Fischer Indolization and Its Related Compounds. XXIV.[1] Fischer Indolization of Ethyl Pyruvate 2-(2-Methoxyphenyl)phenylhydrazone

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In order to clarify the mechanism of Fischer indolization of 2-methoxyphenylhydrazones, Fischer indolization of ethyl pyruvate 2-(2-methoxyphenyl)phenylhydrazone (2) was carried out with hydrochloric acid in ethanol and zinc chloride in acetic acid. The reactions proceeded smoothly to give *N*-arylindoles (11—14) and some chlorinated diphenylamine derivatives (8—10) as by-products. Consideration of the indole products revealed that the Fischer indolization proceeded mainly at the unsubstituted phenyl nucleus rather than at the 2-methoxyphenyl nucleus. This result is inconsistent with the previous result that Fischer indolization of diarylhydrazones proceeded at the electron-richer nucleus. The structures of the diphenylamines were determined by chemical means and the mechanism of their formation is discussed.

Keywords Fischer indolization; *N*-arylphenylhydrazone; chlorinated diphenylamine; Ullmann–Goldberg reaction; *o*-quinone imine

In the previous paper[1] we reported the Fischer indolization of ethyl pyruvate 2-(2,6-dimethoxyphenyl)phenylhydrazone (**1**), in order to clarify the mechanism of abnormal Fischer indolization of 2-methoxyphenylhydrazones.[2] The result revealed that the cyclization proceeded mainly at the 2,6-dimethoxyphenyl nucleus rather than the unsubstituted phenyl one. However, the total amount of indoles formed was too small to allow a difinitive conclusion. Thus, we examined the Fischer indolization of ethyl pyruvate 2-(2-methoxyphenyl)phenylhydrazone (**2**) for the same purpose.[3] The results are presented here.

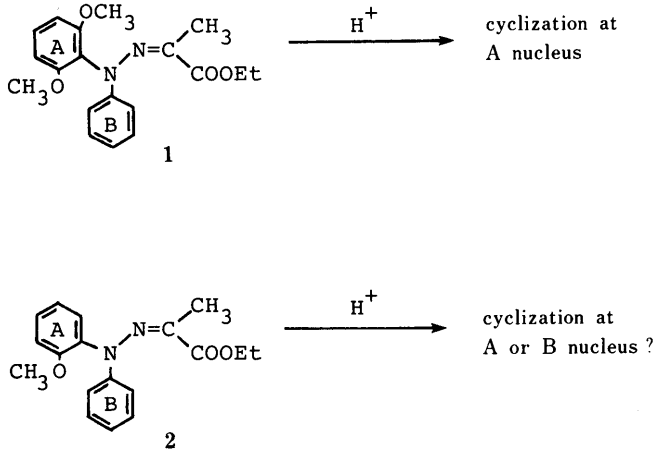


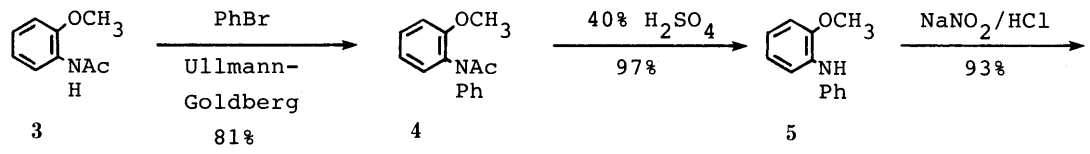
Chart 1

The (2-methoxyphenyl)phenylhydrazone (**2**) was synthesized from *o*-acetanisidide (**3**) by a similar route to that used for the synthesis of the (2,6-dimethoxyphenyl)phenylhydrazone[1] (**1**), as shown in Chart 2. Ullmann–Goldberg reaction[1] of *o*-acetanisidide (**3**) with bromobenzene gave the *N*-phenyl derivative (**4**), which was converted to *N*-phenyl-*o*-anisidine (**5**) by acid hydrolysis. Treatment of **5** with sodium nitrite in acidic media gave the *N*-nitroso derivative (**6**), which was converted to the hydrazine (**7**) by reduction with zinc and acetic acid. The crude hydrazine (**7**) was directly treated with ethyl pyruvate to give the desired hydrazone (**2**).

