Fischer Indolization of Ethyl Pyruvate 2-Bis(2-methoxyphenyl)hydrazone and New Insight into the Mechanism of Fischer Indolization. (Fischer Indolization and Its Related Compounds. XXVII[1])

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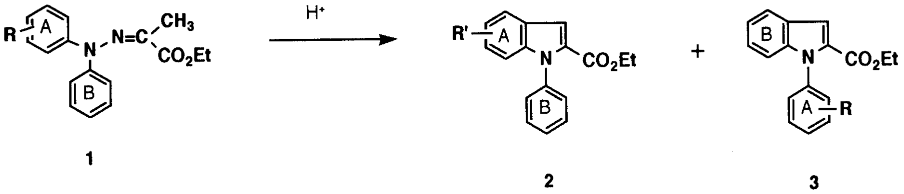
In connection with studies on the direction of cyclization in the Fischer indolization of substituted diphenylhydrazones, the Fischer indolization of ethyl pyruvate 2-bis(2-methoxyphenyl)hydrazone (6) was carried out. The result showed that cyclization in Fischer indolization of diphenylhydrazone does not always proceed to the electron-richer nucleus, but depends on the conformation of the enehydrazine. Thus, the Fischer indolization should proceed *via* a [3,3] sigmatropic route, with an electronic effect.

Key words Fischer indolization; diarylhydrazone; indole; reaction mechanism; chlorodiphenylamine; Goldberg reaction

In the previous studies[2)] we carried out the Fischer indolization of various diphenylhydrazones (**1**) which had electron-attractive or -donative group(s) on one phenyl ring of the two, in order to examine the abnormality of the Fischer indolization of 2-methoxyphenylhydrazone.[3a)] The term "abnormality" means that cyclization occurs on the *ortho* position occupied by the substituent. Later, this abnormality was found[3b)] to occur commonly when the phenylhydrazone has an electron-donative substituent such as a phenyl or an acetoamino group at the *ortho* position. The results on the Fischer indolization of various diphenylhydrazones (**1**) are summarized in Table 1.

From the results[2a)] of the Fischer indolization of hydrazones having a 4-substituted (**1a, c**) or 3,5-dimethoxyphenyl ring (**1b**), it was clarified that Fischer indolization proceeded mainly towards the electron-richer phenyl ring in general. The Fischer indolization[2b)] of the hydrazone having a phenyl and a 2,6-dimethoxy phenyl ring (**1d**) also proceeded mainly towards the electron-richer ring,[2a)] as did that of the hydrazone having a phenyl and a 2-(trifluoromethyl)phenyl ring (**1f**). However, the Fischer indolization[2c)] of the hydrazone having a phenyl and a 2-methoxyphenyl ring (**1e**) proceeded mainly towards the electron-poorer ring. This unexpected result suggested that

Table 1. Summary of the Fischer Indolization of Substituted Phenyl-phenylhydrazone (**1**)



Hydrazone (**1**)	Acid catalyst	Yields of indoles (%) **2**	Yields of indoles (%) **3**	Ratio of **2** to **2**+**3** (%)
R=4-OCH_3 (**1a**)	HCl/EtOH	43	2.3	95
R=3,5-di-OCH_3 (**1b**)	HCl/EtOH	43	17	72
R=4-$COOC_2H_5$ (**1c**)	HCl/EtOH	11	66	15
R=2,6-di-OCH_3 (**1d**)	HCl/EtOH	12	0	100
R=2,6-di-OCH_3 (**1d**)	$ZnCl_2$/AcOH	3.9	1.9	67
R=2-OCH_3 (**1e**)	HCl/EtOH	4.1	35	11
R=2-OCH_3 (**1e**)	$ZnCl_2$/AcOH	4.4	26	15
R=2-CF_3 (**1f**)	HCl/EtOH	17	74	19
R=2-CF_3 (**1f**)	$ZnCl_2$/AcOH	15	82	15

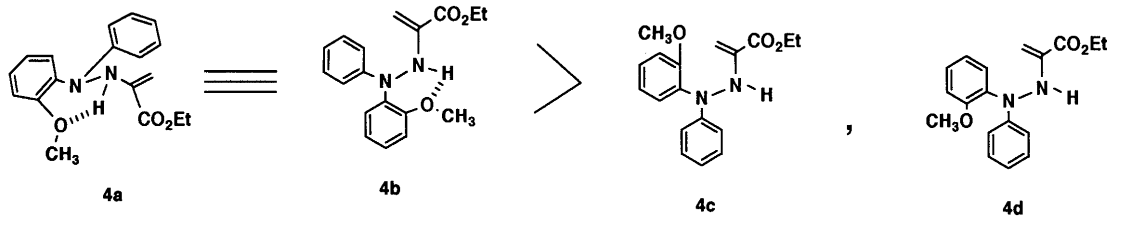


Chart 1

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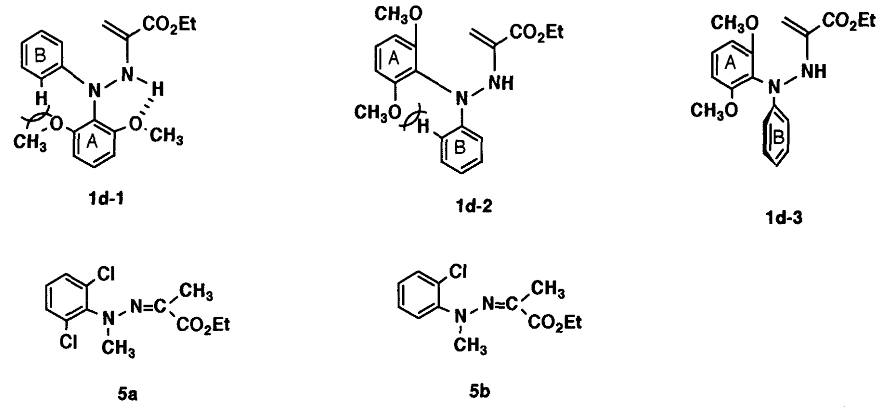
some other factor besides the electron density of phenyl ring, *e.g.*, the conformation of the intermediate on cyclization, would be important.

