# Fischer Indolization of Variously *ortho*-Substituted Phenylhydrazones (Fischer Indolization and Its Related Compounds. XXV[1])

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**Various kinds of ethyl pyruvate 2-(2-substituted phenyl)hydrazones (1) were subjected to Fischer indolization with acid catalysts. All the phenylhydrazones gave corresponding normal 7-substituted indoles (2). In addition, phenylhydrazones whose *ortho*-substituent is electron-donative or has a central atom with an unshared electron pair tended to give the 4- or 5-substituted indole (3), which was produced by migration of the *ortho*-substituent during cyclization, whereas those whose *ortho*-substituent is electron-attractive tended to give little or no such abnormal product. The kind of acid catalyst used had some effect on the yield ratio of products but not on the kind of products.**

**Keywords** Fischer indolization; indole; phenylhydrazone; *ortho*-substituted; migration; substituent effect

In previous papers[2] we reported that Fischer indolization of *ortho*-monosubstituted (methoxy or chloro) phenylhydrazones (**1**) gave abnormal indoles (**3**) as a result of cyclization toward the occupied *ortho*-position, in addition of the expected 7-substituted indole (**2**). It had been believed until that time that Fischer indolization of such phenylhydrazones (**1**) gave only normal indoles (**2**). We called the reactions "abnormal Fischer indolization." In these reactions, the results seemed to vary according to the kind of *ortho*-substituent in the phenylhydrazone and the acid catalyst. Thus, we were interested in what rule governs the abnormal Fischer indolization. We report here the results of the Fischer indolization of variously *ortho*- (or 2-) substituted phenylhydrazones (**1**) and discuss their generality.

## Results and Discussion

**Preparation of *ortho*-Substituted Phenylhydrazones (1)** Phenylhydrazones (**1**) were generally prepared starting from *ortho*-substituted anilines (**4**) *via* diazotization, followed by Japp–Klingemann reaction as used in our previous procedure.[2] The *o*-acetoamidophenylhydrazone (**1b**) was prepared by reduction followed by acetylation of *o*-nitrophenylhydrazone (**1h**), because diazotization of *o*-acetoamidoaniline (**4**, X=NHAc) had been reported[4] to give 1-acetylbenztriazole (**5**) *via* the diazonium salt. Phenylhydrazones (**1**) thus prepared consisted of *Z*- and *E*-geometrical isomers which were easily separated by column chromatography over silica gel. The *Z*- and *E*-isomers were identified from their IR and $^1$H-NMR spectra on the basis of our reported method.[2a] We showed previously that these geometrical isomers are rapidly interconvertible by the acid catalysts used for Fischer indolization and thus give the same result on Fischer indolization.

**Fischer Indolization** The Fischer indolization of the phenylhydrazones (**1**) was carried out mainly with hydrogen chloride in ethanol and zinc chloride in acetic acid for comparison with previous results,[2] but *p*-toluenesulfonic acid[5] (TsOH) in benzene and polyphosphoric acid (PPA) were used when the above two catalysts gave unsatisfactory results. The results are summarized in Table I.

PPA caused the reaction to proceed the most rapidly, whereas HCl/EtOH was least effective. Indeed, the reaction of the 2-trifluoromethylphenylhydrazone (**1i**) proceeded with $ZnCl_2$/AcOH, but not with HCl/EtOH. The reaction of the 2-nitrophenylhydrazone (**1h**) did not proceed until PPA was used (the other reagents gave poor results). The 2-methylthiomethylphenylhydrazone (**1e**) did not react with HCl/EtOH but gave a complex mixture with $ZnCl_2$/AcOH. The reaction was successfully carried out with TsOH in benzene. The Fischer indolization of the 2-chlorophenylhydrazone (**1f**) with HCl/EtOH successfully proceeded at 110°C in a sealed tube to give only the nomal 7-chloroindole (**2f**), whereas the same reaction under atmospheric pressure did not proceed at all.[2b] The reaction

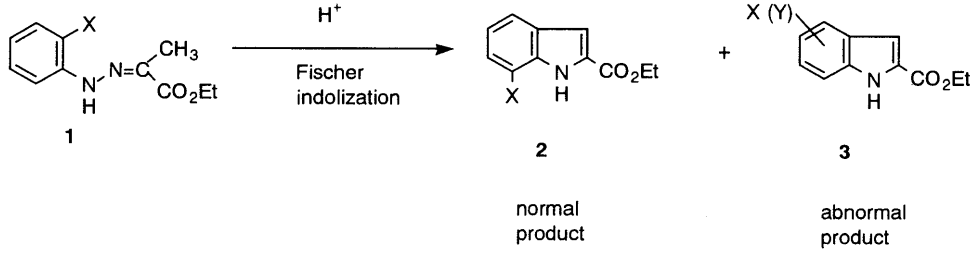



Chart 1

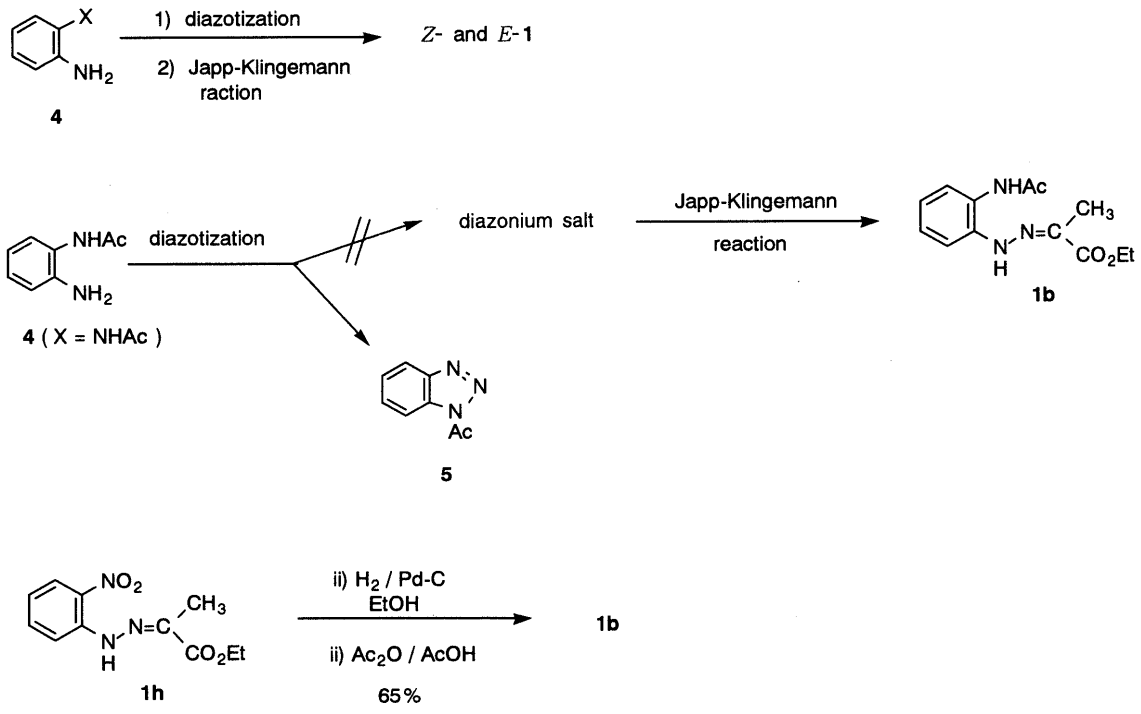



Chart 2

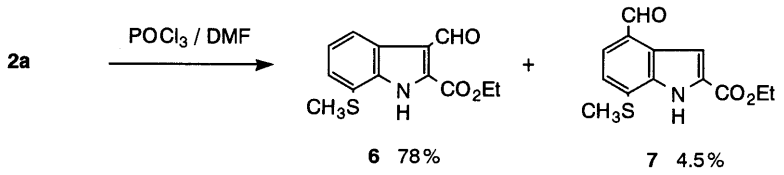
TABLE I. Fischer Indolization of Various *ortho*-Substituted Phenylhydrazones (**1**)

| Phenylhydrazones (**1**), X= | Conditions | | | Products | |
|---|---|---|---|---|---|
| | Acid catalyst | Temp. | Time | Normal (**2**) | Abnormal (**3**) |
| $-SCH_3$ (**1a**) | HCl/EtOH | Reflux | 4.5 h | **2a**,[a] 26% | Ethyl 1*H*-indole-2-carboxylate[a] (**3a-1**), 9.4%<br>Ethyl 3-methylthio-1*H*-indole-2-carboxylate (**3a-2**), 2.6%<br>Ethyl 2-(2-ethoxycarbonylindol-3-yl)acrylate (**3a-3**), 2.7% |
| | $ZnCl_2$/AcOH | Reflux | 5 h | **2a**, 24% | **3a-1**, 11%; **3a-2**, 6.8% |
| –NHAc (**1b**) | HCl/EtOH | Reflux | 1 h | Many spots on TLC, not isolated | |
| | $ZnCl_2$/AcOH | Reflux | 1.5 h | **2b**, 23% | Ethyl 5-acetoamido-1*H*-indole-2-carboxylate (**3b-1**), 27% |
| –Ph (**1c**) | HCl/EtOH | Reflux | 1 h | Many spots on TLC, not isolated | |
| | $ZnCl_2$/AcOH | Reflux | 30 min | **2c**, 61% | Ethyl 4-phenyl-1*H*-indole-2-carboxylate (**3c-1**), 21% |
| $-CH_3$[3] (**1d**) | HCl/EtOH | Reflux | 2 h | **2d**, 36% | Ethyl 1*H*-indole-2-carboxylate (**3d-1**), 10% |
| | $ZnCl_2$/AcOH | 50 °C | 3 h | **2d**, 61% | **3d-1**, 2.0%<br>Ethyl 4-methyl-1*H*-indole-2-carboxylate (**3d-2**), 4.7% |
| $-CH_2SCH_3$ (**1e**) | TsOH/benzene | Reflux | 3 h | **2e**, 32% | No abnormal product isolated |
| –Cl (**1f**) | HCl/EtOH | 110 °C | 2 h | **2f**, 34% | Trace on TLC |
| | $ZnCl_2$/AcOH[2b] | Reflux | 2 h | **2f**, 64% | Ethyl 5-chloro-1*H*-indole-2-carboxylate (**3f-1**), 15% |
| –OTs[6] (**1g**) | PPA | 80 °C | 30 min | **2g**, 37% | Ethyl 5-tosyloxy-1*H*-indole-2-carboxylate (**3g-1**), 9.9% |
| $-NO_2$ (**1h**) | HCl/EtOH | Reflux | 1.5 h | No reaction (starting material recovered) | |
| | $ZnCl_2$/AcOH | Reflux | 4 h | No reaction (starting material recovered) | |
| | PPA[7] | 120 °C | 30 min | **2h**, 78% | No abnormal product isolated |
| $-CF_3$ (**1i**) | HCl/EtOH | 110 °C | 2.5 h | No reaction (starting material recovered) | |
| | $ZnCl_2$/AcOH | Reflux | 1.5 h | **2i**, 25% | No abnormal product isolated |

*a*) The product was found to contain a trace amount of the corresponding 3-chloro derivative.

of **1f** with $ZnCl_2$/AcOH was reported[2b] to give a significant amount of the abnormal 5-chloroindole (**3f-1**). Indolic products formed in these reactions were separated by column chromatography over silica gel. In Table I the abnormal products (**3**) in each run are arranged in order of elution.