Result of Fischer Indolization

Ethyl pyruvate 2-(2-methoxyphenyl)phenylhydrazone (**2**) was allowed to react under Fischer indolization conditions with hydrochloric acid in ethanol to yield seven products (**8**, **9**, **5**, **10**, **11**, **12**, and **13**, in that order of elution on column chromatography).

The first (**8**), the second (**9**), and the fourth (**10**) products were oily. Their mass spectra (MS) showed the same molecular ion peak at *m/z* 233, with *m/z* 235 having 33% relative intensity, which indicated the molecular formula $C_{13}H_{12}ClNO$. The infrared (IR) spectra showed an NH absorption, and the ^{1}H-nuclear magnetic resonance



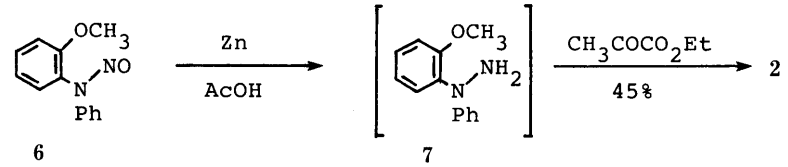
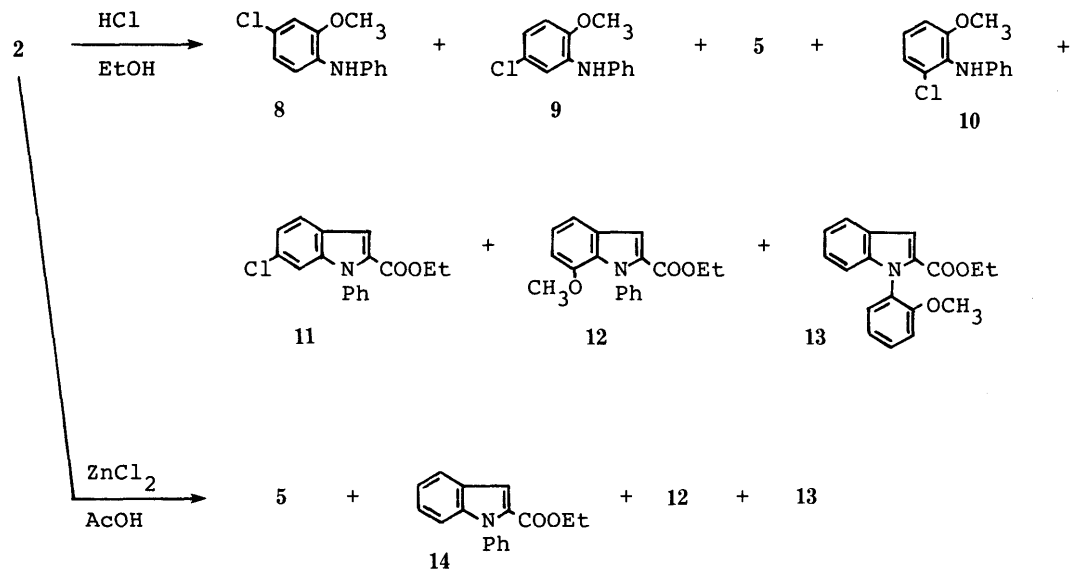


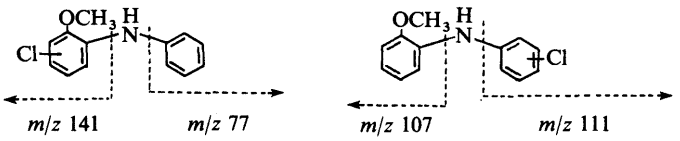
Chart 2



Acid catalyst	Product yields (%)							
	Amines				Indoles			
	5	**8**	**9**	**10**	**11**	**12**	**13**	**14**
HCl/EtOH	1.5	7.1	14.9	2.5	1.3	2.8	34.5	0
$ZnCl_2$/AcOH	1.9	—	—	—	0	1.5	10.2	0.3
Cyclization direction on **2**					A	A	B	A