It is known[4] that the first cyclization step of the Fischer indolization occurs in the enehydrazine intermediate. The conformation of the enehydrazine intermediate is important, since the first step of the Fischer indolization proceeds *via* [3,3] sigmatropic rearrangement of the enehydrazine rather than electrophilic reaction.[2a] In the case of **4a** we can consider three enehydrazine conformers (**4b**—**d**) depending on the position of the methoxy group. In these conformers the reaction sites (phenyl group, N–N bond, and C=C bond) should be planar. Of course, the conformer should have a chair-like arrangement[5] (*e.g.*, **4a** corresponding to **4b**) as seen in the Claisen rearrangement *via* suprafacial-suprafacial [3,3] sigmatropic processes. The result of the Fischer indolization of **1e** shows that **4b** is more favorable than **4c** or **4d**. The reason for this may be the stability of **4b** due to its intramolecular hydrogen bonding between the methoxy oxygen and NH. Application of a similar consideration to the 2,6-dimethoxyhydrazone (**1d**) is shown in Chart 2, where **1d**-1 is expected to be the stable conformer corresponding to **4b**. However, the conformer (**1d**-2) was more favorable than **1d**-1 judged from the experimental outcome. We suggest that the B-ring can not take a chair-like arrangement in **1d**-1 due to the interaction between a methoxy group on ring A and an *ortho*-proton on ring B, while such interaction in **1d**-2 was decreased by rotation of the B-ring having no methoxy group (**1d**-3). Increase of the electron density in ring A by the two methoxy groups would also assist cyclization towards the A ring. However, the hydrazone (**1d**) gave indolic products in only low yields. The importance of chair-like arrangement has already been shown[6] in the Fischer indolization of ethyl pyruvate 2-(2,6-dichloro-*N*-methyl)phenylhydrazone (**5a**), where the *N*-methyl group disfavored the chair-like form of the enehydrazine, leading to difficulty in indolization, although introduction of an *N*-methyl group into ethyl pyruvate 2-chlorophenylhydrazone (**5b**) made the Fischer indolization proceed faster than with the mother NH-hydrazone.[3a]

In order to clarify the effect of an *ortho*-methoxy group on the conformation of the enehydrazine intermediate at the stage of the first cyclization we examined the Fischer indolization of ethyl pyruvate 2-bis(2-methoxyphenyl)hydrazone (**6**), where the intermediate **6a** would be more stable than **6b**, because steric congestion can be expected between a methoxy group in the A ring and an *ortho*-proton in the B ring. Our findings are presented here.

Fischer Indolization The preparation of the ethyl pyruvate 2-bis(2-methoxyphenyl)hydrazone (**6**) has already been reported.[7] This hydrazone (**6**) was submitted to Fischer indolization reaction with hydrogen chloride in ethanol and with zinc chloride in acetic acid. The results are summarized in Chart 4. The reaction with hydrogen chloride in ethanol gave five products, a diphenylamine (**9**), three chlorodiphenylamines (**7**, **8**, **10**), and an indolic product (**11**). The reaction with zinc chloride in acetic acid gave a diphenylamine (**9**) and two indolic products (**11**, **12**). The diphenylamine (**9**) was easily characterized as *N*,*N*-bis(2-methoxyphenyl)amine,[7] the starting material for preparation of the hydrazone (**6**). As similar chlorodiphenylamines had already been obtained in the Fischer indolization of other methoxy diphenylhydrazones[2] (**1a**, **d**, **e**), the structures of **7**, **8**, and **10** were determined from the spectral data and confirmed by alternative synthesis as described later.

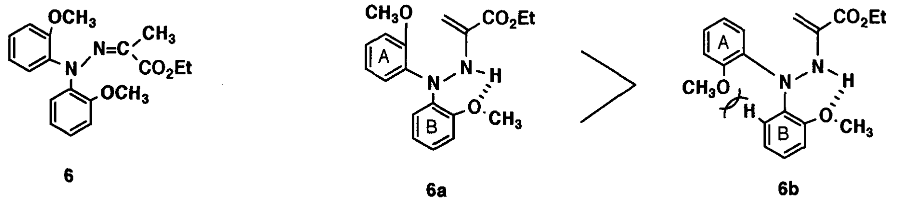
One (**11**) of the indolic products, ethyl 7-methoxy-*N*-(2-methoxyphenyl)indole-2-carboxylate, was the normal product and its structure was confirmed by alternative synthesis through the Goldberg reaction of the correspond-