**Identification of the Indolic Products** As most reactions gave multiple indolic products, careful characterization was required for all products including the normal 7-substituted indole, even in a case where only one product was obtained. The structure of unknown products, especially the position of the substituent, was generally estimated from the $^1$H-NMR spectra and finally determined by 1) alternative synthesis of an authentic sample, 2) leading the product to a known compound, or 3) inspection of the $^1$H-NMR spectrum of the 3-formyl derivative. The last "3-formyl derivative method" is a clear-cut and convenient method for characterizing $C_4$-H on the indole nucleus, which was used in our previous work.[8] Characterization of $C_4$-H is very important, because mere inspection of $^1$H-NMR pattern of the benzenoid protons in Fischer indolization product does not allow a sharp distinction



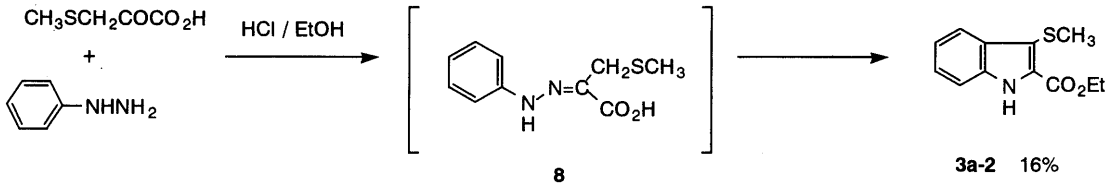
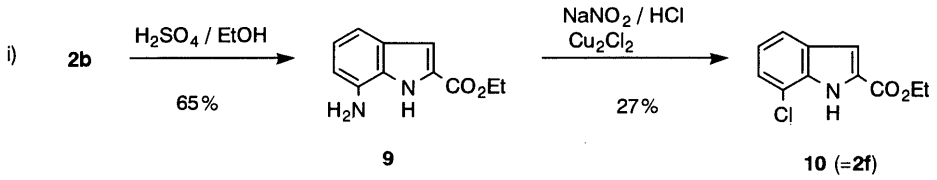




Chart 3



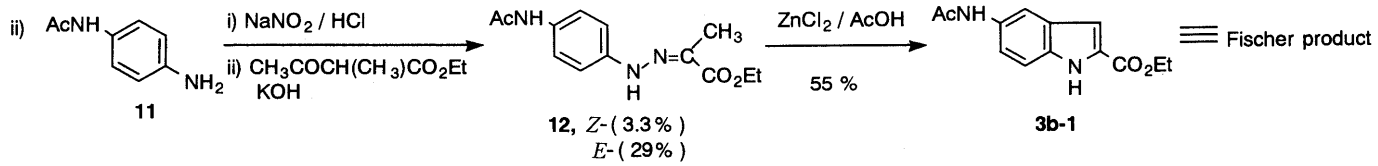




Chart 4

between $C_4$- and $C_7$-H, or $C_5$- and $C_6$-H, although $C_4$-H generally appears in the lowest region if the substituent on the benzenoid ring has a small effect on the chemical shift. Identification of each indolic product was made as follows.

1) The Products from Ethyl Pyruvate 2-(2-Methylthiophenyl)hydrazone (**1a**): The reaction with HCl/EtOH gave four products. The Vilsmeier–Haack reaction of the main product (**2a**) gave two formyl indoles (**6** and **7**). In the $^1$H-NMR of the major product (**6**) the downfield-shifted proton ($C_4$-H, from $\delta$ 7.47 to 8.10) appeared as a diffused double-doublet due to large (6.0 Hz) and small (2.5 Hz) coupling constants, showing that **6** is the 3-formyl-7-methylthioindole. The minor product (**7**) of the Vilsmeier–Haack reaction was found to be the 4-formyl derivative of **2a** by $^1$H-NMR [the presence of $C_3$-H (d, $J$=2.5 Hz), and $C_5$- and $C_6$-H having a large coupling constant (each doublet, $J$=8.0 Hz) with each other]. These data showed **2a** to be the 7-methylthioindole, the normal product.

The first abnormal product (**3a-1**) was found to have no substituent on the ethyl indole-2-carboxylate nucleus by means of the $^1$H-NMR spectrum and MS, being ethyl 1*H*-indole-2-carboxylate itself. The HPLC[2a] measured just after column chromatographic separation showed that this compound (**3a-1**) was contaminated with a trace amount of ethyl 3-chloro-1*H*-indole-2-carboxylate. Contamination of an abnormal indole produced from Fischer indolization with the corresponding 3-chloro congener has sometimes been observed.[2)]

The second abnormal product (**3a-2**) was ethyl 3-methylthio-1*H*-indole-2-carboxylate as judged from the $^1$H-NMR (a methylthio group at $\delta$ 2.40, no $C_3$-H, and four aromatic protons). The structure was confirmed by alternative synthesis as shown in Chart 3. Methylthiopyruvic acid phenylhydrazone (**8**) prepared from methylthiopyruvic acid and phenylhydrazine was refluxed in saturated ethanolic hydrogen chloride to give **3a-2** in 16% yield. The third abnormal product was suggested to be ethyl 2-(2-ethoxycarbonylindol-3-yl)acrylate (**3a-3**) by the $^1$H-NMR spectrum: two olefinic geminal protons appeared at $\delta$ 5.79 and 6.52 (each d, $J$=2.0 Hz), and there was no $C_3$-H signal. This compound was identical with the sample reported[5)] by the present authors.

The reaction with $ZnCl_2$/AcOH gave the normal product (**2a**) and two abnormal products (**3a-1** and **3a-2**). The former abnormal product (**3a-1**) was not contaminated with 3-chloro congeners at all.

2) The Products from Ethyl Pyruvate 2-(2-Acetoamidophenyl)hydrazone (**1b**): The reaction with $ZnCl_2$/AcOH

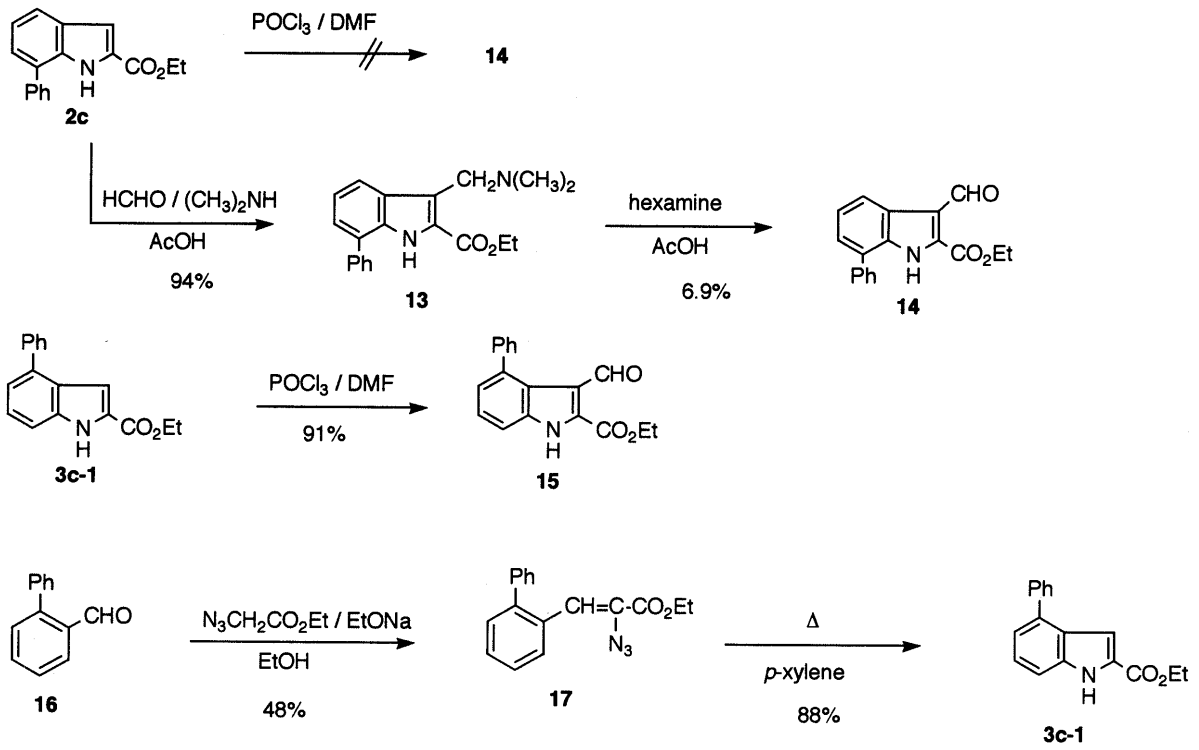



Chart 5

gave the two products (**2b** and **3b-1**), both of which have the same acetoamide group on an ethyl indole-2-carboxylate nucleus. One of the two (**2b**) is the 7-acetoamidoindole as judged from the $^1$H-NMR spectrum [$C_4$-H in the lowest region appeared as a double doublet ($J$=1.0 and 8.0 Hz)]. The other compound should be the 5-acetoamidoindole (**3b-1**) since the aromatic proton in the lowest region ($C_4$-H) appeared as a diffused singlet. Their structures were confirmed by chemical means as follows.

The first Fischer indolization product (**2b**) was hydrolyzed to the 7-aminoindole (**9**), which was converted into known ethyl 7-chloro-1*H*-indole-2-carboxylate[2b] (**10**) by Sandmeyer reaction. The second product (**3b-1**) was identical with an authentic sample prepared by an alternative method (Chart 4). The Fischer indolization of ethyl pyruvate 2-(4-acetoamidophenyl)hydrazone (**12**) prepared from 4-acetoamidoaniline (**11**) gave authentic ethyl 5-acetoamido-1*H*-indole-2-carboxylate (**3b-1**).

3) The Products from Ethyl Pyruvate 2-(2-Phenylphenyl)hydrazone (**1c**): Two phenylindoles (**2c** and **3c-1**) were obtained in the reaction with $ZnCl_2$/AcOH. The main product (**2c**) (all aromatic protons appeared between $\delta$ 7.10—7.80 ppm, as multiplet) was treated under Vilsmeier–Haack reaction conditions in order to obtain the corresponding 3-formyl compound (**14**). However, the expected 3-formylindole was not obtained. Thus, **2c** was converted into the gramine (**13**) by Mannich reaction, and then into the 3-formyl compound (**14**) by Sommelet reaction with hexamine and AcOH. In the $^1$H-NMR spectrum of **14**, the $C_4$-H signal appeared at $\delta$ 8.46 as a multiplet in 9.2 Hz wide, showing **2c** to be the normal 7-phenylindole.

The Vilsmeier–Haack reaction of the minor product (**3c-1**) gave the 3-formyl derivative (**15**). As the benzenoid protons of both compounds (**3c-1** and **15**) appeared as multiplets, the $C_4$-H signals of these two compounds could not be identified. However, the aromatic protons of **3c-1** appeared in the range of $\delta$ 7.10 to 7.80 ppm, and those of the formyl derivative (**15**) appeared in the range of $\delta$ 7.00 to 7.70 ppm, meaning that no lower-field-shifted proton appeared in the formyl derivative (**15**). These data suggested that the phenyl substituent exists at the $C_4$-position. In addition, the 4-phenylindole structure (**3c-1**) was determined by alternative synthesis based on the Hemetsberger reaction[9] (Chart 5). *o*-Phenylbenzaldehyde (**16**) was treated with ethyl azidoacetate to give the azidocinnamate (**17**), which was converted to the 4-phenylindole (**3c-1**) by heating in *p*-xylene.

