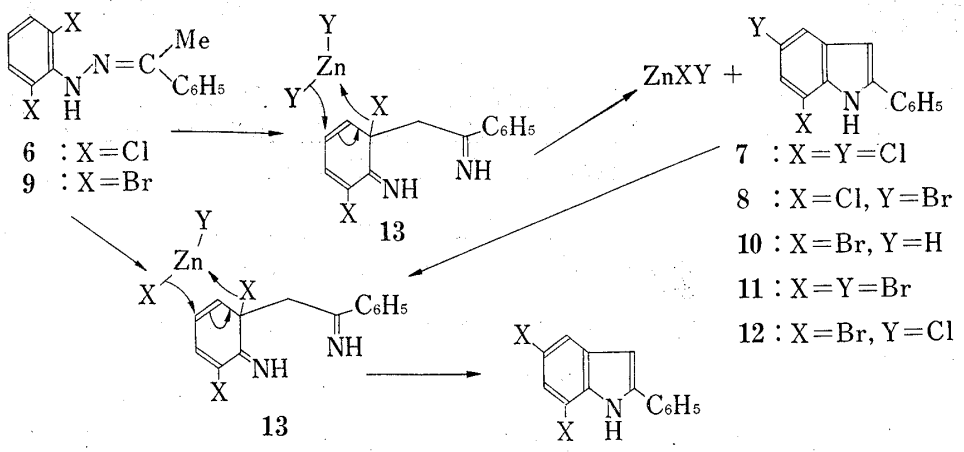


Chart 2

exchange of halogen atom can take place at C_5 position of indole nucleus during indolization. Then, they proposed three mechanism, S_Ni', S_Ni' and S_Ni', in which a replacement of halogen of the intermediate (**13**) with zinc mixed halide molecule produced during the reaction could give a halide migration product as illustrated in Chart 2 for S_Ni' mechanism as an example, but did not find any decisive evidence for a choice of them. These results contrast with our experiments with regard to the reaction site of main product. Replacement has taken place at C_5 position of indole nucleus in Carlin's case, while mainly at C_6 in our experiments. We wondered why the reaction center of the substitution of a methoxy group with chloride anion of ethanolic hydrogen chloride (protic acid) could differ from that of a chlorine atom substituent with the halide anion of zinc halide (Lewis acid) in aprotic solvent. In this paper, we wish to present the results on this matter.

We have examined the dependency of direction of the abnormal transformation on the character of solvent used, because polarity of solvent might define the reaction mechanism. Particularly, since Lewis acid forms a complex with a strong protic acid like hydrogen bromide employed as a co-catalyst and behaves as a protic acid in some reaction as stated by Olah,[5] the combination system of Lewis acid in protic solvent was tested. (Z)-Ethyl pyruvate 2,6-dichlorophenylhydrazone (**14a**) gave ethyl 5,7-dichloroindole-2-carboxylate[6] (**15**) in 82.3% yield, besides a small amount of two minor indolic products, ethyl 5-acetoxy-7-chloroindole-2-carboxylate (**16**) and ethyl 4-acetyl-7-chloro-5-hydroxyindole-2-carboxylate (**17**) on treatment with zinc chloride in acetic acid. However, the same hydrazone (**14a**) was recovered as a mixture of the geometrical isomers quantitatively on treatment with acetic acid itself, zinc chloride in ethanol or ethanolic hydrogen chloride. The structural assignment of the main product on the above reaction came from its nuclear magnetic resonance (NMR) spectrum which shows two 1H doublets coupled with each other (J=2.0 Hz) at 2.45 and 2.70 τ due to aromatic protons. This evidence allows us to assign these signals to two aromatic protons.

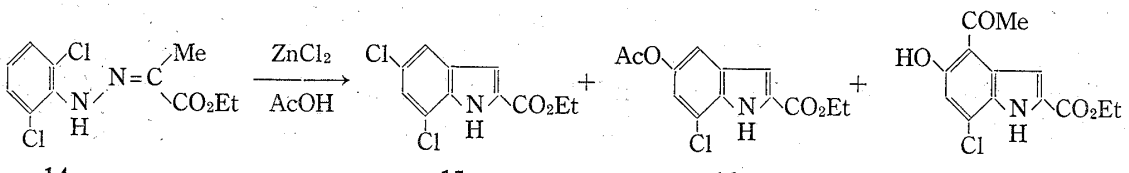


Chart 3

5) G.A. Olah, "Friedel-Crafts and Related Reactions," Vol. I. Interscience Publishers, New York, 1963, p. 212.
6) G. Pappalardo and T. Vitali, *Gazz. Chim. Ital.*, **88**, 1147 (1958) [*C.A.*, **53**, 21876h (1959)].

situated at meta position to each other. And it has the same melting point that is reported to ethyl 5,7-dichloroindole-2-carboxylate (**15**) which was synthesized by Fischer indolization of ethyl pyruvate 2,4-dichlorophenylhydrazone (**18**) in the literature.[6]

The second indole product, ethyl 5-acetoxy-7-chloroindole-2-carboxylate (**16**), was obtained as colourless needles in 0.76% yield whose mass spectrum shows the parent peak at *m/e* 281 corresponded in composition to $C_{13}H_{12}O_4NCl$. The presence of only one chlorine atom in its molecule has been suggested by the fact that $M^+ + 2$ peak at *m/e* 283 appeared with a 38.4% intensity of its parent peak. Its infrared (IR) spectrum shows an additional carbonyl absorption band at 1767 cm^{-1} which suggests the presence of a phenol acetate group in its molecule. Its NMR spectrum also shows a 3H singlet at 7.70 τ ascribed to an acetoxy methyl group and two 1H doublets (J=2.0 Hz) coupled with each other at 2.91 and 2.71 τ due to two aromatic protons situated at meta position. These evidences lead us to the conclusion that the product must be ethyl 5-acetoxy-7-chloroindole-2-carboxylate (**16**).