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

5a **5b**

Chart 2



6 **6a** **6b**

Chart 3

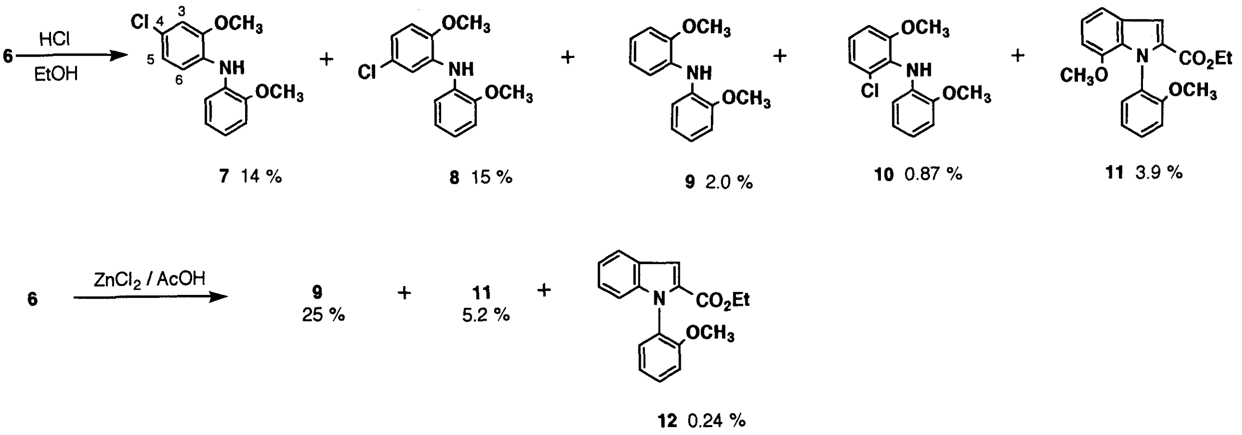


Chart 4

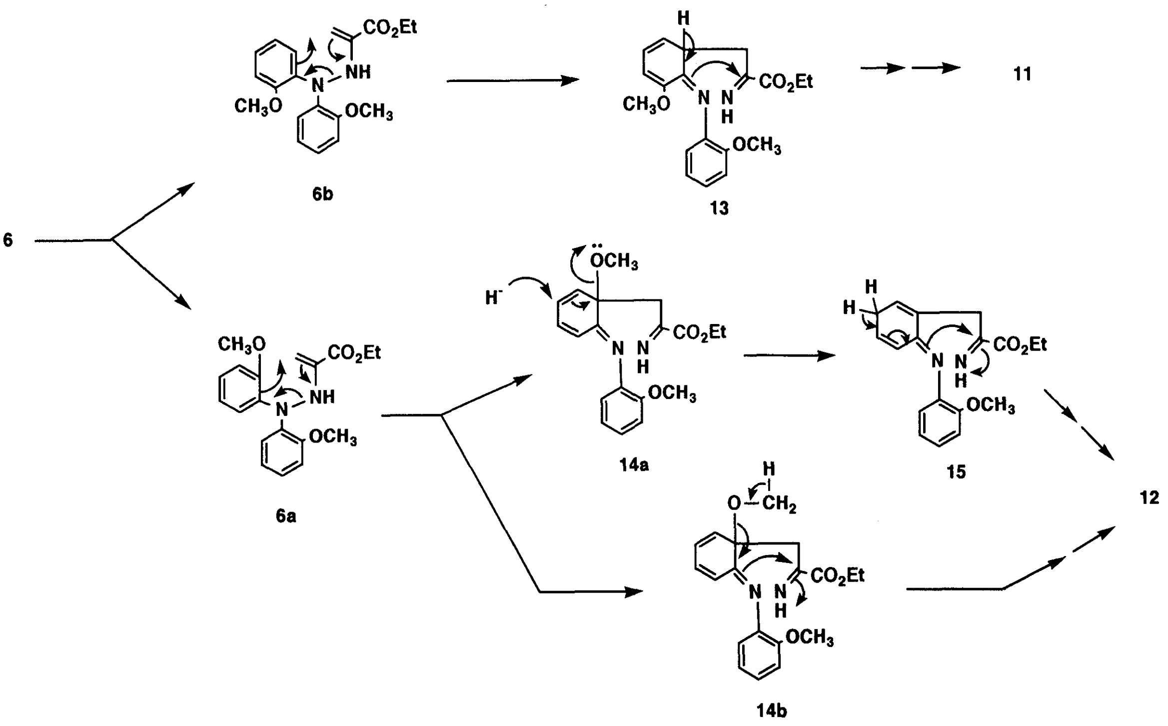


Chart 5

ing NH-indole as described later. Another indolic product (**12**) was identified by us.[2c)]

The mechanism of formation of the indolic products (**11, 12**) is suggested to involve our abnormal Fischer indolization,[2,3)] as shown in Chart 5. The formation of ethyl *N*-(2-methoxyphenyl)-7-methoxyindole-2-carboxylate (**11**) apparently proceeded from the conformer **6b** *via* **13**, whereas ethyl *N*-(2-methoxyphenyl)indole-2-carboxylate (**12**) should be derived from the conformer **6a** *via* **14a** and **15**, or **14b**, because the lack of a methoxy group in the benzene ring of the indole nucleus shows that cyclization occurred at the site of the methoxy group of the hydrazone (**6**). Two possible mechanisms can be considered for the next step (removal of the methoxy group). The loss of the *ortho*-substituent of phenylhydrazone often occurs during Fischer indolization.[3b)] The preferred formation of **11** over **12** implies that our initial assumption might be wrong, although the yields were very low. Marked formation of chlorodiphenylamines was attributed to the structure of the hydrazone (**6**) which has a methoxy group in each phenyl group.[2b,c)]

Alternative Syntheses of the Fischer Products The present chlorodiphenylamines should be the three of the four possible monochloro derivatives of *N*-(2-methoxyphenyl)-*o*-anisidine (**9**). If these three were formed through similar mechanisms to the previous ones,[2)] the position of chlorine should be *meta* to the methoxy group as the first choice and then *meta* to the nitrogen functionality. Steric bulkiness of the substituents has some effect on approach of a chloride anion at the neighboring position. These considerations indicated that the three chlorodiphenylamine products were the 4-, 5-, and 6-chlorodiphenyl amines (**7**, **8**, **10**).

The synthetic routes to them are shown in Chart 6; they were all prepared from known trisubstituted benzene derivatives. 4′-Chloro-*o*-acetanisidide (**16**) was converted into 4′-chloro-*N*-(2-methoxyphenyl)-*o*-acetanisidide (**17**) by means of the Goldberg reaction. The alkaline hydrolysis