Chart 3

TABLE I. Mass Spectral Data for Chlorinated Diphenylamines (**8**—**10**)



Compound	Relative intensities (%) with respect to base peak					
	m/z	77	141	107	111	Base peak
8		55	*ca.* 0	0	0	233
9		48	*ca.* 0	0	0	233
10		43	4.6	0	0	233

(^{1}H-NMR) spectra showed a methoxy group, and eight aromatic protons. These data showed that these three products (**8**—**10**) are structural isomers of chlorinated *N*-phenyl-*o*-anisidines. It was determined by mass spectral inspection, in the same manner as described previously,[1] which nucleus was chlorinated. Table I shows the fragment ions formed due to cleavage of the aryl–nitrogen bond. The fragment at *m/z* 77 was observed clearly, while fragments at *m/z* 107 and 111 were not observed at all. These data indicate that the structure of the chlorinated diphenylamines (**8**—**10**) is **31**, having a chlorine atom and a methoxy group on the same phenyl nucleus, but not **32**, having them on separate nuclei. Thus, the chlorinated diphenylamines (**8**—**10**) are three of the four possible isomers with respect to chlorine. As we could not discriminate the position of chlorine clearly by ^{1}H-NMR spectroscopy, we decided to determine the structures by means of alternative syntheses. We tentatively selected the 4-chloro (**8**), 5-chloro (**9**) and 6-chloro (**10**) compounds of the four as targets for synthesis. The 4-chloro (**8**) and 6-chloro (**10**) compounds were expected to have been formed, based on the previous results[1,4] that similar Fischer indolization of ethyl pyruvate 2-(4-methoxyphenyl)phenylhydrazone and the (2,6-dimethoxyphenyl)phenylhydrazone (**1**) gave diphenylamine derivatives in which the chlorine atom was introduced at the *meta* position with respect to the methoxy group. The third product should be the 3-chloro- or 5-chloro-diphenylamine, and the 5-chloro compound (**9**) was considered more likely, because it would be formed more easily than the 3-chloro one owing to steric hindrance to the attack of chlorine, although the formation mechanism was uncertain at that time.

Chart 4 shows the alternative syntheses of the three chlorinated diphenylamines (**8**—**10**). i) The Hofmann rearrangement of 4-chloro-2-methoxybenzoic acid (**15**) with diphenylphosphorylazide (DPPA), followed by treatment with ethanol gave the carbamate (**16**), which was led to 4-chloro-2-methoxyaniline (**17**) by alkaline hydrolysis. The amine (**17**) was converted to the acetanilide (**18**), which was allowed to react with bromobenzene (Ullmann–Goldberg reaction) to give 4′-chloro-*o*-(*N*-phenyl)acetanisidide (**19**), mp 103—105 °C. This diphenyl compound was identical with the sample, mp 103—105 °C, prepared from the Fischer product (**8**) by acetylation. ii) The Ullmann–Goldberg reaction of 5′-chloro-*o*-acetanisidide (**20**) with bromobenzene gave 5′-chloro-*o*-(*N*-phenyl)acetanisidide (**21**), mp 119—121 °C, which was identical with the sample, mp 121—123 °C, prepared from the Fischer product (**9**) by acetylation. iii) *o*-Chloroaniline (**22**) was converted to

alternative syntheses of chlorinated diphenylamines (**8**—**10**)