4) The Products from Ethyl Pyruvate 2-(2-Methylphenyl)hydrazone (**1d**): Two methylindoles (**2d** and **3d-2**) and unsubstituted indole (**3d-1**) were obtained in the two Fischer indolizations. As the methyl derivatives of ethyl indole-2-carboxylates, ethyl 3-,[10,11] 4-, 5-, 6-, and 7-methyl-1*H*-indole-2-carboxylate,[10,12] are all known compounds, the two-methylindoles in the Fischer products were readily identified as the 7-methyl (**2d**) and the 4-methylindole (**3d-2**).

5) The Product from Ethyl Pyruvate 2-(2-Methylthiomethylphenyl)hydrazone (**1e**): The Fischer product (**2e**) was identified by converting it to the 7-methylindole (**2d**) by desulfurization.

6) The Products from Ethyl Pyruvate 2-(2-Chlorophenyl)hydrazone (**1f**): The single Fischer product (**2f**) obtained in the reaction with HCl/EtOH in a sealed tube was identical with ethyl 7-chloro-1*H*-indole-2-carboxylate (**2f**), whereas the reaction with $ZnCl_2$/AcOH[2b] gave ethyl 5-chloro-1*H*-indole-2-carboxylate (**3f-1**) besides **2f**.

7) The Products from Ethyl Pyruvate 2-(2-Tosyloxyphenyl)hydrazone (**1g**): The product consisted of ethyl 7-tosyloxy- (**2g**) and 5-tosyloxy- (**3g-1**) 1*H*-indole-2-carboxylate (see previous paper).[6] The details will be reported

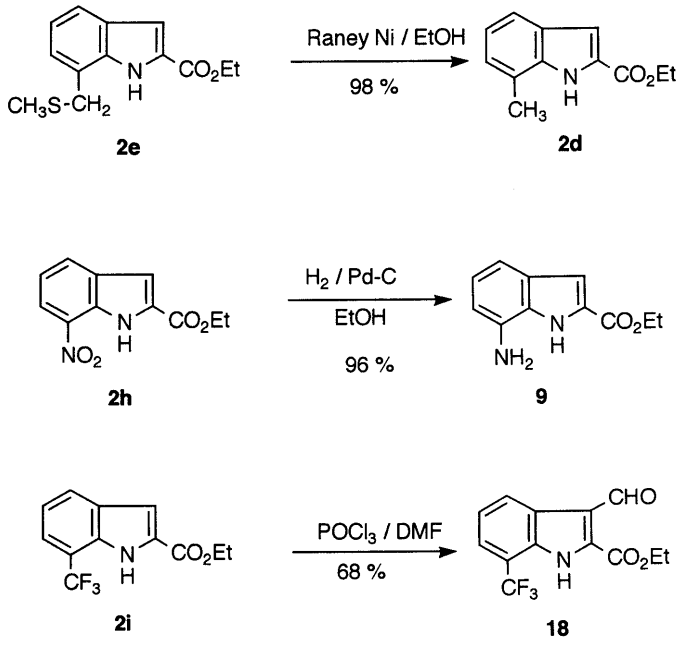



Chart 6

elsewhere.

8) The Product from Ethyl Pyruvate 2-(2-Nitrophenyl)-hydrazone (**1h**): The single Fischer product was ethyl 7-nitro-1*H*-indole-2-carboxylate[7] (**2h**), and it was identified by chemical means as follows. Compound **2h** was converted to the 7-aminoindole (**9**) by catalytic reduction over Pd–C, and this product was identical with the sample obtained by hydrolysis of the 7-acetoamidoindole (**2b**).

9) The Product from Ethyl Pyruvate 2-(2-Trifluoromethylphenyl)hydrazone (**1i**): The single Fischer product (**2i**) was identified as ethyl 7-trifluoromethyl-1*H*-indole-2-carboxylate by converting it to the 3-formylindole (**18**).

**Discussion of the Results of the Abnormal Fischer Indolization** The Abnormal Products and Their Formation Mechanism: The Fischer indolization gave various kinds of abnormal products together with the normal product (**2**), depending on the nature of the *ortho*-substituents of phenylhydrazones. The abnormal indoles could be divided into two classes. One consists of indoles which lost the *ortho*-substituent in the starting phenylhydrazone (**1**) to give unsubstituted indole such as **3a-1** and **3d-1** (they are the same compound). The other group consists of indoles in which the substituent in the starting phenylhydrazones rearranged during cyclization as observed in the phenylhydrazones **1a**, **1b**, **1c**, **1d**, **1f**, and **1g**. The rearrangement involves 1,2-shift and 1,3-shift, depending on the kind of substituent. The substituents undergoing 1,2-shift were phenyl (**1c**) and methyl (**1d**) groups. Methyl (alkyl) group rearrangement in Fischer indolization has been reported,[13] but phenyl (aryl) group rearrangement was not known previously. On the other hand the acetoamide group underwent 1,3-rearrangement. This is the first report as far as we know concerning the acetoamide group rearrangement. However, the methylthio group (in **1a**) behaved very differently; rearrangement occurred from the benzene moiety to the $C_3$-position on the pyrrole ring. Such a rearrangement across two nuclei on abnormal Fischer indolization is unprecedented. A possible mechanism is shown in Chart 7.

In the enehydrazine intermediate **a**, Claisen-type rearrangement occurred at the substituted *ortho* position to give the diimine intermediate **b**. In the latter intermediate **b** the substituent R rearranged to the neighboring position by 1,2-shift to form the intermediate **c**, accompanied by ring closure, when R was methyl or phenyl, leading to the 4-substituted indoles (**3c-1** or **3d-2**).

When R was an acetoamide group, rearrangement occurred again in the intermediate **c**′(=**c**) to give the 5-substituted indole (**3b-1**) *via* the intermediate **d**. For the formation of the 5-substituted indole (**3b-1**), direct 1,3-rearrangement in the intermediate **b**′(=**b**) is also possible. As shown in Table I, the tosyloxy group (**1g**) had also been found to undergo 1,3-rearrangement. These two examples of 1,3-rearrangement would suggest that functional groups whose central atom has an unshared electron pair can undergo 1,3-rearrangement. This led us to speculate that the chlorine atom (in **1f**) might undergo 1,3-rearrangement at least in part, although the 5-chloroindole (**3f-1**) was reported[2b] to be formed *via* chlorine originating from the acid catalyst ($ZnCl_2$). Since the central element does not undergo protonation as the unpaired electron is weakened by an electron-attracting protecting group or is intrinsically less reactive (chloro atom) in these cases, the rearrangement occurs. On the other hand, the methoxy group[2a] in **1** can undergo protonation[2a] and subsequent addition (of nucleophile in the reaction media)–elimination reaction (see intermediates **20** and **21** in Chart 7) would give the 6-substituted indole (**22**).

A possible mechanism for the formation of the 3-methylthioindole (**3a-2**) is shown in Chart 8. The key step is at the intermediate **i**, in which the methylthio group undergoes 1,2-rearrangement to the $C_3$-position. However, we can not explain why the cyclization in **g** did not take a course to the intermediate **c** in Chart 7, which should lead to rearrangement of the methylthio group to the benzene moiety.

The indoleacrylate (**3a-3**) was easily identified as a known compound[8] secondarily formed by the reaction of ethyl indole-2-carboxylate (**3a-1**) with the hydrazone (**1a**) or ethyl pyruvate (**19**) derived from **1a** by hydrolysis.

The Fischer indolization of the 2-phenyl- (**1c**) and 2-methyl- (**1d**) phenylhydrazones gave, as abnormal products, the 4-phenyl- or 4-methylindole, whose formation potentially has synthetic value[13] for obtaining 4-substituted indoles. Thus, we examined the effect of acid catalysts including solvent on the Fischer indolization of the 2-methylphenylhydrazone (**1d**) with the aim of increasing the ratio of the 4- (**3d-2**) to 7-substituted (**2d**) indoles, as shown in Table II. PPA gave the highest ratio of 4-methylindole (**3d-2**), but the yield was not sufficiently high for synthetic purposes.

Consideration of the Ratio of Normal and Abnormal Product: Here we discuss the ratio of normal and abnormal products formed from 2-substituted phenylhydrazones. Table III shows the ratios of abnormal indoles (**3**) to all indoles formed (**2** and **3**), estimated on the basis of the yields shown in Table I. The ratios for phenylhydrazones (**1**) with acid catalysts seemed randomly scattered depending on the catalysts, and so an average ratio was calculated in order to simplify the following discussion.