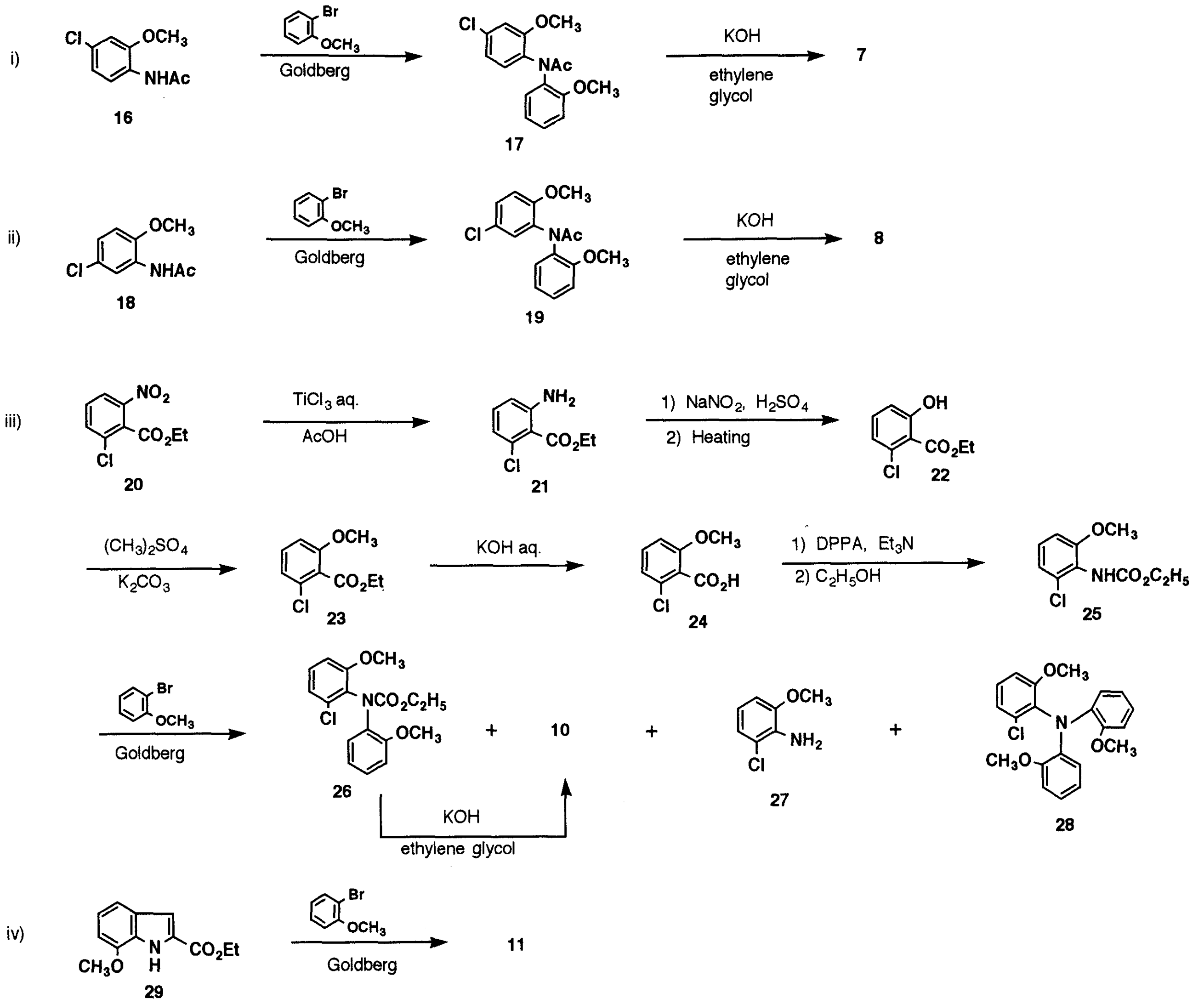


Chart 6

of **17** gave the target product, 4-chloro-*N*-(2-methoxyphenyl)-*o*-anisidine (**7**), which was identical with the Fischer product. The second target compound, 5-chloro-*N*-(2-methoxyphenyl)-*o*-anisidine (**8**), was prepared from 5′-chloro-*o*-acetanisidide (**18**) in a similar manner *via* the diphenylacetamide (**19**). The synthetic material was identical with the Fischer product (**8**).

The third one was prepared starting from ethyl 2-chloro-6-nitrobenzoate (**20**). The nitro compound (**20**) was treated with titanium trichloride to give the aniline (**21**), which was converted into phenol (**22**) by diazotization, followed by hydrolysis. Methylation of **22**, followed by hydrolysis gave anisic acid (**24**), which was converted into the carbamate (**25**) by Curtius rearrangement with diphenyl phosphoroazidate (DPPA). The Goldberg reaction of **25** with 2-bromoanisole gave four products. The first product (**26**) was the desired Goldberg product and the second was the final target compound (**10**), which would be formed by hydrolysis, followed by decarboxylation from **26**. Compound **26** was independently converted by alkaline hydrolysis into **10**, which was identical with the Fischer product. The third product (**27**) was 6-chloro-*o*-anisidine, which was generated by hydrolysis and decarboxylation of **25**. The fourth one (**28**) was the further 2-methoxyphenylated product of **10**. Ethyl 7-methoxy-*N*-(2-methoxyphenyl)indole-2-carboxylate (**11**) was prepared from ethyl 7-methoxyindole-2-carboxylate[3a] (**29**) by Goldberg reaction with 2-bromoanisole.

Consideration of the Results of the Fischer Indolization Although indoles were produced in low yields, we can consider the structures of the indoles formed in the Fischer indolization in terms of the conformation of enehydrazine at the first cyclization step (Charts 2 and 3). The dimethoxyindole (**11**) should be formed through the conformation **6b**, and the monomethoxyindole (**12**) through the conformation **6a**, as shown in Charts 3 and 5. However, the predominant formation of **11** over **12** indicated that our assumption was invalid, even though it was based on the results[3a] that the Fischer indolization of ethyl pyruvate 2-(2-methoxyphenyl)hydrazone occurred mainly at the *ortho* position occupied by the methoxy group. Thus, at the present time the effect of an *ortho*-methoxy group of phenylhydrazone on the first cyclization step in Fischer indolization is not clear. However, we have obtained some information through our studies on Fischer indolization of variously substituted diphenylhydrazones; we assumed on the basis of the results

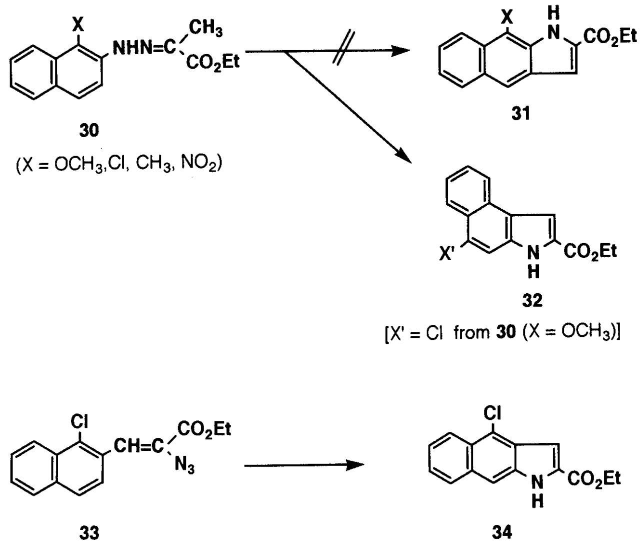


Chart 7

of the Fischer indolization of *para* or *meta*-substituted diphenylhydrazones[2a] that the mechanism is ionic, but it appeared that an *ortho*-substituent works much more effectively on the conformation of the enehydrazine intermediate rather than electronically, as judged from the results of the Fischer indolization of 2-substituted diphenylhydrazones[1,2b,c] and ethyl pyruvate 2,6-dichloro-N_A-methylphenylhydrazone[6] (**5a**). In addition, the Fischer indolization[8] of 1-substituted 2-naphthylhydraoznes (**30**) occurred exclusively towards the 1-(or α)position to give benz[*e*]indoles (**32**), but not benz[*f*]indole (**31**), independently of the substituent at the 1-position, whereas the Hemetzberger reaction, which is believed to proceed *via* a nitrene intermediate, of ethyl α-azido-β-(1-chloro-2-naphthyl)acrylate (**33**) exhibited cyclization towards the 3-position to give the benz[*f*]indole (**34**). The combination of these results suggests that the first cyclization step of Fischer indolization proceeds *via* a [3,3] sigmatropic mechanism involving an electronic effect in part.