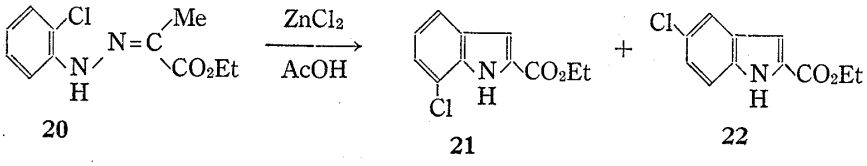
The third product shows a phenolic character in chemical behavior and its molecular formula $C_{13}H_{12}O_4NCl$ has been fixed on the basis of the analytical and mass spectrum data. The IR spectrum shows the presence of a hydrogen bonded carbonyl group with a hydroxy group by an absorption band 1615 cm^{-1} coupled with a broad hydroxy band at 3170—3330 cm^{-1}. Its NMR spectrum showed a 3H singlet at 7.20 τ and 1H singlet at 2.98 τ due to an acetyl methyl and only one benzenoid proton, respectively. We tentatively assigned the indolic product to ethyl 4-acetyl-7-chloro-5-hydroxyindole-2-carboxylate (**17**), because it would be produced by Fries rearrangement[7] of the above 5-acetoxyindole (**16**). In the NMR spectrum of it, the signal due to the proton at C_3 appears in lower field shifted by 15—20 Hz than that of the 5-acetoxyindole (**16**) and this phenomenon may be described to an anisotropic effect of the acetyl group situated at C_4, a peri position.

The formation of the last two indoles suggests that a halogen atom at *ortho* position of a starting phenylhydrazone derivative could be displaced with a nucleophile present in the reaction mixture to give C_5-substituted indole product, when Lewis acid was used as a catalyst. If an acetoxy anion was concerned in this transformation, the presence of an additional amount of an acetoxy anion should increase the total amount of the 5-acetoxyindole product (**16**) and its Fries rearrangement product (**17**). However, indolization did not take place at all, when an equivalent amount of anhydrous zinc acetate was added to the reaction mixture. Two explanation may be offered for the finding. First and less likely, it may be suggested that the addition of zinc acetate lowers pK value of the reaction system. A second and perhaps more likely explanation would be that zinc chloride and zinc acetate forms a complex in acetic acid which could not work as an acid catalyst for indolization. This assumption might be supported by the fact that zinc acetate itself is insoluble in acetic acid but a mixture of equimolar amount of zinc chloride and zinc acetate is freely soluble in the same solvent. It seems that these observations supply a suggestive clue for the elucidation of the chemical behavior of zinc chloride in abnormal Fischer indolization of *ortho* substituted phenylhydrazone derivatives. We will discuss this problem in detail in near future elsewhere.

Ethyl 6,7-dichloroindole-2-carboxylate (**19**) was not detected in the above reaction mixture even in a large scale running. This experimental fact allows us to conclude that the direction of the abnormal Fischer indolization is independent of the nature of the solvent. Furthermore, in contrast to Carlin's experiments, the result indicates that zinc chloride in acetic acid gives the same product in better yield than the same reagent in aprotic solvent. Therefore, this condition has been chosen for a standard reaction due to Lewis acid in our further comparative studies on abnormal Fischer indolization, after it was confirmed that the acetic acid could not cause the indolization of the starting phenylhydrazone derivative by itself in each case.

7) T. Suehiro and M. Niitsu, *Bull. Chem. Soc. Jap.*, **44**, 550 (1971).

The above results still could not be directly compared with that which had been obtained by treating ethyl pyruvate 2-methoxyphenylhydrazone (**1**), because the second chlorine atom substituent on the other side of *ortho* position of the hydrazone (**14**) might effect on the direction of this abnormal transformation. Treatment of (Z)-ethyl pyruvate 2-chlorophenylhydrazone[8] (**20**) with zinc chloride in acetic acid gave the normally expected ethyl 7-chloroindole-2-carboxylate[6,8b] (**21**) and an abnormal product, ethyl 5-chloroindole-2-carboxylate[1] (**22**), in 63.9 and 14.7% yield, respectively, although Rydon, *et al*[8b] reported the formation of the expected indole (**21**) as the sole product in 52% yield on treatment of the same hydrazone (**20**) with polyphosphoric acid. It has been established that the abnormal transformation from *ortho*-chlorophenylhydrazone derivatives to 5-chloroindole product was catalysed by zinc chloride.



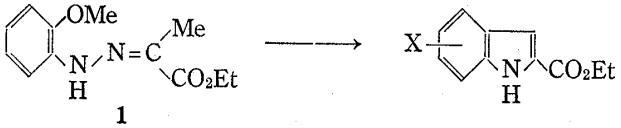
20 **21** **22**

Chart 4

Now, it seems to be very interesting to examine the behavior of ethyl pyruvate 2-methoxyphenylhydrazone (**1**) on treatment with Lewis acid. Treatment of (Z)-ethyl pyruvate 2-methoxyphenylhydrazone[1] with zinc chloride in acetic acid gave a mixture of five indolic compounds as shown in Table 1.

Ethyl 7-methoxyindole-2-carboxylate[1] (**2**), a main product, is the expected product in Fischer sence.[9]

TABLE I. Abnormal Fischer Indolization Products of Ethyl Pyruvate 2-Methoxyphenylhydrazone (1) with Lewis Acid (%)



1

Reagent \ Product (X=)	7-MeO **2**	5-Cl **22**	5-MeO **24**	4-MeO **25**	H **23**
$ZnCl_2$–AcOH	17.7	1.32	0.67	0.26	0.91
BF_3–AcOH	13.5		0.85	—	2.1
BF_3–AcOEt	15.0		4.7	—	2.7
H_2SO_4–AcOH	5.0		0.32	—	0.22

Ethyl indole-2-carboxylate[1] (**23**) is formed by reductive elimination of a substituent placed at an *ortho* position of the starting phenylhydrazone derivatives during cyclization with Lewis acid. Such a reaction pattern is one of the most common abnormal transformation which has been reported[9] on several species of the substituent, even an alkyl group, and whose mechanism has not been so clarified until now.

The formations of ethyl 5-chloro-[1] (**22**) and 5-methoxy-[1,10] (**24**) indole-2-carboxylates show that not only displacement of the methoxy group with halide anion at C_5 position of

8) Synthesis of a mixture of the geometrical isomers had been reported; *a*) J.T. Hewitt, *J. Chem. Soc.*, **59**, 209 (1891); *b*) H.N. Rydon and J. Tweddle, *ibid.*, **1955**, 3499.
9) For a review of the Fischer indole synthesis, see B. Robinson, *Chem. Rev.*, **63**, 373 (1963); **69**, 227 (1969).
10) G. Pappalardo and T. Vitali, *Gazz. Chim. Ital.*, **88**, 574 (1958) [*C.A.*, **53**, 20030a (1959)].

an indolic product but also the migration of it from an *ortho* position of the starting phenylhydrazone to C_5 of the indolic product can take place during cyclization with Lewis acid.