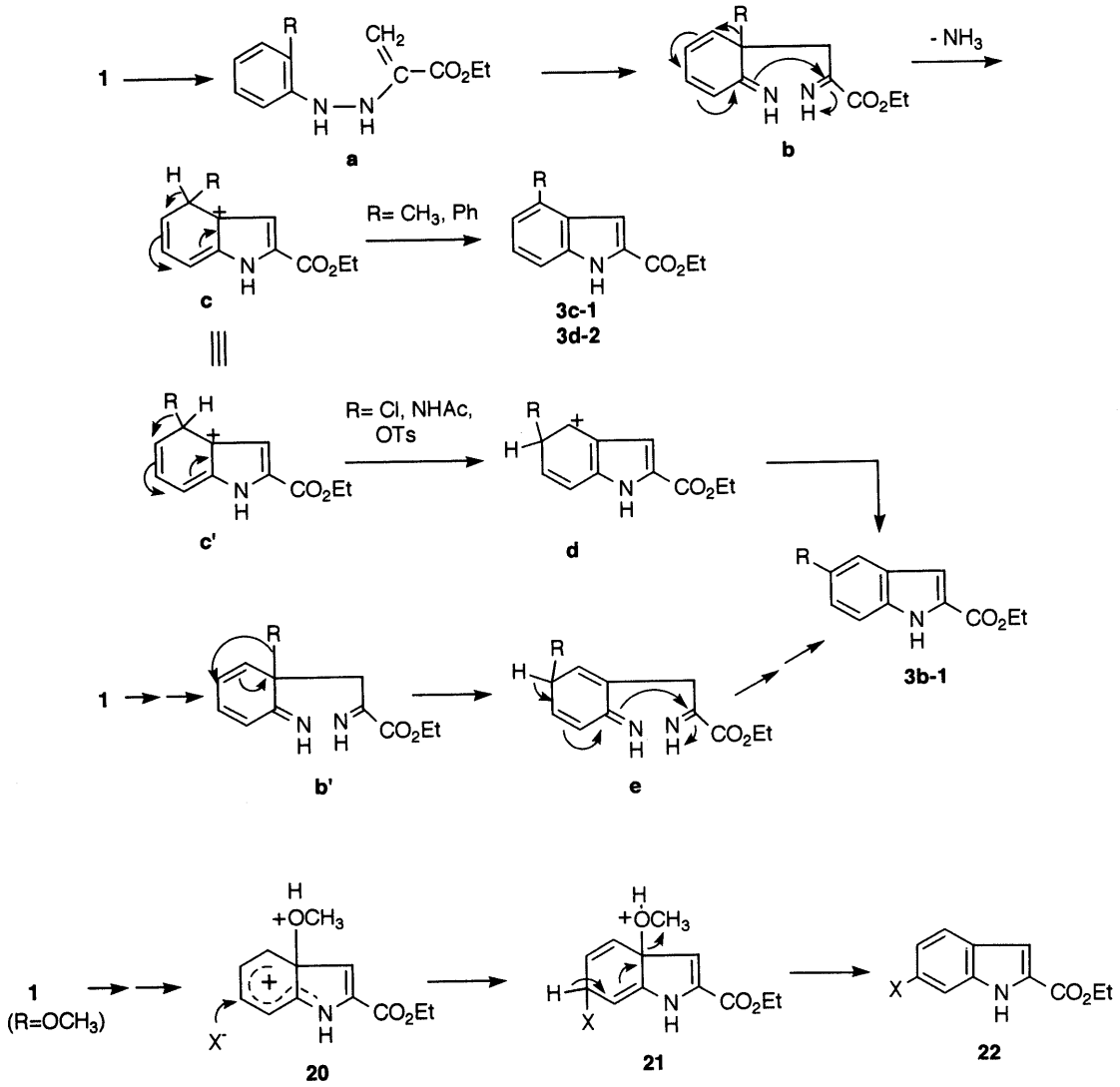



Chart 7. Proposed Formation Mechanism of Abnormal Product

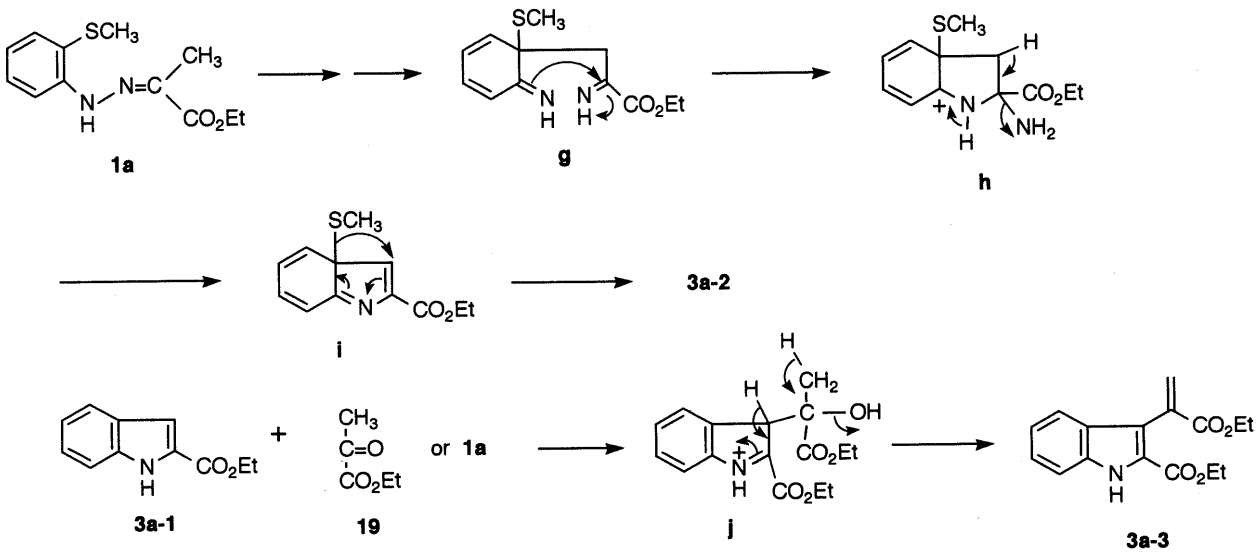
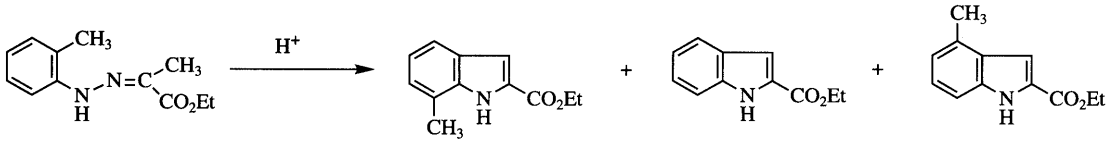



Chart 8

TABLE II. The Results of the Fischer Indolization of Ethyl Pyruvate 2-(2-Methylphenyl)hydrazone (**1d**) with Various Acid Catalysts



**1d** **2d** **3d-1** **3d-2**

| Acid catalyst | Reaction conditions | | Total yield (%) | Product ratio | | |
|---|---|---|---|---|---|---|
| | Temp. (°C) | Time (h) | | **2d** | **3d-1** | **3d-2** |
| PPA | 120—140 | 1.5 | 33 | 80 | 0 | 20 |
| HCl/EtOH | Reflux | 2 | 46 | 78 | 22 | 0 |
| *p*-TsOH/benzene | Reflux | 5 | 62 | 96 | Trace | 4 |
| $H_2SO_4$/EtOH | Reflux | 1.5 | 31 | 93 | Trace | 7 |
| $H_2SO_4$/AcOH | 40 | 3 | 22 | 95 | 0 | Trace |
| $ZnCl_2$/AcOH | 50 | 3 | 68 | 90 | 3 | 7 |
| *p*-TsOH/AcOH | Reflux | 2 | 58 | 92 | Trace | 8 |

The ratios were estimated by HPLC.

TABLE III. The Ratio of Abnormal Product to All Products in Fischer Indolization

| Phenylhydrazones (**1**) X= | Acid catalyst | Ratio (%) | |
|---|---|---|---|
| | | **3/2+3** | Average |
| $-SCH_3$ (**1a**) | HCl/EtOH | 36 | 39 |
| | $ZnCl_2$/AcOH | 42 | |
| –NHAc (**1b**) | $ZnCl_2$/AcOH | 54 | 54 |
| –Ph (**1c**) | $ZnCl_2$/AcOH | 25 | 25 |
| $-CH_3$ (**1d**) | HCl/EtOH | 22 | 16 |
| | $ZnCl_2$/AcOH | 10 | |
| $-CH_2SCH_3$ (**1e**) | TsOH/benzene | 0 | 0 |
| –Cl (**1f**) | HCl/EtOH | 0 | 10 |
| | $ZnCl_2$/AcOH | 19 | |
| –OTs (**1g**) | PPA | 21 | 21 |
| $-NO_2$ (**1h**) | PPA | 0 | 0 |
| $-CF_3$ (**1i**) | $ZnCl_2$/AcOH | — | 0 |
| $-OCH_3$[2a] | HCl/EtOH | 91 | 53 |
| | $ZnCl_2$/AcOH | 15 | |

At first glance, the ratio of abnormal product to all indolic products seems to be related to the electronegativity of the 2-substituent in the phenylhydrazones (**1**). Electron-donative substituents [methylthio (**1a**), acetoamide (**1b**), and methoxy groups] increased the ratio of abnormal product, whereas electron-withdrawing substituents [tosyloxy (**1g**), nitro (**1h**), and trifluoromethyl (**1i**) groups] formed the normal product predominantly or exclusively. The rest, having weak electronic effects [phenyl (**1c**), methyl (**1d**), methylthiomethyl (**1e**), and chloro (**1f**) groups] gave intermediate results in terms of the ratio of abnormal product. This tendency that phenylhydrazones with more electron-donative substituents undergo *ipso* cyclization reaction more easily to yield abnormal products can be explained by the fact that the electron-rich nucleus undergoes the Fischer indolization more easily, as seen in the Fischer indolization of 4-monosubstituted diphenylhydrazones.[14] On the other hand, *ipso* cyclization would not readily proceed, due to the steric hindrance of the 2-substituent, in less reactive phenylhydrazones with an electron-poor nucleus.

In conclusion, the direction of cyclization in Fischer indolization of *ortho*-substituted phenylhydrazone is fundamentally controlled by the character of the *ortho*-substituent. A more electron-attractive substituent tends to favor cyclization towards the unoccupied *ortho*-position to yield the normal 7-substituted indole, whereas a more electron-donative substituent favors cyclization towards the occupied *ortho* position to yield the abnormally substituted indole (abnormal Fischer indolization). In the abnormal Fischer indolization the behavior of *ortho*-substituent is modified by the character of the central atom of the substituent group. When the central atom has an unshared electron pair, the substituent undergoes 1,3-migration or *SN2'* type substitution. When the central atom lacks an unshared electron pair, the substituent undergoes 1,2-migration. The kind of acid catalyst (including solvent) used influences the degree of abnormality to some extent but to a lesser extent than does the *ortho*-substituent.

## Experimental

Melting points were determined on a Yanagimoto micro-melting point hot-stage apparatus and are uncorrected. IR spectra were recorded in Nujol mulls (unless otherwise stated) on a Shimadzu IR-400 spectrometer. $^1$H-NMR spectra were recorded in deuteriochloroform (unless otherwise stated) on a Hitachi R-24B (60 MHz) spectrometer with tetramethylsilane as an internal reference. Mass spectra were measured with a JEOL JMS-01-SG-2 spectrometer using a direct inlet system. For column chromatography, $SiO_2$ (Merck Kieselgel 60) was used.

**Preparation of Ethyl 2-(2-Substituted Phenyl)hydrazones (1) from 2-Substituted Anilines *via* Japp–Klingemann Reaction. General Procedure Represented by the Preparation of Ethyl Pyruvate 2-(2-Methylthiophenyl)-hydrazone (1a)** Solid $NaNO_2$ (2.20 g, 32 mmol) was added portionwise to a solution of 2-methylthioaniline[15] (4.00 g, 29 mmol) and concentrated HCl (6.4 g) in $H_2O$ (22 ml) at 0—4 °C. The resulting diazonium salt solution was added dropwise to a solution of ethyl α-methylacetoacetate (4.23 g, 29 mmol) and 50% aqueous KOH in EtOH (28 ml) at 0—7 °C, and the whole was stirred for 1 h under ice-cooling. The reaction mixture was poured into $H_2O$, and extracted with $Et_2O$. The organic solution was dried over $MgSO_4$ and evaporated. The residue (7.15 g) was dissolved in EtOH (20 ml) and refluxed with phosphoric acid (4 ml) for 20 min. The reaction mixture was poured into $H_2O$, and extracted with $Et_2O$. The organic solution was washed with 5% aqueous $NaHCO_3$, dried over $MgSO_4$, and evaporated to give a reddish oil (6.0 g). Column chromatography with benzene–cyclohexane (1 : 1) gave the (*Z*)- and (*E*)-hydrazones (**1a**) in order of elution.

(*Z*)-Ethyl Pyruvate 2-(2-Methylthiophenyl)hydrazone [(*Z*)-**1a**]: The yield was 1.89 g (26%). Pale yellow columns from hexane, mp 62—63 °C. *Anal.* Calcd for $C_{12}H_{16}N_2O_2S$: C, 57.12; H, 6.39; N, 11.10. Found: C, 57.27; H, 6.40; N, 11.06. IR $\nu_{max}$ $cm^{-1}$: 3211 (NH), 1684 (C=O). $^1$H-NMR ($CCl_4$) $\delta$: 1.38 (3H, t, $J$=7.5 Hz, $CH_2C\underline{H}_3$), 2.15 (3H, s, N=C–$CH_3$), 2.35 (3H, s, $SCH_3$), 4.28 (2H, q, $J$=7.5 Hz, $OC\underline{H}_2CH_3$), 6.67—7.60 (4H, m, ArH), 12.46 (1H, s, NH). MS *m/z*: 252 ($M^+$, 70%), 136 (100%).