The formation of the chlorodiphenylamines (**7, 8, 10**) in the Fischer indolization with hydrogen chloride in ethanol should be similar to that of the chlorodiphenylamines from ethyl pyruvate 2-(2,6-dimethoxyphenyl)-phenylhydrazone[2b] (**1d**) and ethyl pyruvate 2-(2-methoxyphenyl)phenylhydrazone[2c] (**1e**), in which the methoxy group played a crucial role. As the present hydrazone (**6**) has a methoxy group on each nucleus, the side reaction which formed **7**, **8**, and **10** was accelerated and thus the yields of the indoles were very low.

Experimental

All melting points were measured on a micro melting point hot stage (Yanagimoto) and are uncorrected. For spectral data following instruments were used: IR, Shimadzu IR-400; ^{1}H-NMR, Hitachi R-24B (60 MHz); MS, JEOL JMS-01-SG-2 spectrometer. The NMR chemical shifts are given in δ-values referred to internal tetramethylsilane, and the assignments of all NH and OH signals were confirmed by the disappearance of the signals after addition of D_2O. Mass spectra were measured with a direct inlet system. For column chromatography, silica gel (Kiesel gel 60, 70—230 mesh, Merck) and for TLC, Kiesel gel GF_{254}, Merck, were used. The abbreviations used are as follows: s, singlet; d, doublet; dd, double doublet; t, triplet; q, quartet; m, multiplet; dif, diffused; br, broad; arom, aromatic. All starting materials were commercially available unless otherwise stated. The reaction temperature shown was measured in the bath.

Fischer Indolization of Ethyl Pyruvate 2-Bis(2-methoxyphenyl)hydrazone (6) with HCl/EtOH A solution of ethyl pyruvate 2-bis(2-methoxyphenyl)hydrazone[7] (**6**) (3.00 g) in absolute EtOH (60 ml) saturated with dry HCl gas was stirred for 1 h at room temperature, then poured into H_2O. The whole was extracted with Et_2O, and the organic layer was washed with H_2O, dried over $MgSO_4$, and evaporated to dryness *in vacuo*. The residue (1.91 g) was chromatographed over silica gel with benzene to afford two fractions. The first fraction (740 mg) was repeatedly chromatographed with benzene, and then Et_2O–hexane (1 : 10) to give four products.

4-Chloro-*N*-(2-methoxyphenyl)-*o*-anisidine (**7**): The first product (312 mg, 14%) was recrystallized with hexane–AcOEt to give colorless needles, mp 66—69 °C. *Anal.* Calcd for $C_{14}H_{14}ClNO_2$: C, 63.76; H, 5.35; N, 5.31. Found: C, 63.71; H, 5.24; N, 5.28. IR $\nu_{\max}^{\text{Nujol}}$ cm^{-1}: 3390 (NH). ^{1}H-NMR ($CDCl_3$) δ: 3.85 (6H, s, $2\times OCH_3$), 6.35 (1H, br s, NH), 6.65—7.40 (7H, m, arom H). MS *m/z*: 265 ($M^+ + 2$, 38% intensity of M^+), 263 (M^+, base peak). This compound was indentical with an authentic sample.

5-Chloro-*N*-(2-methoxyphenyl)-*o*-anisidine (**8**): The second product (344 mg, 15%) was a colorless oil. IR $\nu_{\max}^{\text{neat}}$ cm^{-1}: 3400 (NH). ^{1}H-NMR ($CDCl_3$) δ: 3.83 (6H, s, $2\times OCH_3$), 6.47 (1H, br s, NH), 6.68—7.50 (7H, m, arom H). MS *m/z*: 265 ($M^+ + 2$, 34% intensity of M^+), 263 (M^+, base peak). High-resolution MS: Calcd for $C_{14}H_{14}ClNO_2$: 263.071. Found: 263.068. This compound was identical with an authentic sample.

N,*N*-Bis(2-methoxyphenyl)amine (**9**): The third product (40 mg, 2.0%) was a pale yellow oil. IR $\nu_{\max}^{\text{neat}}$ cm^{-1}: 3400 (NH). MS *m/z*: 229 (M^+). This compound was identical with an authentic sample.[7]

6-Chloro-*N*-(2-methoxyphenyl)-*o*-anisidine (**10**): The fourth product (20 mg, 0.87%) was recrystallized from hexane–Et_2O to give colorless prisms, mp 96—97.5 °C. *Anal.* Calcd for $C_{14}H_{14}ClNO_2$: C, 63.76; H, 5.35; N, 5.31. Found: C, 63.51; H, 5.14; N, 5.37. IR $\nu_{\max}^{\text{Nujol}}$ cm^{-1}: 3400 (NH). ^{1}H-NMR ($CDCl_3$) δ: 3.75 and 3.88 (each 3H, s, OCH_3), 6.05 (1H, br s, NH), 6.20—7.15 (7H, m, arom H). MS *m/z*: 265 ($M^+ + 2$, 38% intensity of M^+), 263 (M^+). This compound was identical with an authentic sample.

Ethyl 7-Methoxy-1-(2-methoxyphenyl)indole-2-carboxylate (**11**): The second fraction (147 mg) was re-chromatographed over silica gel with Et_2O–hexane (1 : 10) to give a solid (112 mg). Recrystallization from Et_2O–hexane gave colorless prisms, mp 88.5—92.5 °C. *Anal.* Calcd for $C_{19}H_{19}NO_4$: C, 70.14; H, 5.89; N, 4.30. Found: C, 69.77; H, 5.75; N, 4.29. IR $\nu_{\max}^{\text{Nujol}}$ cm^{-1}: 1720 (C=O). ^{1}H-NMR ($CDCl_3$) δ: 1.18 (3H, t, J=7.0 Hz, $CH_2\underline{CH_3}$), 3.51 and 3.65 (each 3H, s, OCH_3), 4.15 (2H, q, J=7.0 Hz, $O\underline{CH_2}CH_3$), 6.50—7.50 (8H, m, arom H). MS *m/z*: 325 (M^+). This compound was identical with an authentic sample.