The formation of ethyl 5-chloro- (**22**) and 4-methoxy- (**25**) indole-2-carboxylates have been explained in the preceding paper.[1)]

It should be emphasized that ethyl 6-chloroindole-2-carboxylate (**4**) which was a main product on treatment of the same starting material with ethanolic hydrogen chloride[1)] was not found in the above reaction mixture even on thin-layer chromatography (TLC) and vaper phase chromatography (VPC). We also examined cyclization of the same hydrazone (**1**) with boron trifluoride in acetic acid and in ethyl acetate, because this Lewis acid does not accomodate a halide anion, fluorine anion, to the reaction mixture like zinc chloride and obtained three indolic products, ethyl 7-methoxy- (**2**), 5-methoxy- (**24**) and unsubstituted (**23**) indole-2-carboxylates, as expected. There is no evidence of the presence of an indolic compound having a fluorine atom in its molecule in the reaction mixture. These evidences provided the enough proof to show that the *ortho*-methoxy substituent of the starting phenylhydrazone underwent an abnormal transformation during Fischer indolization with Lewis acid to give a migrated 5-methoxyindole product as well as the chlorine atom substituent shown by Carlin's group. Consideration of the evidences mentioned so far might lead to a formal deduction that the reagent employed was the sole determinant for the direction of the abnormal transformation. However, this deduction is denied by the following experiments.

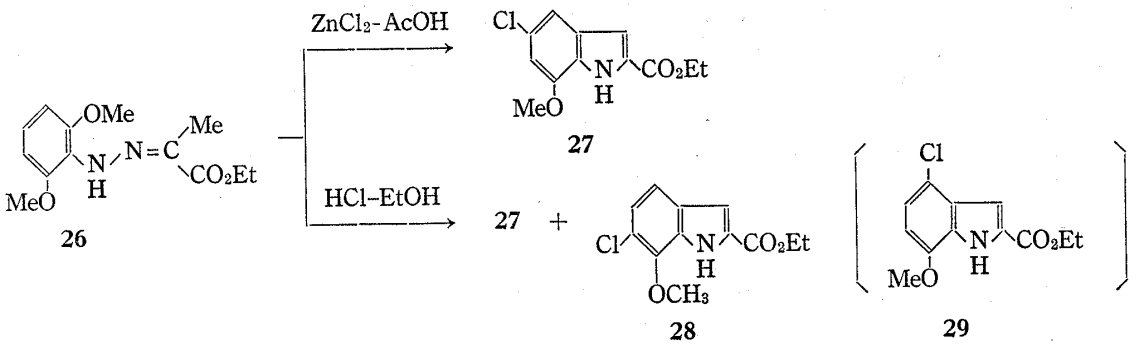


Chart 5

Treatment of (E)-ethyl pyruvate 2,6-dimethoxyphenylhydrazhone (**26**) with zinc chloride gave ethyl 5-chloro-7-methoxyindole-2-carboxylate (**27**) as a sole indolic product in 3.9% yield. On the other hand, treatment of the above hydrazone (**26**) with ethanolic hydrogen chloride gave the same indole (**27**) as a main product in 36.7% yield together with a small amount of ethyl 6-chloro-7-methoxyindole-2-carboxylate (**28**) in 5.5% yield, which had been predicted to be a main product on treatment with protic acid from formal deduction. The structure of the former indole product (**27**) was established by the fact that its NMR spectrum has two doublets at 3.14 and 2.81 τ coupled with each other (J=1.7 Hz). Such a smaller coupling constant shows that the indole derivative (**27**) has two aromatic protons situated at the *meta* position to each other. On the latter compound (**28**), its NMR spectrum has two 1H doublets having a rather larger coupling constant (J=8.6 Hz) at 3.00 and 2.74 τ coupled with each other. This spectral data remained only two structural possibilities of ethyl 6-chloro-7-methoxy- (**28**) or 4-chloro-7-methoxy- (**29**) indole-2-carboxylate for the product. Since the above product, mp 90—91°, has quite different physical properties from those of an authentic sample of ethyl 4-chloro-7-methoxyindole-2-carboxylate (**29**), mp 133—134°, which was synthesized by Fischer indolization of ethyl pyruvate 5-chloro-2-methoxyphenylhydrazone[11)] (**30**), it should be assigned to ethyl 6-chloro-7-methoxyindole-2-carboxylate

11) H. Ishii and Y. Murakami, unpublished results.

(**28**). These observation demonstrates the fact that an introduction of some additional substituent on the benzene ring of the starting phenylhydrazone affected the direction of the main process of the abnormal transformation by its electronic effect. The consideration of the above data allows us to suppose that the electron density of a benzene ring of a starting phenylhydrazone is another important factor for determination of direction of the abnormal transformation in addition to the nature of the acid catalyst. In other words, the substituent on the benzene ring of the phenylhydrazone has a big effect on the mode of these abnormal transformation.

This explanation leads us to suppose that the acid strength of the reagent employed as a catalyst is also an important factor for direction of the abnormal transformation from different point of view. In fact, ethyl pyruvate 2,6-dichlorophenylhydrazone (**14**) did not subject to Fischer indolization, when treated with ethanolic hydrogen chloride or sulfuric acid in ethanol, but to give ethyl 5,7-dichloroindole-2-carboxylate (**15**), when treated with mixed sulfuric and acetic acids. Since, in comparing the acidities of solution of a single acid in a number of different solvents, the most strong acid solution is that in which ionization is least, we may conclude that the acid strength of sulfuric acid in acetic acid is stronger than ethanol.[12] Therefore, the above experiment shows the propriety of our assumption that acid strength is of importance on the abnormal Fischer indolization.

Furthermore, treatment of ethyl pyruvate 2-methoxyphenylhydrazone (**1**) with mixed sulfuric and acetic acids gave a mixture of three indolic products, ethyl 7-methoxy- (**2**), 5-methoxy- (**24**) and unsubstituted (**23**) indole-2-carboxylates. Evidently, this product pattern is similar to that by the reaction due to Lewis acid rather than due to protic acid. As described in the preceding paper,[1] the result obtained by treatment of the same hydrazone (**1**) with sulfuric acid in ethanol is compatible with those by the cyclization with other protic acid. The difference of these product patterns due to changing the solvent also illustrates the importance of acid strength of an acid catalyst to the direction of the abnormal transformation.