(*E*)-Ethyl Pyruvate 2-(2-Methylthiophenyl)hydrazone [(*E*)-**1a**]: The yield was 1.20 g (17%). Pale yellow columns from pentane, mp 52—53 °C. *Anal.* Calcd for $C_{12}H_{16}N_2O_2S$: C, 57.12; H, 6.39; N, 11.10. Found: C, 57.22; H, 6.39; N, 11.25. IR $\nu_{max}$ $cm^{-1}$: 3295 (NH), 1710 (C=O). $^1$H-NMR ($CCl_4$) $\delta$: 1.35 (3H, t, $J$=7.5 Hz, $CH_2C\underline{H}_3$), 2.07 (3H, s, N=C–$CH_3$), 2.32 (3H, s, $SCH_3$), 4.22 (2H, q, $J$=7.5 Hz, $OC\underline{H}_2CH_3$), 6.80—7.70 (4H, m, ArH), 8.69 (1H, s, NH). MS *m/z*: 252 ($M^+$, 100%).

(*E*)-Ethyl Pyruvate 2-(2-Acetoamidophenyl)hydrazone [(*E*)-**1b**]: (*E*)-Ethyl pyruvate 2-(2-nitrophenyl)hydrazone [(*E*)-**1h**] (preparation of (*E*)-**1h** is described later in this paper) (3.00 g, 11.9 mmol) was dissolved in EtOH (550 ml) and hydrogenated over 5% Pd–C (340 mg). After the reaction was complete, the catalyst was filtered off, and the filtrate was evaporated to dryness *in vacuo* to give the crude ethyl pyruvate 2-(2-aminophenyl)hydrazone (2.58 g, 98%). This 2-aminohydrazone was dissolved in AcOH (30 ml) and $Ac_2O$ (1.33 ml, 14 mmol) was added to the solution. The mixture was refluxed for 1 h, then poured into $H_2O$, and allowed to stand overnight. The precipitates were filtered with suction and, after drying overnight, recrystallized from benzene to give pale yellow prisms (2.036 g, 65%), mp 130.5—131 °C. *Anal.* Calcd for $C_{13}H_{17}N_3O_3$: C, 59.30; H, 6.51; N, 15.96. Found: C, 59.27; H, 6.44; N, 15.99. IR $\nu_{max}$ $cm^{-1}$: 3250 (NH), 1720 (C=O), 1650 (C=O). $^1$H-NMR $\delta$: 1.35 (3H, t, $J$=8.0 Hz, $CH_2C\underline{H}_3$), 2.02 (3H, s, $COCH_3$), 2.16 (3H, s, =C–$CH_3$), 4.30 (2H, q, $J$=8.0 Hz, $OC\underline{H}_2CH_3$), 6.68—7.58 (4H, m, ArH), 8.48 and 9.32 (1H each, br s, NH). MS *m/z*: 263 ($M^+$, 48%), 107 (100%).

(*Z*)-Ethyl Pyruvate 2-(2-Phenylphenyl)hydrazone [(*Z*)-**1c**]: The yield was 357 mg (47%) from commercially available 2-biphenylamine (490 mg) *via* the Japp–Klingemann reaction. Yellow needles from EtOH, mp 72—72.5 °C. *Anal.* Calcd for $C_{17}H_{18}N_2O_2$: C, 72.32; H, 6.43; N, 9.92. Found: C, 72.21; H, 6.40; N, 9.87. IR $\nu_{max}$ $cm^{-1}$: 3270 (NH), 1675 (C=O). $^1$H-NMR $\delta$: 1.19 (3H, t, $J$=7.5 Hz, $CH_2C\underline{H}_3$), 2.12 (3H, s, =C–$CH_3$), 4.10 (2H, q, $J$=7.5 Hz, $OC\underline{H}_2CH_3$), 6.86—7.82 (9H, m, ArH), 11.91 (1H, s, NH). MS *m/z*: 282 ($M^+$, 50%), 167 (100%).

(*E*)-Ethyl Pyruvate 2-(2-Phenylphenyl)hydrazone [(*E*)-**1c**]: The yield was 353 mg (46%), prepared with (*Z*)-**1c**. Yellow prisms from EtOH, mp 105.5—108 °C. *Anal.* Calcd for $C_{17}H_{18}N_2O_2$: C, 72.32; H, 6.43; N, 9.92. Found: C, 72.47; H, 6.49; N, 9.79. IR $\nu_{max}$ $cm^{-1}$: 3375 (NH), 1705 (C=O). $^1$H-NMR $\delta$: 1.36 (3H, t, $J$=7.5 Hz, $CH_2C\underline{H}_3$), 1.79 (3H, s, =C–$CH_3$), 4.30 (2H, q, $J$=7.5 Hz, $OC\underline{H}_2CH_3$), 6.90—8.00 (9H, m, ArH), 7.86 (1H, br s, NH). MS *m/z*: 282 ($M^+$, 40%), 167 (100%).

(*Z*)-Ethyl Pyruvate 2-(2-Methylthiomethylphenyl)hydrazone [(*Z*)-**1e**]: Prepared from 2-(methylthiomethyl)aniline[16] (3.06 g, 20.0 mmol) with (*E*)-**1e**. The yield was 1.422 g (27%). Recrystallization was unsuccessful owing to the lability of the product. Orange-yellow prisms, mp 46—49 °C. *Anal.* Calcd for $C_{13}H_{18}N_2O_2S$: C, 58.62; H, 6.81; N, 10.52. Found: C, 58.35; H, 6.92; N, 10.26. IR $\nu_{max}$ $cm^{-1}$: 3250 (NH), 1680 (C=O). $^1$H-NMR $\delta$: 1.32 (3H, t, $J$=7.0 Hz, $CH_2C\underline{H}_3$), 1.99 (3H, s, $SCH_3$), 2.14 (3H, s, N=C–$CH_3$), 3.68 (2H, s, –$C\underline{H}_2$S–), 4.25 (2H, q, $J$=7.0 Hz, $OC\underline{H}_2CH_3$), 6.65—7.73 (4H, m, ArH), 12.13 (1H, br s, NH). MS *m/z*: 266 ($M^+$, 12%), 136 (100%).

(*E*)-Ethyl Pyruvate 2-(2-Methylthiomethylphenyl)hydrazone [(*E*)-**1e**]: Prepared with (*Z*)-**1e**. The yield was 2.209 g (42%). Pale pink prisms from hexane–$Et_2O$, mp 57—58 °C. *Anal.* Calcd for $C_{13}H_{18}N_2O_2S$: C, 58.62; H, 6.81; N, 10.52. Found: C, 58.70; H, 6.94; N, 10.27. IR $\nu_{max}$ $cm^{-1}$: 3275 (NH), 1700 (C=O). $^1$H-NMR $\delta$: 1.36 (3H, t, $J$=7.5 Hz, –$CH_2C\underline{H}_3$), 1.93 (3H, s, $SCH_3$), 2.12 (3H, s, =C–$CH_3$), 3.73 (2H, s, –$CH_2$S–), 4.28 (2H, q, $J$=7.5 Hz, $OC\underline{H}_2CH_3$), 6.65—7.74 (4H, m, ArH), 8.81 (1H, br s, NH). MS *m/z*: 268 ($M^+$+2, 5% of $M^+$), 266 ($M^+$, 100%).

(*E*)-Ethyl Pyruvate 2-(2-Methylphenyl)hydrazone [(*E*)-**1d**]: Prepared according to our previous paper.[10]

(*Z*)-Ethyl Pyruvate 2-(2-Nitrophenyl)hydrazone[17] [(*Z*)-**1h**]: Prepared from 2-nitroaniline *via* the Japp–Klingemann reaction with (*E*)-**1h**. The yield was 0.130 g (13%). Yellow needles from hexane, mp 94—95.5 °C. *Anal.* Calcd for $C_{11}H_{13}N_3O_4$: C, 52.59; H, 5.22; N, 16.72. Found: C, 52.72; H, 5.14; N, 16.48. IR $\nu_{max}$ $cm^{-1}$: 3230 (NH), 1695 (C=O). $^1$H-NMR $\delta$: 1.42 (3H, t, $J$=7.0 Hz, $CH_2C\underline{H}_3$), 2.27 (3H, s, =C–$CH_3$), 4.39 (2H, q, $J$=7.0 Hz, $OC\underline{H}_2CH_3$), 6.75—8.29 (4H, m, ArH), 13.70 (1H, br s, NH). MS *m/z*: 251 ($M^+$, 100%).

(*E*)-Ethyl Pyruvate 2-(2-Nitrophenyl)hydrazone [(*E*)-**1h**]: Prepared with (*Z*)-**1h**. The yield was 0.59 g (60%). Yellow needles from hexane, mp 117—118 °C. *Anal.* Calcd for $C_{11}H_{13}N_3O_4$: C, 52.59; H, 5.22; N, 16.72. Found: C, 52.79; H, 5.14; N, 16.54. IR $\nu_{max}$ $cm^{-1}$: 3300 (NH), 1700 (C=O). $^1$H-NMR $\delta$: 1.41 (3H, t, $J$=7.0 Hz, $CH_2C\underline{H}_3$), 2.25 (3H, s, =C–$CH_3$), 4.35 (2H, q, $J$=7.0 Hz, $OC\underline{H}_2CH_3$), 6.95—8.15 (4H, m, ArH), 10.82 (1H, br s, NH). MS *m/z*: 251 ($M^+$, 88%), 42 (100%).

(*Z*)-Ethyl Pyruvate 2-(2-Trifluoromethylphenyl)hydrazone [(*Z*)-**1i**]: Prepared from commercially available 2-trifluoromethylaniline (1.00 g) *via* the Japp–Klingemann reaction with (*E*)-**1i**. The yield was 328 mg (18%). Pale yellow leaflets from pentane, mp 71—71.5 °C. *Anal.* Calcd for $C_{12}H_{13}F_3N_2O_2$: C, 52.56; H, 4.78; N, 10.21. Found: C, 52.76; H, 4.70; N, 10.33. IR $\nu_{max}^{CHCl_3}$ $cm^{-1}$: 3240 (NH), 1685 (C=O). $^1$H-NMR ($CCl_4$) $\delta$: 1.36 (3H, t, $J$=7.0 Hz, $CH_2C\underline{H}_3$), 2.16 (3H, s, =C–$CH_3$), 4.30 (2H, q, $J$=7.0 Hz, $OC\underline{H}_2CH_3$), 6.80—7.88 (4H, m, ArH), 12.53 (1H, br s, NH). MS *m/z*: 274 ($M^+$, 44%), 159 (100%).