Fischer Indolization of Ethyl Pyruvate 2-Bis(2-methoxyphenyl)hydrazone (6) with $ZnCl_2$/AcOH Anhydrous $ZnCl_2$ (0.92 g) was added to a solution of the hydrazone (**6**) (1.540 g) in AcOH (26 ml). The reaction mixture was stirred at 55—60 °C for 1.3 h, then poured into H_2O and the whole was extracted with $CHCl_3$. The organic layer was washed with saturated $NaHCO_3$ and H_2O, dried over $MgSO_4$, and evaporated to dryness *in vacuo*. The oily residue was chromatographed over silica gel with benzene.

N,*N*-Bis(2-methoxyphenyl)amine (**9**): The product from the first eluate (295 mg) was re-chromatographed on silica gel with benzene–hexane (1 : 8) to give a pale yellow oil (260 mg, 25%). IR $\nu_{\max}^{\text{neat}}$ cm^{-1}: 3400 (NH). MS *m/z*: 229 (M^+). This compound was identical with an authentic sample.[7]

The product from the second eluate was re-chromatographed over silica gel with AcOEt–hexane (1 : 10) to give two compounds.

Ethyl 7-Methoxy-1-(2-methoxyphenyl)indole-2-carboxylate (**11**): The first product was a pale yellow solid (76 mg, 5.2%). Recrystallization from Et_2O–hexane gave colorless prisms, mp 89.5—91.0 °C. *Anal.* Calcd for $C_{19}H_{19}NO_4$: C, 70.14; H, 5.89; N, 4.30. Found: C, 69.93; H, 5.71; N, 4.19. IR $\nu_{\max}^{\text{Nujol}}$ cm^{-1}: 1725 (C=O).

Ethyl 1-(2-Methoxyphenyl)indole-2-carboxylate (**12**): The product from the second eluate was a pale yellow solid. IR $\nu_{\max}^{\text{CHCl}_3}$ cm^{-1}: 1710 (C=O). MS *m/z*: 295 (M^+). This compound was identical with an authentic sample.[2c]

Independent Syntheses. 4′-Chloro-*N*-(2-methoxyphenyl)-*o*-acetanisidide (17) The mixture of 4′-chloro-*o*-acetanisidide[9] (**16**) (200 mg), anhydrous K_2CO_3 (150 mg), Cu_2Br_2 (38 mg) in *o*-bromoanisole (1 ml) was heated at 210 °C for 13 h under an Ar atmosphere, then poured into H_2O. The whole was extracted with Et_2O, and the organic layer was washed with saturated NaCl, and dried over anhydrous K_2CO_3. The solvent was evaporated *in vacuo* to leave an oily residue, which was chromatographed on silica gel with Et_2O–hexane (5 : 1) to give crystals (240 mg, 78%). Recrystallization from benzene–hexane gave colorless prisms, mp 92—94 °C. *Anal.* Calcd for $C_{16}H_{16}ClNO_3$: C, 62.85; H, 5.27; N, 4.58. Found: C, 63.15; H, 5.25; N, 4.71. IR ν_{max}^{Nujol} cm^{-1}: 1670 (C=O). ^1H-NMR ($CDCl_3$) δ: 2.02 (3H, s, $COCH_3$), 3.90 (6H, s, $2\times OCH_3$), 6.65—7.50 (7H, m, arom H).

4-Chloro-*N*-(2-methoxyphenyl)-*o*-anisidine (7) A mixture of the acetate (**17**) (79 mg) and KOH (250 mg) in ethylene glycol (2 ml) was heated at 140 °C for 5 h under an Ar atmosphere, then poured into H_2O, and the whole was extracted with Et_2O. The organic layer was washed with saturated NaCl, and dried over $MgSO_4$. The solvent was evaporated *in vacuo* to give a pale brown oil (61 mg), which was chromatographed over silica gel with benzene to give crystals (46 mg, 68%). Recrystallization from Et_2O–hexane gave colorless fine needles, mp 66—68 °C. *Anal.* Calcd for $C_{14}H_{14}ClNO_2$: C, 63.76; H, 5.35; N, 5.31. Found: C, 63.80; H, 5.23; N, 5.19. IR ν_{max}^{Nujol} cm^{-1}: 3390 (NH).

5′-Chloro-*N*-(2-methoxyphenyl)-*o*-acetanisidide (19) A mixture of 5′-chloro-*o*-acetanisidide[10] (**18**) (200 mg), K_2CO_3 (150 mg), and Cu_2Br_2 (39 mg) in *o*-bromoanisole (1 ml) was heated at 200—210 °C for 18 h under an Ar atmosphere. The reaction mixture was poured into H_2O, and the whole was extracted with Et_2O. The organic layer was washed with saturated NaCl, and dried over $MgSO_4$. Removal of the solvent *in vacuo* left an oily residue, which was chromatographed over silica gel with Et_2O–hexane gave pale brown prisms (238 mg, 78%). Recrystallization from benzene–hexane gave pale brown prisms, mp 122—125 °C. *Anal.* Calcd for $C_{16}H_{16}ClNO_3$: C, 62.85; H, 5.27; N, 4.58. Found: C, 62.79; H, 5.12; N, 4.59. IR ν_{max}^{Nujol} cm^{-1}: 1680 (C=O). ^1H-NMR ($CDCl_3$) δ: 2.00 (3H, s, $COCH_3$), 3.80 and 3.82 (each 3H, s, OCH_3), 6.55—7.55 (7H, m, arom H). MS *m/z*: 307 ($M^+ +2$, 35% intensity of M^+), 305 (M^+).