It seems that the evidences mentioned so far provided a fairly complicated situation on the discussion of the determinants of the direction of the abnormal Fischer indolization. However, we may roughly summarize the above phenomenon to the following categories.

The first is an electron density and its distribution on a benzene ring of the starting phenylhydrazone. Although it is very difficult to express the effect of it quantitatively, it is well known that the presence of electron donative group on a benzene ring facilitates the cyclization of a phenylhydrazone in the reaction with acid catalyst. This chemical common sence was also observed in our abnormal Fischer indolization. Acceleration of cyclization by introduction of an alkyl group at the N_A-nitrogen of a phenylhydrazone and the effect of the second substituent on a benzene ring may be ascribed to this factor. And also, we may say that the *ortho* substituted phenylhydrazone having a high electron density on its benzene ring is apt to give the 5-substituted indolic products rather than the 6-substituted on the abnormal Fischer indolization.

The second is the acid strength of the reagent used for a catalyst. It is well known that the comparative study of behavior of acid strength of protic acid (Brønsted acid) is relatively easy, because their catalytic action must be a protopy of them and there are a number of measures of acid strength like pH or H_0 function.[13] On the other hand, the acid strength of Lewis acid can not be evaluated unequivocally by a single common criterion, because it depends upon many factors such as ionic radii, the mode of the bonding in the molecule and so on.[13] Moreover, the direction of formation of product must be actually corresponding

12) H.S. Gould, "Mechanism and Structure in Organic Chemistry," Henry Holt and Company, Inc., New York, 1960, p. 96.

13) K. Tanabe and T. Takeshita, "Acid-Base Catalysis," Sangyo-Tosho Pub. Co., Ltd., Tokyo, 1966, p. 99.

to the correlationship between an electron density of phenylhydrazone and an acid strength of an acid catalyst applied. Therefore, presumption of direction of abnormal Fischer indolization is impossible from the consideration of a single factor. In spite of such a complexity of the determinants, the abnormal Fischer indolization is very favourably inclined toward formation of the 5-substituted indole products under the stronger acidic condition.

The third is a nucleophilicity of nucleophiles present in the reaction mixture. This factor could be supposed to be of real importance, because the process to a 6-substituted indole derivative should be controlled by possibility of addition of nucleophiles to the key intermediate cation (**3**). These considerations provide us a plausible explanation to the difference in formation of products due to ethanolic hydrogen chloride and zinc chloride in acetic acid on cyclization of ethyl pyruvate 2-methoxyphenylhydrazone (**1**). Under the condition of ethanolic hydrogen chloride, ethanol molecule and chloride anion could behave as nucleophiles and add to the key intermediate cation (**3**) at C_6 to give a neutral intermediate followed by loss of methanol molecule. The acidity of this reagent system is not enough to take place substitution of a methoxy group of the key intermediate cation (**3**) with chloride anion at C_5 as a main process. On the other hand, zinc chloride in acetic acid is so stronger acidic than the former reagent system that it is enough to occur S_N2' (S_N1' or S_Ni') reaction at a methoxy group and C_5 position of the key intermediate cation (**3**). It may be accounted as one of accelerative factors for such a substitution reaction that the coordinate complex of the cation (**3**) with zinc chloride easily collapsed to 5-chloroindole product by S_Ni' mechanism (Chart 2) proposed by Carlin. The almost same mechanism may be adapted to formation of 5-chloroindole derivative on treatment of ethyl pyruvate 2-methoxyphenylhydrazone derivative with zinc chloride.

It should be noted here that the strong acid on the indolization of the *ortho*-substituted phenylhydrazone gives a migrated indolic product of the substituent to C_5 position of the indole nucleus. Such a migration might be formally explained by a suprafacial 1,3-shift accompanying an inversion of a σ orbital on an oxygen atom or chlorine. However, we are not allowed to conclude in such a manner, because there is no chemical evidences that establish the mechanism, a concerted process or an ionic one, for the reaction pathway from the key intermediate cation (**3**). Therefore, although the mechanism is remained unclear, it is reasonably supposed that indolization of the *ortho*-substituted phenylhydrazone having high electron density on a benzene ring would give a migrated indolic product of the substituent to C_5 position in addition to a normally expected 7-substituted indole in Fischer sense under the rather stronger acid condition and in the absence of an active nucleophile in the reaction mixture.

In the addition to the above three factors, we may imagine some other factors such as a nucleophilicity of a leaving group, steric factors of additional substituent on the starting phenylhydrazone and so on. However, further experiments are required to discuss on these matters.

Experimental[14]

(Z)-Ethyl Pyruvate 2,6-Dichlorophenylhydrazone (14a)——A solution of 2,6-dichlorobenzene diazonium chloride prepared from 16.2 g of 2,6-dichloroaniline, 26 ml of conc. HCl, 40 ml of water and 7.6 g of $NaNO_2$ was partially neutralized with 6.6 g of AcONa at 0°. A solution of 7.2 g of KOH in 10 ml of water was added to a solution of 15.8 g of ethyl α-methylacetoacetate in 100 ml of EtOH at 0°, followed by addition of 150 g of ice. The diazotized solution was then added dropwise to the mixture with stirring and the pH was adjusted to 5. After stirring for 6 hr at 0°, the product was extracted with ether. The extract was washed with dil. $NaHCO_3$ aq., dried over $MgSO_4$ and evaporated. The residue (32.3 g) was dissolved in 100 ml of 10% v/v ethanolic H_3PO_4 and refluxed for 20 min. After cooling, the mixture was poured into water and extracted with ether. The ethereal solution was washed with dil. $NaHCO_3$ aq., dried over $MgSO_4$ and evaporated.

14) The remark to the experimental part and physical constants and preparation of the compound marked with asterisk appeared in the preceding paper.