(*E*)-Ethyl Pyruvate 2-(2-Trifluoromethylphenyl)hydrazone [(*E*)-**1i**]: Prepared with (*Z*)-**1i**. The yield was 458 mg (25%). Pale yellow columns from pentane, mp 53—55 °C. *Anal.* Calcd for $C_{12}H_{13}F_3N_2O_2$: C, 52.56; H, 4.78; N, 10.21. Found: C, 52.74; H, 4.51; N, 10.30. IR $\nu_{max}^{CHCl_3}$ $cm^{-1}$: 3400 (NH), 1705 (C=O). $^1$H-NMR ($CCl_4$) $\delta$: 1.36 (3H, t, $J$=7.0 Hz, $CH_2C\underline{H}_3$), 2.10 (3H, s, =C–$CH_3$), 4.31 (2H, q, $J$=7.0 Hz, $OC\underline{H}_2CH_3$), 6.88—7.92 (4H, m, ArH), 8.08 (1H, br s, NH). MS *m/z*: 274 ($M^+$, 44%), 159 (100%).

**General Procedure for Fischer Indolization** The phenylhydrazone (**1**) was treated with an acid catalyst in an appropriate solvent under the conditions described in Table I. Usually the reaction was continued until the phenylhydrazone (**1**) was no longer detectable by thin layer chromatography. The reaction mixture was poured into water and extracted with an appropriate solvent. The mixture of products thus obtained was subjected to column chromatography on $SiO_2$ to separate into components. Data for the products were as follows.

**1) The Products from Ethyl Pyruvate 2-(2-Methylthiophenyl)hydrazone (1a)** A) Reaction with HCl/EtOH: a) Ethyl 7-Methylthio-1*H*-indole-2-carboxylate (**2a**): Colorless needles from hexane, mp 67—68 °C. Identical with the sample obtained in the following reaction (B) with $ZnCl_2$/AcOH.

b) Ethyl 1*H*-Indole-2-carboxylate (**3a-1**): Colorless needles from hexane, mp 115—116 °C. Identical with an authentic commercial sample.

c) Ethyl 3-Methylthio-1*H*-indole-2-carboxylate (**3a-2**): Colorless needles from hexane, mp 114—116 °C. Identical with the sample obtained in the following reaction (B) with $ZnCl_2$/AcOH.

d) Ethyl 2-(2-Ethoxycarbonylindol-3-yl)acrylate (**3a-3**): Colorless columns from benzene, mp 85—90 °C. This sample was identical with the known compound (lit.,[5] mp 84.5—85.5 °C). *Anal.* Calcd for $C_{16}H_{17}NO_4$: C, 66.89; H, 5.96; N, 4.88. Found: C, 66.84; H, 6.02; N, 4.88. IR $\nu_{max}$ $cm^{-1}$: 3310 (NH), 1705 (C=O). $^1$H-NMR ($CCl_4$) $\delta$: 1.23 (6H, t, $J$=7.5 Hz, $CH_2C\underline{H}_3\times2$), 4.18 (4H, q, $J$=7.5 Hz, $OC\underline{H}_2CH_3\times2$), 5.79 (1H, d, $J$=2.0 Hz, C=C$\underline{H}_2$), 6.52 (1H, d, $J$=2.0 Hz, C=C$\underline{H}_2$), 6.90—7.35 (3H, m, ArH), 7.50 (1H, dd, $J$=7.5, 2.5 Hz, ArH), 9.68 (1H, br s, NH). MS *m/z*: 287 ($M^+$, 100%).

B) Reaction with $ZnCl_2$/AcOH: a) Ethyl 7-Methylthio-1*H*-indole-2-carboxylate (**2a**): Colorless needles from hexane, mp 72—73 °C. *Anal.* Calcd for $C_{12}H_{13}NO_2S$: C, 61.25; H, 5.57; N, 5.95. Found: C, 61.31; H, 5.68; N, 5.84. IR $\nu_{max}$ $cm^{-1}$: 3280 (NH), 1698 (C=O). $^1$H-NMR ($CCl_4$) $\delta$: 1.40 (3H, t, $J$=7.5 Hz, $CH_2C\underline{H}_3$), 2.47 (3H, s, $SCH_3$), 4.36 (2H, q, $J$=7.5 Hz, $OC\underline{H}_2CH_3$), 7.00 (1H, t, $J$=7.5 Hz, $C_5$-H), 7.11 (1H, d, $J$=2.5 Hz, $C_3$-H), 7.25 (1H, dd, $J$=7.5, 1.5 Hz, $C_6$-H), 7.47 (1H, dd, $J$=7.5, 1.5 Hz, $C_4$-H), 9.02 (1H, s, NH). MS *m/z*: 235 ($M^+$, 100%).

b) Ethyl 1*H*-Indole-2-carboxylate (**3a-1**): Colorless needles from hexane, mp 120—120.5 °C. This compound was identical with an authentic commercial sample.

c) Ethyl 3-Methylthio-1*H*-indole-2-carboxylate (**3a-2**): Colorless needles from hexane, mp 113—114 °C. *Anal.* Calcd for $C_{12}H_{13}NO_2S$: C, 61.25; H, 5.57; N, 5.95. Found: C, 61.45; H, 5.62; N, 5.87. IR $\nu_{max}$ $cm^{-1}$: 3308 (NH), 1673 (C=O). $^1$H-NMR ($CCl_4$) $\delta$: 1.47 (3H, t, $J$=7.5 Hz, $CH_2C\underline{H}_3$), 2.40 (3H, s, $SCH_3$), 4.47 (2H, q, $J$=7.5 Hz, $OC\underline{H}_2CH_3$), 7.00—7.45 (3H, m, ArH), 7.81 (1H, d, $J$=7.5 Hz, $C_4$-H), 9.55 (1H, br s, NH). MS *m/z*: 235 ($M^+$, 100%).

**2) The Products from Ethyl Pyruvate 2-(2-Acetoamidophenyl)hydrazone (1b)** Reaction with $ZnCl_2$/AcOH: a) Ethyl 7-acetoamido-1*H*-indole-2-carboxylate (**2b**): Colorless needles from benzene, mp 143—143.5 °C. *Anal.* Calcd for $C_{13}H_{14}N_2O_3$: C, 63.40; H, 5.73; N, 11.38. Found: C, 63.48; H, 5.73; N, 11.22. IR $\nu_{max}$ $cm^{-1}$: 3220 (NH), 1698 (C=O), 1635 (C=O). $^1$H-NMR (DMSO-$d_6$) $\delta$: 1.35 (3H, t, $J$=7.0 Hz, $CH_2C\underline{H}_3$), 2.18 (3H, s, $COCH_3$), 4.35 (2H, q, $J$=7.0 Hz, $OC\underline{H}_2CH_3$), 6.84—8.00 (4H, m, ArH), 9.73 (1H, br s, NH), 11.49 (1H, br s, NH). MS *m/z*: 246 ($M^+$, 52%), 158

(100%).

b) Ethyl 5-Acetoamido-1*H*-indole-2-carboxylate (**3b-1**): Colorless needles from AcOEt, mp 218.5—219.5 °C. *Anal.* Calcd for $C_{13}H_{14}N_2O_3$: C, 63.40; H, 5.73; N, 11.38. Found: C, 63.34; H, 5.76; N, 11.35. IR $\nu_{max}$ cm$^{-1}$: 3315 (NH), 1680 (C=O), 1654 (C=O). $^1$H-NMR (DMSO-$d_6$) $\delta$: 1.31 (3H, t, $J$=7.0 Hz, $CH_2C\underline{H}_3$), 2.02 (3H, s, $COCH_3$), 4.28 (2H, q, $J$=7.0 Hz, $OC\underline{H}_2CH_3$), 6.99 (1H, d, $J$=1.5 Hz, $C_3$-H), 7.18—8.01 (3H, m, ArH), 9.65 (1H, br s, NH), 11.58 (1H, br s, NH). MS *m/z*: 246 ($M^+$, 48%), 158 (100%). This compound was identical with the authentic sample whose preparation is described later in this paper.

**3) The Products from Ethyl Pyruvate 2-(2-Phenylphenyl)hydrazone (1c)** Reaction with $ZnCl_2$/AcOH: a) Ethyl 7-Phenyl-1*H*-indole-2-carboxylate (**2c**): Colorless prisms from benzene–hexane, mp 91.5—92.5 °C. *Anal.* Calcd for $C_{17}H_{15}NO_2$: C, 76.96; H, 5.70; N, 5.28. Found: C, 76.77; H, 5.73; N, 5.30. IR $\nu_{max}$ cm$^{-1}$: 3280 (NH), 1675 (C=O). $^1$H-NMR $\delta$: 1.36 (3H, t, $J$=7.0 Hz, $CH_2C\underline{H}_3$), 4.36 (2H, q, $J$=7.0 Hz, $OC\underline{H}_2CH_3$), 7.10—7.39 (3H, m, ArH), 7.39—7.80 (6H, m, ArH), 8.98 (1H, br s, NH). MS *m/z*: 265 ($M^+$, 95%), 219 (100%).

b) Ethyl 4-Phenyl-1*H*-indole-2-carboxylate (**3c-1**): Colorless needles from benzene–hexane, mp 153—154 °C. *Anal.* Calcd for $C_{17}H_{15}NO_2$: C, 76.96; H, 5.70; N, 5.28. Found: C, 76.96; H, 5.70; N, 5.32. IR $\nu_{max}$ cm$^{-1}$: 3325 (NH), 1685 (C=O). $^1$H-NMR $\delta$: 1.37 (3H, t, $J$=7.5 Hz, $CH_2C\underline{H}_3$), 4.41 (2H, q, $J$=7.5 Hz, $OC\underline{H}_2CH_3$), 7.10—7.32 (2H, m, ArH), 7.32—7.60 (5H, m, ArH and $C_3$-H), 7.60—7.80 (2H, m, ArH), 9.47 (1H, br s, NH). MS *m/z*: 265 ($M^+$, 77%), 219 (100%).

**4) The Products from Ethyl Pyruvate 2-(2-Methylphenyl)hydrazone (1d)** Reaction with HCl/EtOH: The products were ethyl 7-methyl-1*H*-indole- (**2d**) and ethyl 1*H*-indole (**3d-1**)-2-carboxylate. They were identical with the compounds obtained in the following reaction of **1d** with $ZnCl_2$/AcOH.

Reaction with $ZnCl_2$/AcOH: The products were ethyl 7-methyl-1*H*-indole- (**2d**), ethyl 1*H*-indole- (**3d-1**), and ethyl 4-methyl-1*H*-indole-2-carboxylate (**3d-2**). **2d** and **3d-2** were identical with authentic samples,[10] and **3d-1** was identical with a commercial sample.

**5) The Products from Ethyl Pyruvate 2-(2-Methylthiomethylphenyl)-hydrazone (1e)** Reaction with TsOH/Benzene: Ethyl 7-Methylthiomethyl-1*H*-indole-2-carboxylate (**2e**): Pale yellow fine prisms from hexane, mp 101—102 °C. *Anal.* Calcd for $C_{13}H_{15}NO_2S$: C, 62.63; H, 6.06; N, 5.62. Found: C, 62.54; H, 6.03; N, 5.51. IR $\nu_{max}$ cm$^{-1}$: 3340 (NH), 1690 (C=O). $^1$H-NMR $\delta$: 1.40 (3H, t, $J$=7.0 Hz, $CH_2C\underline{H}_3$), 1.93 (3H, s, $SCH_3$), 3.96 (2H, s, $CH_2S$), 4.38 (2H, q, $J$=7.0 Hz, $OC\underline{H}_2CH_3$), 6.95—7.66 (4H, m, ArH), 9.32 (1H, br s, NH). MS *m/z*: 249 ($M^+$, 29%), 156 (100%).