5-Chloro-*N*-(2-methoxyphenyl)-*o*-anisidine (8) A mixture of the acetate (**19**) (102 mg) and KOH (240 mg) in ethylene glycol (2 ml) was heated at 150 °C for 3 h under an Ar atmosphere. The reaction mixture was poured into H_2O, and the whole was extracted with Et_2O. The organic layer was washed with saturated NaCl, and dried over anhydrous K_2CO_3. Removal of the solvent left an oily residue (80 mg), which was chromatographed over silica gel with benzene to give a colorless oil (74 mg, 84%). IR ν_{max}^{neat} cm^{-1}: 3400 (NH). High-resolution MS: Calcd for $C_{14}H_{14}ClNO_2$: 263.071. Found: 263.069.

Ethyl 6-Chloroanthranilate (21) $TiCl_3$ (25%, 2.9 ml) was added to a solution of ethyl 2-chloro-6-nitrobenzoate[11] (**20**) (200 mg) in AcOH (3 ml). The mixture was stirred at room temperature for 9 min, basified with 20% NaOH, and extracted with CH_2Cl_2–MeOH (95 : 5). The organic layer was washed with saturated NaCl, dried over $MgSO_4$ and evaporated *in vacuo* to give a pale yellow oil (165 mg, 95%). IR ν_{max}^{neat} cm^{-1}: 3470 and 3370 (NH), 1700 (C=O). ^1H-NMR ($CDCl_3$) δ: 1.40 (3H, t, J=8.0 Hz, $CH_2C\underline{H_3}$), 4.40 (2H, q, J=8.0 Hz, $OC\underline{H_2}CH_3$), 6.54 (1H, dd, J=2.0, 8.0 Hz, $\underline{C_5}$-H), 6.69 (1H, dd, J=8.0, 2.0 Hz, $\underline{C_3}$-H), 7.04 (1H, t, J=8.0 Hz, C_4-H). MS *m/z*: 201 ($M^+ +2$, 39% intensity of M^+), 199 (M^+). This compound was used for the following reaction without further purification.

Ethyl 6-Chlorosalicylate (22) A solution of $NaNO_2$ (2.51 g) in H_2O (56 ml) was added dropwise during 5 min to a suspension of the aniline (**21**) (6.96 g) and concentrated H_2SO_4 (15.4 ml) in a mixture of H_2O (21 ml) and ice (42 g) under ice-cooling. The resulting clear diazonium salt solution was heated at 120 °C for 1 h until generation of N_2 ceased. The reaction mixture was poured into ice-H_2O, and the whole was extracted with Et_2O. The organic layer was dried over $MgSO_4$ and evaporated to dryness *in vacuo* to give a reddish brown oily residue (5.121 g), which was chromatographed over silica gel with hexane–AcOEt (3 : 1) to give a brown oily residue (3.225 g, 46%). IR ν_{max}^{neat} cm^{-1}: 3040 (OH), 1665 (C=O). ^1H-NMR ($CDCl_3$) δ: 1.44 (3H, t, J=7.5 Hz, $CH_2C\underline{H_3}$), 4.45 (2H, q, J=7.5 Hz, $OC\underline{H_2}CH_3$), 7.08 (3H, m, arom H). MS *m/z*: 202 ($M^+ +2$, 37% intensity of M^+), 200 (M^+).

Ethyl 6-Chloro-2-methoxybenzoate (23) A mixture of the phenol (**22**) (850 mg), anhydrous K_2CO_3 (1.47 g), and Me_2SO_4 (0.60 ml) in acetone (25 ml) was refluxed for 3.5 h. The reaction mixture was basified with 10% KOH and left standing overnight. After dilution with H_2O, the reaction mixture was extracted with Et_2O. The organic layer was washed with saturated NaCl, dried over $MgSO_4$, and evaporated to dryness *in vacuo*. The residue (1.706 g) was chromatographed over silica gel with AcOEt–hexane (1 : 10) to give a pale yellow oil (736 mg, 81%). IR ν_{max}^{neat} cm^{-1}: 1730 (C=O). ^1H-NMR ($CDCl_3$) δ: 1.38 (3H, t, J=8.0 Hz, $CH_2C\underline{H_3}$), 3.80 (3H, s, OCH_3), 4.39 (2H, q, J=8.0 Hz, $OC\underline{H_2}CH_3$), 6.75 (1H, dd, J=8.5, 2.0 Hz, C_5-H), 6.91 (1H, dd, J=8.5, 2.0 Hz, $\underline{C_3}$-H), 7.22 (1H, t, J=8.5 Hz, C_4-H). High Resolution MS: Calcd for $C_{10}H_{11}ClO_3$: 214.040. Found: 214.040.

6-Chloro-*o*-anisic Acid (24) A suspension of the ester (**23**) (1.36 g) in 10% KOH (100 ml) was refluxed for 3 h. After cooling, the reaction mixture was acidified with concentrated HCl and extracted with AcOEt. The organic layer was dried over $MgSO_4$ and evaporated to dryness *in vacuo* to give a pale yellow solid (1.156 g, 98%). Recrystallization from benzene–hexane gave colorless prisms, mp 141—143 °C (lit.,[12] mp 144—145 °C). *Anal.* Calcd for $C_8H_7ClO_3$: C, 51.50; H, 3.78. Found: C, 51.33; H, 3.69. IR ν_{max}^{Nujol} cm^{-1}: 1715 (C=O). ^1H-NMR ($CDCl_3$) δ: 3.88 (3H, s, OCH_3), 6.81 (1H, dd, J=1.5, 8.0 Hz, C_5-H), 6.96 (1H, dd, J=1.5, 8.0 Hz, C_3-H), 7.27 (1H, t, J=8.0 Hz, C_4-H), 11.22 (1H, s, $CO_2\underline{H}$). MS *m/z*: 188 ($M^+ +2$, 37% intensity of M^+), 186 (M^+).