The residue (28.8 g) in benzene was chromatographed on silicic acid. First elution with benzene gave 8.33 g of yellow needles, mp 61—62°, which were recrystallized from hexane. *Anal.* Calcd. for $C_{11}H_{12}O_2N_2Cl_2$: C, 48.02; H, 4.40; N, 10.18. Found: C, 48.23; H, 4.45; N, 10.45. IR ν_{max}^{Nujol} cm^{-1}: 3210 (NH), 1670 (C=O). NMR (CCl_4) τ: 8.63 (3H, t, J=7.5 Hz, $CH_2C\underline{H}_3$), 7.88 (3H, s, vinyl CH_3), 5.72 (2H, q, J=7.5 Hz, $OC\underline{H}_2CH_3$), 3.15 (1H, t, J=8.0 Hz, C_4-H), 2.75 (2H, d, J=8.0 Hz, C_3 and C_5-H), −1.94 (1H, br. s, NH). Mass Spectrum *m/e*: 276 (M^++2, 69.6% intensity of M^+), 274 (M^+).

(E)-Ethyl Pyruvate 2,6-Dichlorophenylhydrazone (14b)——Second elution with benzene gave 3.78 g of yellow needles, mp 47—49°, which were recrystallized from hexane–ether. *Anal.* Calcd. for $C_{11}H_{12}O_2N_2Cl_2$: C, 48.02; H, 4.40; N, 10.18. Found: C, 48.11; H, 4.14; N, 10.07. IR ν_{max}^{Nujol} cm^{-1}: 3350 (NH), 1685 (C=O). NMR (CCl_4) τ: 8.70 (3H, t, J=7.5 Hz, $CH_2C\underline{H}_3$), 7.90 (3H, s, vinyl CH_3), 5.81 (2H, q, J=7.5 Hz, $OC\underline{H}_2CH_3$), 3.07 (1H, t, J=8.0 Hz, C_4-H), 2.71 (2H, d. J=8.0 Hz, C_3 and C_5-H), 2.50 (1H, br. s, NH). Mass Spectrum *m/e*: 276 (M^++2, 68.2% intensity of M^+), 274 (M^+).

Fischer Indolization of (Z)-Ethyl Pyruvate 2,6-Dichlorophenylhydrazone (14a) with Zinc Chloride in Acetic Acid. Ethyl 5,7-Dichloroindole-2-carboxylate (15)——A mixture of 10 g of (Z)-ethyl pyruvate 2,6-dichlorophenylhydrazone (**14a**) and 100 g of anhydrous $ZnCl_2$ in 120 ml of AcOH was refluxed for 30 min, cooled, diluted with water and then extracted with ether. The ethereal solution was washed with $NaHCO_3$ aq., dried over $MgSO_4$ and evaporated. The residue was recrystallized from EtOH or benzene alternatively to give 6.22 g of colourless needles, mp 156—156.5° (lit.[6] 156—156.5°). An additional amount of this material was obtained by the following separation work. Total yield 7.71 g. *Anal.* Calcd. for $C_{11}H_9O_2NCl_2$: C, 51.18; H. 3.51; N. 5.43. Found: C. 51.26; H. 3.37; N, 5.07. IR ν_{max}^{Nujol} cm^{-1}: 3290 (NH), 1695 (C=O). NMR ($CDCl_3$) τ: 8.59 (3H, t, J=7.3 Hz, $CH_2C\underline{H}_3$), 5.58 (2H, q, J=7.3 Hz, $OC\underline{H}_2CH_3$), 2.86 (1H, d, J=2.0 Hz, C_3-H), 2.70 (1H, d, J=2.0 Hz, C_4 or C_6-H), 2.45 (1H, d, J=2.0 Hz, C_6 or C_4-H), 0.90 (1H, br. s, NH). Mass Spectrum *m/e*: 259 (M^++2, 66.6% intensity of M^+), 257 (M^+).

Ethyl 5-Acetoxy-7-chloroindole-2-carboxylate (16)——The mother liquor of the above recrystallization of ethyl 5,7-dichloroindole-2-carboxylate (**15**) was evaporated to dryness *in vacuo*. The residue (2.41 g) in benzene was chromatographed on silicic acid. Elution with benzene gave 1.49 g of above ethyl 5,7-dichloroindole-2-carboxylate (**15**). Followed elution with chloroform gave 78 mg of colourless needles, mp 160—165°, which were recrystallized from ether. IR ν_{max}^{Nujol} cm^{-1}: 3320 (NH), 1767 (phenol acetate), 1705 (C=O). NMR ($CDCl_3$) τ: 8.60 (3H, t, J=7.0 Hz, $CH_2C\underline{H}_3$), 7.70 (3H, s, $COCH_3$), 5.60 (2H, q, J=7.0 Hz, $OC\underline{H}_2CH_3$), 2.91 (1H, d, J=2.0 Hz, C_4 or C_6-H), 2.81 (1H, d, J=2.0 Hz, C_3-H), 2.71 (1H, d, J=2.0 Hz, C_6 or C_4-H), 0.98 (1H, br. s, NH). Mass Spectrum *m/e*: 283 (M^++2, 38.4% intensity of M^+), 281 (M^+).

Ethyl 4-Acetyl-7-chloro-3-hydroxyindole-2-carboxylate (17)——Elution with AcOEt on the above column chromatography gave 600 mg of an oily product. It was triturated with chloroform to give 121 mg of colourless needles, mp 207—208°, which were recrystallized from ether. *Anal.* Calcd. for $C_{13}H_{12}O_4NCl$: C, 55.43; H, 4.29; N, 4.97. Found: C, 55.43; H, 4.29; N, 5.27. IR ν_{max}^{Nujol} cm^{-1}: 3295 (NH), 3250 (br.) (OH), 1725, 1615 (C=O). NMR ($CDCl_3$) τ: 8.57 (3H, t, J=7.2 Hz, $CH_2C\underline{H}_3$), 7.20 (3H, s, $COCH_3$), 5.57 (2H, q, J=7.2 Hz, $OC\underline{H}_2CH_3$), 2.98 (1H s, C_6-H), 2.68 (1H, d, J=2.0 Hz, C_3-H), 0.79 (1H, br. s, NH), −3.54 (1H, s, OH).
Mass Spectrum *m/e*: 283 (M^++2, 39.6% intensity of M^+), 281 (M^+).