**6) Product from Ethyl Pyruvate 2-(2-Chlorophenyl)hydrazone (1f)** Reaction with HCl/EtOH in a Sealed Tube: The product was 7-chloro-1*H*-indole-2-carboxylate (**2f**), which was identified by comparison with an authentic sample.[2b]

**7) The Product from Ethyl Pyruvate 2-(2-Nitrophenyl)hydrazone (1h). The Reaction with PPA** Ethyl 7-Nitro-1*H*-indole-2-carboxylate[7] (**2h**): Yellow needles from EtOH, mp 95—95.5 °C (lit.,[7] mp 92—93 °C). *Anal.* Calcd for $C_{11}H_{10}N_2O_4$: C, 56.41; H, 4.30; N, 11.96. Found: C, 56.48; H, 4.32; N, 11.92. IR $\nu_{max}$ cm$^{-1}$: 3250 (NH), 1705 (C=O). $^1$H-NMR $\delta$: 1.42 (3H, t, $J$=7.0 Hz, $CH_2C\underline{H}_3$), 4.45 (2H, q, $J$=7.0 Hz, $OC\underline{H}_2CH_3$), 7.18 (1H, t, $J$=8.0 Hz, $C_5$-H), 7.25 (1H, d, $J$=2.0 Hz, $C_3$-H), 7.95 (1H, diffused d, $J$=8.0 Hz, $C_4$-H), 8.18 (1H, dd, $J$=8.0, 1.0 Hz, $C_6$-H), 10.01 (1H, br s, NH). MS *m/z*: 234 ($M^+$, 100%).

**8) The Product from Ethyl Pyruvate 2-(2-Trifluoromethylphenyl)hydrazone (1i)** Reaction with $ZnCl_2$/AcOH: Ethyl 7-(Trifluoromethyl)-1*H*-indole-2-carboxylate (**2i**): Colorless needles from pentane, mp 81.5—82 °C. *Anal.* Calcd for $C_{12}H_{10}F_3NO_2$: C, 56.04; H, 3.92; N, 5.45. Found: C, 56.33; H, 3.93; N, 5.63. IR $\nu_{max}$ cm$^{-1}$: 3313 (NH), 1710 (C=O). $^1$H-NMR ($CCl_4$) $\delta$: 1.43 (3H, t, $J$=7.0 Hz, $CH_2C\underline{H}_3$), 4.40 (2H, q, $J$=7.0 Hz, $OC\underline{H}_2CH_3$), 7.18 (1H, m, $C_5$-H), 7.19 (1H, d, $J$=2.0 Hz, $C_3$-H), 7.55 (1H, diffused d, $J$=8.0 Hz, $C_4$-H), 7.81 (1H, diffused d, $J$=8.0 Hz, $C_6$-H), 9.10 (1H, br s, NH). MS *m/z*: 257 ($M^+$, 50%), 211 (100%).

**Preparation of the 3-Formyl Derivatives of the Indoles (2). 1) Ethyl 3-Formyl-7-methylthio-1*H*-indole-2-carboxylate (6). General Procedure of Vilsmeier–Haack Reaction Represented by the Reaction of Ethyl 7-Methylthio-1*H*-indole-2-carboxylate (2a)** A solution of **2a** (500 mg) in dimethylformamide (DMF, 3 ml) was added to a solution of $POCl_3$ (3.26 g) in DMF (12 ml). The mixture was heated at 100—105 °C for 1 h, then poured into $H_2O$ (130 ml), basified with $Na_2CO_3$, and extracted with $Et_2O$. The organic layer was washed with $H_2O$, dried over $MgSO_4$, and evaporated to dryness *in vacuo*. The residue (533 mg) was chromatographed over $SiO_2$ with $CHCl_3$ to give the title compound (230 mg, 78%). Recrystallization from EtOH gave pale orange needles, mp 150—151.5 °C. *Anal.* Calcd for $C_{13}H_{13}NO_3S$: C, 59.30; H, 4.98; N, 5.32. Found: C, 59.12; H, 4.97; N, 5.19. IR $\nu_{max}$ cm$^{-1}$: 3150 (NH), 1721 (C=O), 1646 (C=O). $^1$H-NMR (DMSO-$d_6$) $\delta$: 1.40 (3H, t, $J$=7.5 Hz, $CH_2C\underline{H}_3$), 2.53 (3H, s, $SCH_3$), 4.43 (2H, q, $J$=7.5 Hz, $OC\underline{H}_2CH_3$), 7.20—7.38 (2H, m, $C_5$ and $C_6$-H), 8.10 (1H, dd, $J$=6.0, 2.0 Hz, $C_4$-H), 10.52 (1H, s, CHO), 12.38 (1H, br s, NH). MS *m/z*: 263 ($M^+$, 71%), 234 (100%).

Ethyl 4-Formyl-7-methylthio-1*H*-indole-2-carboxylate (**7**): Further chromatography with $CHCl_3$ after elution of the 3-formyl derivative (**6**) gave the title compound (25 mg, 4.5%). Recrystallization from EtOH gave colorless needles, mp 159—161.5 °C. *Anal.* Calcd for $C_{13}H_{13}NO_3S$: C, 59.30; H, 4.98; N, 5.32. Found: C, 59.33; H, 4.91; N, 5.18. IR $\nu_{max}$ cm$^{-1}$: 3134 (NH), 1715 (C=O), 1650 (C=O). $^1$H-NMR (DMSO-$d_6$) $\delta$: 1.37 (3H, t, $J$=7.5 Hz, $CH_2C\underline{H}_3$), 2.63 (3H, s, $SCH_3$), 4.34 (2H, q, $J$=7.5 Hz, $OC\underline{H}_2CH_3$), 7.28 (1H, d, $J$=8.0 Hz, $C_6$-H), 7.70 (1H, d, $J$=8.0 Hz, $C_5$-H), 7.73 (1H, d, $J$=2.0 Hz, $C_3$-H), 10.05 (1H, s, CHO), 12.11 (1H, br s, NH). MS *m/z*: 263 ($M^+$, 100%).

**2) Ethyl 3-Formyl-7-phenyl-1*H*-indole-2-carboxylate (14)** Ethyl 3-(Dimethylamino)methyl-7-phenyl-1*H*-indole-2-carboxylate (**13**): Aqueous dimethylamine (40%, 0.05 ml) and 37% aqueous HCHO was added to a solution of **2c** (83 mg) in AcOH (0.16 ml), and the whole was stirred at 100 °C for 30 min. The reaction mixture was poured into $H_2O$, basified with $NaHCO_3$, and extracted with $Et_2O$. The organic layer was washed with $H_2O$, dried over $MgSO_4$, and evaporated to dryness *in vacuo*. The residue (101 mg) was recrystallized from aqueous EtOH to give colorless prisms (96 mg, 94%), mp 110—115 °C. This compound was used for the following reaction without further purification: IR $\nu_{max}$ cm$^{-1}$: 3300 (NH), 1680 (C=O). $^1$H-NMR $\delta$: 1.39 (3H, t, $J$=7.0 Hz, $CH_2C\underline{H}_3$), 2.32 [6H, s, $N(CH_3)_2$], 3.96 (2H, s, $ArCH_2N$), 4.37 (2H, q, $J$=7.0 Hz, $OC\underline{H}_2CH_3$), 7.06—7.68 (7H, m, ArH), 7.82 (1H, dd, $J$=7.0, 2.0 Hz, $C_4$-H), 8.88 (1H, s, NH). MS *m/z*: 322 ($M^+$, 21%), 307 (100%).

Compound **14**: Hexamine (552 mg) was added to a refluxing solution of the gramine (**13**) (400 mg) in AcOH (2.3 ml), and the whole was refluxed for 40 min. The reaction mixture was poured into ice-water, adjusted to *ca.* pH 5 with saturated $NaHCO_3$, and extracted with $CHCl_3$. The organic layer was washed with saturated $NaHCO_3$, dried over $MgSO_4$, and evaporated to dryness *in vacuo*. The residue (371 mg) was purified by column chromatography over $SiO_2$ with benzene to give the title compound (23 mg, 6.9%). Recrystallization from benzene–hexane gave colorless fine needles, mp 141.5—142.5 °C. *Anal.* Calcd for $C_{18}H_{15}NO_3$: C, 73.71; H, 5.15; N, 4.78. Found: C, 73.40; H, 5.15; N, 4.69. IR $\nu_{max}$ cm$^{-1}$: 3245 (NH), 1710 (C=O), 1645 (C=O). $^1$H-NMR $\delta$: 1.44 (3H, t, $J$=7.0 Hz, $CH_2C\underline{H}_3$), 4.49 (2H, q, $J$=7.0 Hz, $OC\underline{H}_2CH_3$), 7.32—7.70 (7H, m, ArH), 8.46 (1H, m, $C_4$-H), 9.35 (1H, br s, NH), 10.78 (1H, s, CHO). MS *m/z*: 293 ($M^+$, 38%), 264 (100%).

**3) Ethyl 3-Formyl-4-phenyl-1*H*-indole-2-carboxylate (15)** Compound (**3c-1**) (98 mg, 0.37 mmol) was treated with $POCl_3$ (0.36 ml, 3.9 mmol) in DMF (2.5 ml) under Vilsmeier–Haack reaction conditions. The product (99 mg, 91%) was recrystallized from MeOH to give pale yellow plates, mp 141.5—142.5 °C. *Anal.* Calcd for $C_{18}H_{15}NO_3$: C, 73.71; H, 5.15; N, 4.78. Found: C, 73.66; H, 5.17; N, 5.08. IR $\nu_{max}$ cm$^{-1}$: 3290 (NH), 1725 (C=O), 1650 (C=O). $^1$H-NMR $\delta$: 1.40 (3H, t, $J$=7.0 Hz, $CH_2C\underline{H}_3$), 4.46 (2H, q, $J$=7.0 Hz, $OC\underline{H}_2CH_3$), 7.00—7.70 (8H, m, ArH), 9.86 (1H, br s, NH), 10.44 (1H, s, CHO). MS *m/z*: 293 ($M^+$, 27%), 246 (100%).

**4) Ethyl 3-Formyl-7-trifluoromethyl-1*H*-indole-2-carboxylate (18)** Compound **2i** (120 mg, 0.47 mmol) was treated with $POCl_3$ (716 mg, 4.7 mmol) in DMF (2 ml) under Vilsmeier–Haack reaction conditions. The product (90 mg, 68%) was recrystallized from hexane–benzene to give colorless needles, mp 123—123.5 °C. *Anal.* Calcd for $C_{13}H_{10}F_3NO_3$: C, 54.74; H, 3.53; N, 4.91. Found: C, 54.72; H, 3.51; N, 4.98. IR $\nu_{max}$ cm$^{-1}$: 3315 (NH), 1710 (C=O), 1665 (C=O). $^1$H-NMR $\delta$: 1.47 (3H, t, $J$=7.0 Hz, $CH_2C\underline{H}_3$), 4.55 (2H, q, $J$=7.0 Hz, $OC\underline{H}_2CH_3$), 7.35 (1H, t, $J$=8.0 Hz, $C_5$-H), 7.68 (1H, diffused d, $J$=8.0 Hz, $C_6$-H), 8.65 (1H, diffused d, $J$=8.0 Hz, $C_4$-H), 9.50 (1H, br s, NH), 10.65 (1H, s, CHO). MS *m/z*: 285 ($M^+$, 20%), 256 (100%), 238 (66%).