Ethyl 6-Chloro-2-methoxycarbanilate (25) DPPA (1.62 ml) and then Et_3N (1.27 ml) were added to a solution of the carboxylic acid (**24**) (1.170 g) in dioxane (20 ml), and the mixture was stirred at room temperature for 30 min. Then EtOH (4.7 ml) was added, and the whole was refluxed for a further 2 h. After evaporation of the solvent *in vacuo*, the residue was dissolved in Et_2O. This solution was washed with 5% citric acid, 5% $NaHCO_3$, and then saturated NaCl, and dried over $MgSO_4$. Removal of the solvent gave a brown solid (1.651 g), which was chromatographed over silica gel with benzene–AcOEt (10 : 1) to give colorless prisms (1.409 g, 98%). Recrystallization from AcOEt–hexane gave colorless prisms, mp 100.5—101.5 °C. *Anal.* Calcd for $C_{10}H_{12}ClNO_3$: C, 52.30; H, 5.27; N, 6.10. Found: C, 52.43; H, 5.22; N, 6.04. IR ν_{max}^{Nujol} cm^{-1}: 3230 (NH), 1710 (C=O). ^1H-NMR ($CDCl_3$) δ: 1.34 (3H, t, J=7.0 Hz, $CH_2C\underline{H_3}$), 3.87 (3H, s, OCH_3), 4.24 (2H, q, J=7.0 Hz, $OC\underline{H_2}CH_3$), 6.15 (1$\underline{H}$, br s, NH), 6.72—7.30 (3H, m, arom H). MS *m/z*: 231 ($\underline{M}^+ +2$, 33% intensity of M^+), 229 (M^+).

Ullmann Reaction of the Carbanilate (25) A mixture of the carbanilate (**25**) (550 mg), anhydrous K_2CO_3 (399 mg), Cu_2Br_2 (32 mg), and *o*-bromoanisole (0.605 ml) in nitrobenzene (8 ml) was heated at 180 °C for 3 h, and then the nitrobenzene was evaporated off *in vacuo*. The residue was poured into H_2O and the whole was extracted with Et_2O. The organic layer was washed with saturated NaCl, dried over $MgSO_4$, and evaporated to dryness *in vacuo*. The residue (516 mg) was chromatographed over silica gel with hexane–AcOEt to give the following four compounds, in order of elution.

Ethy 6-Chloro-2-methoxy-*N*-(2-methoxyphenyl)carbanilate (**26**): A pale brown oil (68 mg, 8.5%). IR ν_{max}^{neat} cm^{-1}: 1710 (C=O). ^1H-NMR ($CDCl_3$) δ: 1.22 (3H, t, J=7.0 Hz, $CH_2C\underline{H_3}$), 3.76 and 3.86 (each 3H, s, OCH_3), 4.20 (2H, q, J=7.0 Hz, $OC\underline{H_2}CH_3$), 6.60—7.32 (7H, m, arom H). High-resolution MS: Calcd for $\underline{C_{17}}H_{18}ClNO_4$: 335.093. Found: 335.089.

6-Chloro-*o*-anisidine[13] (**27**): A pale yellow oil (93 mg, 25%). IR ν_{max}^{neat} cm^{-1}: 3440 and 3350 (NH_2). ^1H-NMR ($CDCl_3$) δ: 3.82 (3H, s, OCH_3), 4.14 (2H, br s, NH_2), 6.55—6.95 (3H, m, arom H). High-resolution MS *m/z*: Calcd for C_7H_8ClNO: 157.030. Found: 157.028.

6-Chloro-*N*-(2-methoxyphenyl)-*o*-anisidine (**10**): A solid (15 mg, 2.4%). Recrystallization from Et_2O–hexane gave colorless prisms, mp 95.5—96.5 °C. This sample was identical with the sample prepared by hydrolysis of the carbanilate (**26**).

6-Chloro-*N*,*N*-bis(2-methoxyphenyl)-*o*-anisidine (**28**): A solid (12 mg, 1.4%). Recrystallization from hexane gave colorless prisms, mp 83—85 °C. *Anal.* Calcd for $C_{21}H_{20}ClNO_3$: C, 68.20; H, 5.45; N, 3.79. Found: C, 68.10; H, 5.37; N, 3.66. IR $\nu_{max}^{CHCl_3}$ cm^{-1}: no characteristic band. ^1H-NMR ($CDCl_3$) δ: 3.49 (9H, s, $3\times OCH_3$), 6.65—7.05 (11H, m, arom H). MS *m/z*: 371 ($M^+ +2$, 40% intensity of M^+), 369 (M^+).

Conversion of the Carbanilate (26) into 6-Chloro-*N*-(2-methoxyphenyl)-*o*-anisidine (10) A mixture of the carbanilate (**26**) (65 mg) and KOH (163 mg) in ethylene glycol was heated at 180 °C for 6 h under an Ar atmosphere. The reaction mixture was poured into H_2O, and the whole was extracted with Et_2O. The organic layer was washed with saturated NaCl, dried over $MgSO_4$, and evaporated to dryness *in vacuo*. The oily residue (478 mg) was chromatographed over silica gel with hexane–AcOEt (15 : 1) to give a solid (33 mg, 65%). Recrystallization from Et_2O–hexane gave colorless prisms, mp 95.5—96.5 °C. *Anal.* Calcd for $C_{14}H_{14}ClNO_2$: C, 63.76; H, 5.35; N, 5.31. Found: C, 63.77; H, 5.24; N, 5.11. IR ν_{max}^{Nujol} cm^{-1}: 3400 (NH).

Further elution gave the starting carbanilate (**26**) (25%).

Ethyl 7-Methoxy-1-(2-methoxyphenyl)indole-2-carboxylate (11) A mixture of ethyl 7-methoxyindole-2-carboxylate[3a)] (**29**) (111 mg), anhydrous K_2CO_3 (116 mg), Cu_2Br_2 (14 mg), *o*-bromoanisole (405 mg), and pyridine (0.2 ml) in nitrobenzene (1.6 ml) was heated at 210 °C for 5 h under an Ar atmosphere. The reaction mixture was evaporated and the residue was chromatographed over silica gel with benzene–AcOEt (20 : 1) to give pale yellow needles (120 mg, 73%). Recrystallization from Et_2O–hexane gave pale yellow prisms, mp 91—93 °C. *Anal.* Calcd for $C_{19}H_{19}NO_4$: C, 70.14; H, 5.89; N, 4.30. Found: C, 70.00; H, 5.81; N, 4.26. IR $\nu_{\max}^{\text{Nujol}}$ cm^{-1}: 1720 (C=O). ^{1}H-NMR ($CDCl_3$) δ: 1.18 (3H, t, J=7.0 Hz, $CH_2\underline{CH_3}$), 3.51 and 3.65 (each 3H, s, OCH_3), 4.15 (2H, q, J=7.0 Hz, $O\underline{CH_2}CH_3$), 6.50—7.50 (8H, m, arom H). MS *m/z*: 325 (M^+).

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