(Z)-Ethyl Pyruvate 2-Chlorophenylhydrazone[8] (20a)——To a solution of 14.7 g of ethyl α-methylacetoacetate in 100 ml of EtOH was added 13.7 g of 50% KOH aq. The 2-chlorobenzene diazonium chloride solution prepared from 13.0 g of *o*-chloroaniline, 22.0 g of conc. HCl, 80 ml of water and 7.75 g of $NaNO_2$ was added to the first solution under cooling. After addition, the mixture was stirred for 30 min, poured into water and extracted with benzene. The benzene extract was dried over $MgSO_4$ and evaporated to dryness *in vacuo*. The residue (22.716 g) was dissolved in a mixed solution of 12 ml of 85% H_3PO_4 and 50 ml of EtOH. The mixture was refluxed for 15 min, poured into water and extracted with benzene. The organic layer was washed with 5% $NaHCO_3$ aq., dried over $MgSO_4$ and evaporated to drynees *in vacuo*. The residue (19.282 g) in benzene was chromatographed on silicic acid. Elution with benzene gave 7.34 g of pale orange pillars, mp 72—73°, which were recrystallized from EtOH. *Anal.* Calcd. for $C_{11}H_{13}O_2N_2Cl$: C, 54.89; H, 5.44; N, 11.64. Found: C, 55.21; H, 5.16; N, 11.24. IR ν_{max}^{Nujol} cm^{-1}: 3212 (NH), 1679 (C=O). NMR (CCl_4) τ: 8.64 (3H t, J=7.0 Hz, $CH_2C\underline{H}_3$), 7.86 (3H s, vinyl CH_3), 5.73 (2H, q, J=7.0 Hz, $OC\underline{H}_2CH_3$), 3.33—2.35 (4H m, aromatic protons), −2.30 (1H, br. s, NH). Mass Spectrum *m/e*: 242 (M^++2, 34.0% intensity of M^+), 240 (M^+).

(E)-Ethyl Pyruvate 2-Chlorophenylhydrazone[8] (20b)——Further elution with benzene gave 5.386 g of pale yellow leaflets, mp 55—56.5°, which were recrystallized from pentane. *Anal.* Calcd. for $C_{11}H_{13}O_2N_2Cl$: C, 54.89; H, 5.44; N, 11.64. Found: C, 55.01; H, 5.39; N, 11.55. IR ν_{max}^{Nujol} cm^{-1}: 3350 (NH), 1694 (C=O). NMR (CCl_4) τ: 8.64 (3H, t, J=7.5 Hz, $CH_2C\underline{H}_3$), 7.91 (3H, s, vinyl CH_3), 5.77 (2H, q, J=7.5 Hz, $OC\underline{H}_2CH_3$), 3.28—2.27 (4H m, aromatic protons), 2.02 (1H, br. s, NH). Mass Spectrum *m/e*: 242 (M^++2, 35.0% intensity of M^+), 240 (M^+).

Fischer Indolization of (Z)-Ethyl Pyruvate 2-Chlorophenylhydrazone (20a) with Anhydrous Zinc Chloride in Acetic Acid——A mixture of 3.00 g of (E)-ethyl pyruvate 2-chlorophenylhydrazone (**20a**) and 12.0 g of anhydrous $ZnCl_2$ in 25 ml of AcOH was refluxed for 2 hr, 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 showed only two spots on TLC.

Ethyl 7-Chloroindole-2-carboxylate[8] (**21**)——The residue (2.44 g) in chloroform was chromatographed on silicic acid. Elution with chloroform gave 1.777 g of colourless needles, mp 113.5—114°, 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, 59.26; H, 4.58; N, 6.23. IR ν_{max}^{Nujol} cm^{-1}: 3313 (NH), 1715 (C=O). NMR (CCl_4) τ: 8.60 (3H, t, J=7.5 Hz, $CH_2C\underline{H}_3$), 5.64 (2H, q, J=7.5 Hz, $OC\underline{H}_2CH_3$), 3.02 (1H, t, J=8.2 Hz, C_5-H), 2.88 (1H, d, J=2.8 Hz, C_3-H), 2.77 (1H, d, J=8.2 Hz, C_6-H), 2.52 (1H, d, J=8.2 Hz, C_4-H), 0.98 (1H br. s, NH). Mass Spectrum *m/e*: 225 (M^++2, 35.0% intensity of M^+), 223 (M^+).

Ethyl 5-Chloroindole-2-carboxylate[8b] (**22**)——Further elution with chloroform gave 408 mg of ethyl 5-chloroindole-2-carboxylate* (**22**) as colourless needles, mp 172—173°, which were recrystallized from benzene–hexane.

Fischer Indolization of (Z)-Ethyl Pyruvate 2-Methoxyphenylhydrazone (1a) with Anhydrous Zinc Chloride in Acetic Acid——A mixture of 8.00 g of (Z)-ethyl pyruvate 2-methoxyphenylhydrazone* (**1a**) and 8.00 g of anhydrous $ZnCl_2$ in 60 ml of AcOH was refluxed for 25 min, cooled, diluted with water and extracted with ether. The ethereal solution was washed with dil. $NaHCO_3$ aq., dried over $MgSO_4$ and evaporated to dryness *in vacuo*. The residue (7.063 g) in benzene was chromatographed on Al_2O_3 (neutral, grade I) and divided into two fractions, elution with benzene (fraction A; 1.685 g) and with chloroform (fraction B; 1.950 g).

Ethyl 7-Methoxyindole-2-carboxylate* (**2**)——Recrystallization of fraction A from hexane–benzene gave 504 mg of ethyl 7-methoxyindole-2-carboxylate* (**2**) as colourless needles, mp 116—117°. An additional amount of this material was obtained from fraction B and D. Total yield 1.312 g.

Ethyl Indole-2-carboxylate* (**23**)——The mother liquor of recrystallization of ethyl 7-methoxyindole-2-carboxylate (**2**) was evaporated to dryness *in vacuo*. The residue in benzene was chromatographed on silicic acid. Elution with benzene was diveded into three fractions (fraction C, 186 mg, fraction D. 836 mg, and fraction E, 14 mg, in the order of elution). Fraction C gave a mixture of two indolic compounds detected by TLC. The mixture in a mixed solution of cyclohexane and EtOH (95: 5) was rechromatographed on silicic acid. First elution with the mixed solution gave 58 mg of ethyl indole-2-carboxylate* (**23**) as colourless needles, mp 121—123°, which were recrystallized from hexane–benzene.

Ethyl 5-Chloroindole-2-carboxylate* (**22**)——Further elution with the mixed solution on the above rechromatography gave 100 mg of ethyl 5-chloroindole-2-carboxylate* (**22**) as colourless needles, mp 171—172°, which were recrystallized from hexane–benzene.