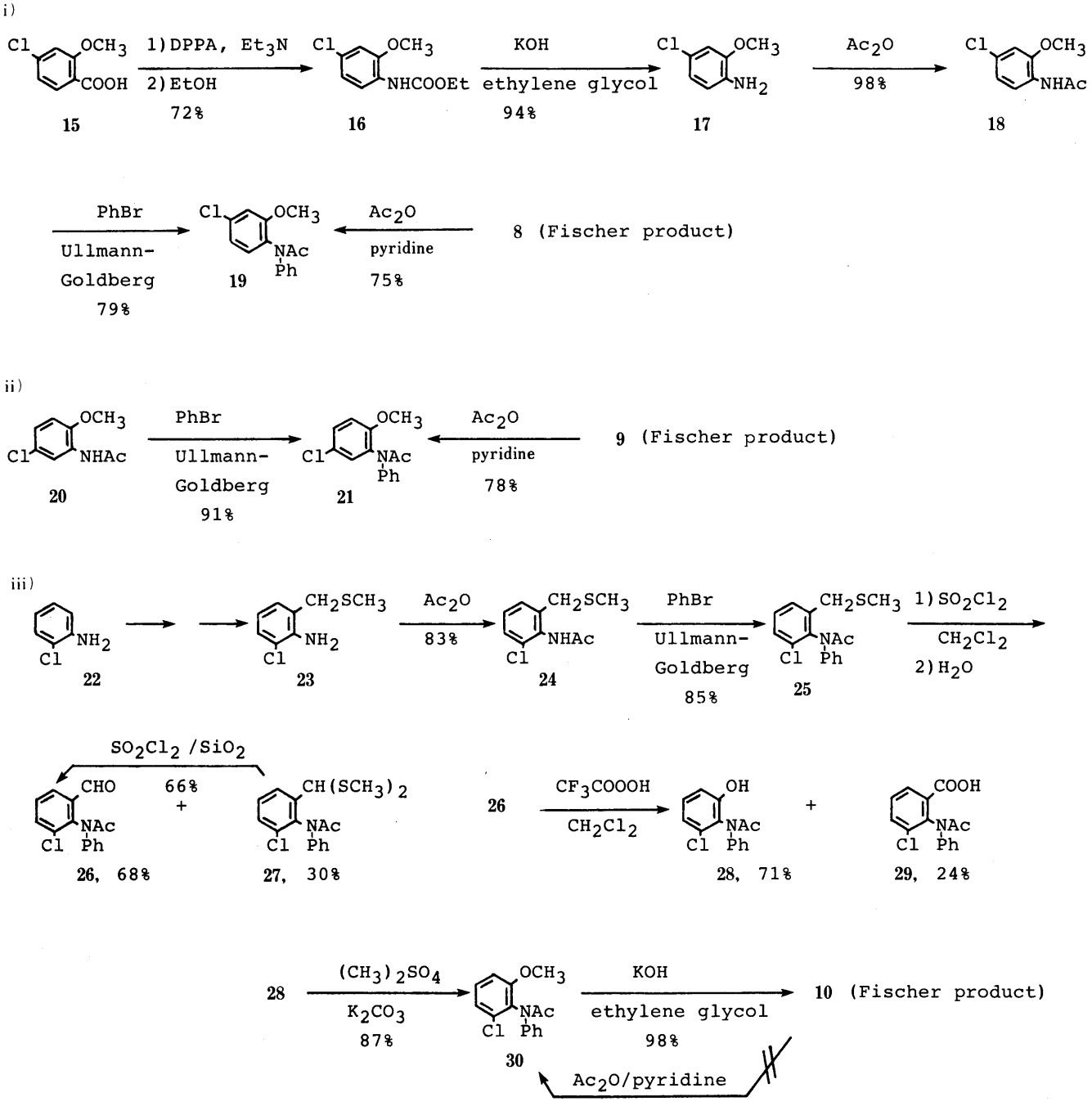


Chart 4

6-chloro-(α-methylthio)-*o*-toluidine (**23**) according to the known procedure.[5] The aniline (**23**) was converted to the *N*-acetyldiphenylamine (**25**) *via* **24** by acetylation followed by phenylation. Chlorination followed by hydrolysis of the *N*-acetyldiphenylamine (**25**) gave the expected aldehyde (**26**) with the thioacetal (**27**) as by-product. The latter (**27**) was easily converted to the former aldehyde (**26**) by hydrolysis using sulfuryl chloride and silica gel.