**Preparation of Authentic Samples and Related Compounds. Ethyl 3-Methylthio-1*H*-indole-2-carboxylate (3a-2)** Methylthiopyruvic acid[18] (2.00 g) and phenylhydrazine (1.00 g) were dissolved in EtOH (15 ml) and the solution was refluxed for 3 h. Evaporation of the solvent *in vacuo* gave the crude phenylhydrazone, which was dissolved in EtOH (100 ml) saturated with dry HCl and the whole was refluxed for 1.5 h. The reaction mixture was concentrated *in vacuo* to about 20 ml, poured into $H_2O$, and extracted with $Et_2O$. The organic layer was washed with 5% $NaHCO_3$ and $H_2O$ successively, dried over $MgSO_4$, and evaporated to dryness *in vacuo*. The residue (933 mg) was chromatographed on $SiO_2$ with benzene to give colorless crystals. Recrystallizations from hexane–benzene gave

colorless needles (288 mg, 16%), mp 110—112 °C. *Anal.* Calcd for $C_{12}H_{13}NO_2S$: C, 61.25; H, 5.57; N, 5.95. Found: C, 61.29; H, 5.51; N, 5.89. This compound was identical with the Fischer product (**3a-2**) formed in the Fischer indolization of **1a**.

**Ethyl 7-Amino-1*H*-indole-2-carboxylate (9)** A solution of **2b** (960 mg, 3.9 mmol) and 2 N $H_2SO_4$ (39 ml) in EtOH (20 ml) was refluxed for 6 h. The reaction mixture was poured into $H_2O$, basified with 5% NaOH, and extracted with $Et_2O$. The organic layer was washed with saturated NaCl, dried over $MgSO_4$, and evaporated to dryness *in vacuo*. The residue (520 mg, 65%) was recrystallized from benzene to give colorless needles, mp 163—164 °C. *Anal.* Calcd for $C_{11}H_{12}N_2O_2$: C, 64.69; H, 5.92; N, 13.72. Found: C, 64.67; H, 5.94; N, 13.60. IR $\nu_{max}$ $cm^{-1}$: 3400, 3310 (NH), 1670 (C=O). $^1$H-NMR (DMSO-$d_6$) $\delta$: 1.40 (3H, t, $J$=7.0 Hz, $CH_2C\underline{H}_3$), 4.35 (2H, q, $J$=7.0 Hz, $OC\underline{H}_2CH_3$), 5.40 (2H, br s, NH), 6.40—7.20 (4H, m, ArH), 11.29 (1H, br s, NH). MS *m/z*: 204 ($M^+$, 45%), 158 (100%).

**Ethyl 7-Chloro-1*H*-indole-2-carboxylate (10)** A solution of $NaNO_2$ (70 mg, 1.0 mmol) in $H_2O$ (2 ml) was added dropwise to a suspension of **9** (206 mg, 1.0 mmol) in concentrated HCl (1 ml) under ice-cooling. The resulting diazonium solution was added to a mixed suspension of $Cu_2Cl_2$ (811 mg, 4.2 mmol) in concentrated HCl (3 ml) under ice-cooling. After active evolution of nitrogen had ceased, the mixture was heated at 50 °C for 40 min, then poured into $H_2O$ and extracted with $Et_2O$. The organic layer was washed with $H_2O$, dried over $MgSO_4$, and evaporated to dryness *in vacuo*. The residue (170 mg) was chromatographed over $SiO_2$ with hexane–$Et_2O$ (10:1) to give the title compound (**10**) (61 mg, 27%). Recrystallization from hexane gave colorless needles, mp 111—112.5 °C (lit.[2b] mp 113.5—114 °C). *Anal.* Calcd for $C_{11}H_{10}ClNO_2$: C, 59.07; H, 4.51; N, 6.26. Found: C, 58.86; H, 4.38; N, 6.09. This compound was identical with an authentic sample.[2b]

**Ethyl 5-Acetoamido-1*H*-indole-2-carboxylate (3b-1)** 4-Aminoacetanilide (3.260 g, 22 mmol) was diazotized with concentrated HCl (8.5 ml) and $NaNO_2$ (1.7 g, 24 mmol) in a mixture of $H_2O$ (19 ml) and EtOH (12 ml) in a usual manner. The Japp–Klingemann reaction of the resulting diazonium salt with ethyl α-methylacetoacetate (3.42 ml, 25 mmol) according to the general procedure for 2-substituted phenyl-hydrazones (**1**) gave (*Z*)- and (*E*)-ethyl pyruvate 2-(4-acetoamidophenyl)hydrazones in 0.190 g (3.3%) and 1.67 g (29%) yield, respectively. No attempt was made to purify the (*Z*)-form further. (*E*)-Ethyl pyruvate 2-(4-aceto amidophenyl)hydrazone: pale pink plates from EtOH, mp 233—235 °C. *Anal.* Calcd for $C_{13}H_{17}N_3O_3$: C, 59.30; H, 6.51; N, 15.96. Found: C, 59.25; H, 6.68; N, 15.79. IR $\nu_{max}$ $cm^{-1}$: 3330 and 3260 (NH), 1700 and 1670 (C=O). $^1$H-NMR (DMSO-$d_6$) $\delta$: 1.28 (3H, t, $J$=7.0 Hz, $CH_2C\underline{H}_3$), 2.01 (3H, s, =C–$CH_3$ or $COCH_3$), 2.05 (3H, s, =C–$CH_3$ or $COCH_3$), 4.23 (2H, q, $J$=7.0 Hz, $OC\underline{H}_2CH_3$), 7.20 (2H, d, $J$=9.0 Hz, $C_3$- and $C_5$-H), 7.53 (2H, d, $J$=9.0 Hz, $C_2$- and $C_6$-H), 9.76 (2H, br s, NH×2). MS *m/z*: 263 ($M^+$, 59%), 107 (100%).

$ZnCl_2$ (4.52 g, 33 mmol) was added to a solution of (*E*)-ethyl pyruvate 2-(4-acetoamidophenyl)hydrazone (2.59 g, 9.8 mmol) in AcOH (200 ml), and the mixture was refluxed for 3.5 h, then poured into $H_2O$ and extracted with $CHCl_3$. The organic layer was washed with saturated NaCl, dried over $MgSO_4$, and evaporated to dryness *in vacuo*. The residue (1.83 g) was purified by column chromatography over $SiO_2$ using benzene–AcOEt (2:1) to give crystals (1.33 g, 55%). Recrystallization from AcOEt gave pale yellow plates (1.08 g, 45%), mp 216—218.5 °C. *Anal.* Calcd for $C_{13}H_{14}N_2O_3$: C, 63.40; H, 5.73; N, 11.38. Found: C, 63.44; H, 5.76; N, 11.37. This sample was identical with the Fischer product (**3b-1**) formed from ethyl pyruvate 2-(2-acetoamidophenyl)hydrazone (**1b**).

**Ethyl 1-Azido-2-(2-phenyl)cinnamate (17)** A solution of *o*-phenylbenzaldehyde[19] (**16**) (1.480 g, 8.12 mmol) and ethyl azidoacetate (4.219 g, 32.7 mmol) in absolute EtOH (15 ml) was added dropwise to a solution of EtONa [prepared from Na (787 mg, 34.2 mmol)] in EtOH (30 ml) under ice-cooling and the whole was stirred for 45 min. The reaction mixture was poured into ice-water containing excess $NH_4Cl$, and extracted with $Et_2O$. The organic layer was washed with saturated NaCl, dried over $MgSO_4$, and evaporated to dryness *in vacuo*. The residue (2.30 g) was purified by column chromatography over $SiO_2$ using hexane–AcOEt (10:1) to give the title compound (**17**) (1.138 g, 48%). Recrystallizations from $Et_2O$–hexane gave colorless needles, mp 83—84 °C. *Anal.* Calcd for $C_{17}H_{15}N_3O_2$: C, 69.61; H, 5.15; N, 14.33. Found: C, 69.72; H, 5.20; N, 14.12. IR $\nu_{max}$ $cm^{-1}$: 2125 ($N_3$), 1710 (C=O). $^1$H-NMR $\delta$: 1.23 (3H, t, $J$=7.0 Hz, $OCH_2C\underline{H}_3$), 4.21 (2H, q, $J$=7.0 Hz, $OC\underline{H}_2CH_3$), 6.80 (1H, s, –CH=C), 7.14—7.60 (8H, m, ArH), 8.10 (1H, m, ArH). MS *m/z*: 265 ($M^+-N_2$, 9%), 165 (100%).

**Ethyl 4-Phenyl-1*H*-indole-2-carboxylate (3c-1)** A solution of **17** (587 mg, 2.0 mmol) in *p*-xylene (20 ml) was refluxed for 20 min. After the reaction was complete, the solvent was evaporated off *in vacuo*. The residual pale yellow crystals (552 mg) were purified by column chromatography over $SiO_2$ using hexane–AcOEt (10:1) to give colorless needles (464 mg, 88%), mp 150.5—154.5 °C. Recrystallizations from benzene–hexane gave colorless needles, mp 154—155 °C. *Anal.* Calcd for $C_{17}H_{15}NO_2$: C, 76.96; H, 5.70; N, 5.28. Found: C, 76.99; H, 5.72; N, 5.52. This compound was identical with the Fischer product (**3c-1**) obtained from ethyl pyruvate 2-(2-phenylphenyl)hydrazone (**1c**).

**Ethyl 7-Methyl-1*H*-indole-2-carboxylate (2d) from Ethyl 7-Methylthiomethyl-1*H*-indole-2-carboxylate (2e)** Compound **2e** (50 mg) was refluxed in EtOH (7 ml) with Raney Ni ($W_4$) prepared from Ni alloy (1.0 g). The reaction mixture was filtered with suction and the filtrate was evaporated to dryness *in vacuo*. The residue (43 mg) was purified by column chromatography with benzene–AcOEt (10:1) to give colorless crystals (40 mg, 98%). Recrystallization from $Et_2O$–hexane gave colorless needles, mp 132—133 °C. This sample was identical with an authentic sample.[10]

**Compound 9 from Ethyl 7-Nitro-1*H*-indole-2-carboxylate (2h)** Compound **2h** (118 mg, 0.5 mmol) was hydrogenated over 5% Pd–C (14 mg) in EtOH (15 ml) at room temperature under atmospheric pressure. It took 1.5 h for the reaction to reach completion. After removal of the catalyst by filtration, the filtrate was evaporated to dryness *in vacuo*. The residue was chromatographed using benzene–AcOEt (5:1) to give the title compound (99 mg, 96%). Recrystallization from benzene–hexane gave colorless needles, mp 163—165 °C. *Anal.* Calcd for $C_{11}H_{12}N_2O_2$: C, 64.69; H, 5.92; N, 13.72. Found: C, 64.68; H, 5.90; N, 13.66. This compound was identical with the sample prepared from **2b** by hydrolysis.

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