Recrystallization of fraction D from hexane–benzene gave additional 726 mg of ethyl 7-methoxyindole-2-carboxylate* (**2**).

Ethyl 5-Methoxyindole-2-carboxylate (**24**)——Recrystallization of fraction E from hexane–benzene gave 10 mg of colourless leaflets, mp 158—162°. *Anal.* Calcd. for $C_{12}H_{13}O_3N$: C, 65.74; H, 5.98; N, 6.39. Found: C, 65.94; H, 5.90; N, 6.40. IR ν_{max}^{KBr} cm^{-1}: 3296 (NH), 1681 (C=O). NMR ($CDCl_3$) τ: 8.61 (3H, t, J=7.5 Hz, $CH_2C\underline{H}_3$), 6.18 (3H, s, OCH_3), 5.62 (2H, q, J=7.5 Hz, $OC\underline{H}_2CH_3$), 3.09—2.42 (4H, m, aromatic protons and C_3-H), 1.17 (1H, br. s, NH). It was identified with an authentic sample of ethyl 5-methoxyindole-2-carboxylate (**24**) prepared from ethyl pyruvate 4-methoxyphenylhydrazone[15] by Fischer indolization. Fraction B gave additional 40 mg of this material. Total yield 50 mg.

Ethyl 4-Methoxyindole-2-carboxylate* (**25**)——Fraction B showed three spots on TLC. Then fraction B in benzene was rechromatographed on silicic acid. After removal of first elution with benzene which gave additional 82 mg of ethyl 7-methoxyindole-2-carboxylate* (**2**), second elution gave 19 mg of ethyl 4-methoxyindole-2-carboxylate* (**25**) as colourless prisms, mp 170—175°, which were recrystallized from hexane. Further elution with benzene gave 40 mg of ethyl 5-methoxyindole-2-carboxylate* (**24**).

Fischer Indolization of (Z)-Ethyl Pyruvate 2-Methoxyphenylhydrazone (1a) with Boron Trifluoride in Acetic Acid——A mixture of 1.00 g of (Z)-ethyl pyruvate 2-methoxyphenylhydrazone* (**1a**) and 1.00 g of BF_3·ether in 10 ml of AcOH was refluxed for 30 min, poured into water and extracted with benzene. The benzene layer was washed with 5% $NaHCO_3$ aq., dried over $MgSO_4$ and evaporated to dryness *in vacuo*. The residue (511 mg) in benzene was chromatographed on silicic acid. Elution with benzene was followed by TLC and divided into three fractions (fraction A, B and C in the order of elution). Recrystallization of fraction A from hexane gave 17 mg of ethyl indole-2-carboxylate* (**23**) as colourless needles, mp 123—124°.

Recrystallization of fraction B from hexane gave 126 mg of ethyl 7-methoxyindole-2-carboxylate* (**2**) as colourless needles, mp 113—116°.

Recrystallization of fraction C from hexane gave 27 mg of ethyl 5-methoxyindole-2-carboxylate (**24**) as colourless pillars, mp 158—161°.

Fischer Indolization of (Z)-Ethyl Pyruvate 2-Methoxyphenylhydrazone* (1a) with Boron Trifluoride in Ethyl Acetate——A mixture of 1.00 g of (Z)-ethyl pyruvate 2-methoxyphenylhydrazone* (**1a**) and 5.00 g

15) G.K. Hughes, F. Lion, J.G. McKean, A.J. Murray, V. Callana, D.H. Freeman, C.S. Ralph, R. Rassack, J. Dombroski, F. Finch, R. Andrews, R.C. Betty, R.H. Scott, C.W. Vernon, A. Flack and C.H. Laurence, *J. Pro. Roy. Soc. N.S. Wales*, **71**, 475 (1938) [*C. A.*, **33**, 587[8] (1939)].

of BF_3·ether in 50 ml of ethyl acetate was refluxed for 4.5 hr. After cooling, the mixture was diluted with ethyl acetate, washed with 5% $NaHCO_3$ aq., dried over $MgSO_4$ and evaporated to dryness *in vacuo*. The same isolation and purification work of the residue as described in the above item with BF_3·ether in AcOH gave 22 mg of ethyl indole-2-carboxylate* (**23**), mp 123—124°, 139 mg of ethyl 7-methoxyindole-2-carboxylate* (**2**), mp 117.5—118.5°, and 44 mg of ethyl 5-methoxyindole-2-carboxylate (**24**), mp 160—161.5°.

Fischer Indolization of (Z)-Ethyl Pyruvate 2-Methoxyphenylhydrazone* (1a) with Mixed Sulfuric and Acetic Acids——A mixture of 1.00 g of (Z)-ethyl pyruvate 2-methoxyphenylhydrazone* (**1a**) and 650 mg of sulfuric acid in 10 ml of AcOH was refluxed for 30 min. 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 *in vacuo*. The same isolation and purification work of the residue (388 mg) as described in the item with BF_3·ether in AcOH gave 2 mg of ethyl indole-2-carboxylate* (**23**), mp 121.2—124°, 46 mg of ethyl 7-methoxyindole-2-carboxylate* (**2**), mp 115—117°, and 3 mg of ethyl 5-methoxyindole-2-carboxylate (**24**), mp 158—161°.

(E)-Ethyl Pyruvate 2,6-Dimethoxyphenylhydrazone (26)——To a mixture of 13.8 g of 2,6-dimethoxyaniline,[16] 20.7 g of conc. HCl and 72 ml of water was added 6.8 g of $NaNO_2$ by a small portion below 4°. A solution of 6.1 g of KOH in 6.1 ml of water was added to a solution of 13.7 g of ethyl α-methyl acetoacetate in 90 ml of EtOH and the diazotized solution was added dropwise to the mixture below 4°. After stirring for 30 min, the mixture was diluted with a lot of water, extracted with benzene, dried over $MgSO_4$ and evaporated to dryness *in vacuo*. The residue (21.5 g) in benzene was chromatographed on silicic acid. Elution with benzene was divided into two fractions followed by TLC. The first fraction gave 276 mg of colourless oil which was purified by the distillation, bp 87° at 25 mmHg. NMR (CCl_4) τ: 6.27 (6H, s, $2\times OCH_3$), 3.73—3.56 (3H, m, aromatic protons), 2.95 (1H, t, $J=7.5$ Hz, C_5-H). Mass Spectrum *m/e*: 138 (M^+). This substance was identified with a sample of 1,3-dimethoxybenzene by comparison of IR spectra. The second fraction gave 1.62 g of yellow oil which may be composed by (Z)-isomer. But, as (Z)-isomer was observed to be isomerized to (E)-isomer during column chromatography, purification of (Z)-form was given up. Following elution with a mixed solution of benzene and chloroform (1: 1) gave 6.6 g of yellow needles, mp 70—71°, which were recrystallized from hexane. *Anal.* Calcd. for $C_{13}H_{18}O_4N_2$: C, 58.63; H, 6.81; N, 10.52. Found: C, 58.38; H, 6.75; N, 10.37. IR ν_{max}^{Nujol} cm^{-1}: 3313 (NH), 1692 (C=O). NMR (CCl_4) τ: 8.68 (3H, t, $J=7.0$ Hz, $CH_2C\underline{H}_3$), 7.92 (3H, s, vinyl CH_3), 6.16 (6H, s, $2\times OC\underline{H}_3$), 5.78 (2H, q, $J=7.0$ Hz, $OC\underline{H}_2CH_3$), 3.46 (2H, d, $J=8.0$ Hz, C_3 and C_5-H), 3.09 (1H, t, $J=8.0$ Hz, C_4-H), 2.56 (1H, br. s, NH). Mass Spectrum *m/e*: 266 (M^+).

Fischer Indolization of (E)-Ethyl Pyruvate 2,6-Dimethoxyphenylhydrazone (26) with Zinc Chloride in Acetic Acid. Ethyl 5-Chloro-7-methoxyindole-2-carboxylate (27)——A mixture of 2.13 g of (E)-ethyl pyruvate 2,6-dimethoxyphenylhydrazone (**26**) and 2.18 g of anhydrous $ZnCl_2$ in 20 ml of AcOH was refluxed for 25 min, cooled, poured into ice water and extracted with ether. The ethereal solution was washed with 5% $NaHCO_3$ aq., dried over $MgSO_4$ and evaporated to dryness. The residue in benzene was chromatographed on silicic acid. Elution with benzene gave 79 mg of colourless needles, mp 137—137.5°, which were recrystallized from hexane. *Anal.* Calcd. for $C_{12}H_{12}O_3NCl$: C, 56.81; H, 4.77; N, 5.52. Found: C, 56.89; H, 4.66; N, 5.39. IR ν_{max}^{Nujol} cm^{-1}: 3318 (NH), 1709 (C=O). NMR (CCl_4) τ: 8.60 (3H, t, $J=7.0$ Hz, $CH_2C\underline{H}_3$), 6.08 (3H, s, OCH_3), 5.65 (2H, q, $J=7.0$ Hz, $OC\underline{H}_2CH_3$), 3.41 (1H, d, $J=1.7$ Hz, C_4 or C_6-H), 3.02 (1H, d, $J=1.0$ Hz, C_3-H), 2.83 (1H, d, $J=1.7$ Hz, C_6 or C_4-H), 0.92 (1H, br. s, NH). Mass Spectrum *m/e*: 255 (M^++2, 34.4% intensity of M^+), 253 (M^+).

Fischer Indolization of (E)-Ethyl Pyruvate 2,6-Dimethoxyphenylhydrazone (26) with Ethanolic Hydrogen Chloride. i) Ethyl 5-Chloro-7-methoxyindole-2-carboxylate (27)——A solution of 1.00 g of ethyl pyruvate 2,6-dimethoxyphenylhydrazone (**26**) in 20 ml of saturated ethanolic hydrogen chloride was refluxed for 10 min. After cooling, the mixture was diluted with water and extracted with ether. The ethereal solution was dried over $MgSO_4$ and evaporated to dryness. Recrystallization of the residue from benzene–hexane gave 132 mg of colourless needles, mp 137—137.5°, which were identified with a sample of ethyl 5-chloro-7-methoxyindole-2-carboxylate (**27**) by comparison of IR spectra and the mixed melting point determination. Additional amount of this material was obtained by the following separation work. Total yield 349 mg.

ii) Ethyl 6-Chloro-7-methoxyindole-2-carboxylate (28)——The mother liquor of the above recrystallization was evaporated to dryness *in vacuo*.. The residue (564 mg) was chromatographed on silicic acid. First elution with benzene gave 217 mg of ethyl 5-chloro-7-methoxyindole-2-carboxylate (**27**). Successive elution with benzene gave 48 mg of colourless plates, mp 90—91°, which were recrystallized from hexane. *Anal.* Calcd. for $C_{12}H_{12}O_3NCl$: C, 56.81; H, 4.77; N, 5.52. Found: C, 57.05; H, 4.75; N, 5.40. IR ν_{max}^{Nujol} cm^{-1}: 3305 (NH), 1696 (C=O). NMR (CCl_4) τ: 8.59 (3H t, $J=7.5$ Hz, $CH_2C\underline{H}_3$), 6.00 (3H, s, OCH_3), 5.58 (2H, q, $J=7.5$ Hz, $OC\underline{H}_2CH_3$), 3.00 (1H, d, $J=8.6$ Hz, C_4 or C_5-H), 2.92 (1H, d, $J=2.0$ Hz, C_3-H), 2.74 (1H, d, $J=8.6$ Hz, C_5 or C_4-H), 0.44 (1H br. s, NH). Mass Spectrum *m/e*: 255 (M^++2, 33.0% intensity of M^+), 253 (M^+). The melting point was depressed on admixture with a sample of ethyl 4-chloro-7-methoxyindole-2-carboxylate[11] (**29**), mp 133—134°.

16) H. Kauffmann and E. de Pay, *Ber.*, **37**, 725 (1904).

Fischer Indolization of (Z)-Ethyl Pyruvate 2,6-Dichlorophenylhydrazone (14a) with Mixed Sulfuric and Acetic Acids——A mixture of 2.00 g of (Z)-ethyl pyruvate 2,6-dichlorophenylhydrazone (**14a**) and 1.10 g of sulfuric acid in 15 ml of AcOH was refluxed for 1 hr. After cooling, the 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. The residue (718 mg) in benzene was chromatographed on silicic acid. Elution with benzene gave 40 mg of ethyl 5,7-dichloroindole-2-carboxylate (**15**) as colourless needles, mp 159—160°, which were recrystallized from cyclohexane.

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