The Baeyer–Villiger reaction of the aldehyde (**26**) was unsuccessful with usual peracids, performic acid, peracetic acid, or *m*-chloroperbenzoic acid [the starting aldehyde (**26**) was recovered unchanged]. We next attempted this reaction with trifluoroperacetic acid by a modified procedure. Although the peracid has been prepared[6] from equimolar 90% hydrogen peroxide and trifluoroacetic anhydride, we prepared it safely from 6 eq of trifluoroacetic anhydride and 1 eq of 30% hydrogen peroxide. This reagent successfully gave the corresponding phenol (**28**) accompanied with a by-product, *N*-acetyl-3-chloro-*N*-phenylanthranilic acid (**29**). The phenol (**28**) was converted to the methoxy compound (**30**) with dimethyl sulfate. However, we were unable to acetylate the Fischer product (**10**) for identification, presumably because of steric hindrance. Thus, the acetyl compound (**30**) was hydrolyzed to 6-chloro-(*N*-phenyl)-*o*-anisidine (**10**), which was identical with the Fischer product.

The third product of Fischer indolization of the hydrazone (**2**) was *N*-phenyl-*o*-anisidine (**5**), which would be formed directly by degradation of the hydrazone (**2**).

The fifth compound (**11**), obtained in a minute amount, was positive to the Ehrlich reagent[7] and Beilstein's halogen test. The mass spectrum (MS) showed a molecular ion at *m/z* 299, corresponding to $C_{17}H_{14}ClNO_2$. These data suggested that **11** is ethyl 6-chloro-1-phenylindole-2-carboxylate formed as a result of *ortho*-C_6-abnormal Fischer indolization.[4] The structure was determined by alternative synthesis using the corresponding NH-indole (**33**) as shown in Chart 5.

Both the sixth (**12**) and the seventh (**13**) compounds showed positive Ehrlich reagent and had the same molecular ion at *m/z* 295, corresponding to $C_{18}H_{17}NO_3$, in the MS. Their ^{1}H-NMR spectra each showed a signal due to a methoxy group. These data suggested that these two compounds were ethyl 7-methoxy-1-phenyl- (**12**) and ethyl 1-(2-methoxyphenyl)- (**13**) -indole-2-carboxylate, expected to be formed by normal cyclization. Alternative syntheses of the two from the corresponding NH-indoles (**34** and **35**) as shown in Chart 5 revealed that the sixth product (**12**) was the former and the seventh (**13**) was the latter.

The result of this Fischer indolization (see the table in Chart 3) revealed that the cyclization proceeded at the electron-poorer B-nucleus of the hydrazone (**2**) (Chart 1). In order to confirm this, the Fischer indolization of the hydrazone (**2**) was also carried out by using anhydrous zinc chloride, a different kind of acid catalyst from hydrochloric acid in ethanol. The reaction gave four compounds, three (**5**, **12**, and **13**) of which were common to those obtained with hydrochloric acid in ethanol. The new compound (**14**) was identified as ethyl 1-phenylindole-2-carboxylate from the spectral data and finally by alternative synthesis as shown in Chart 5. The indolic compound (**14**) should be formed[3] by cyclization at the position occupied by the methoxy group, followed by reductive elimination of the

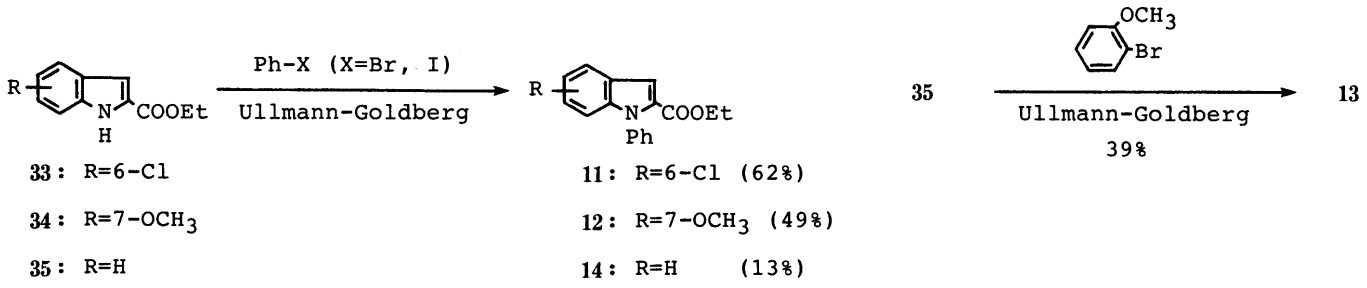
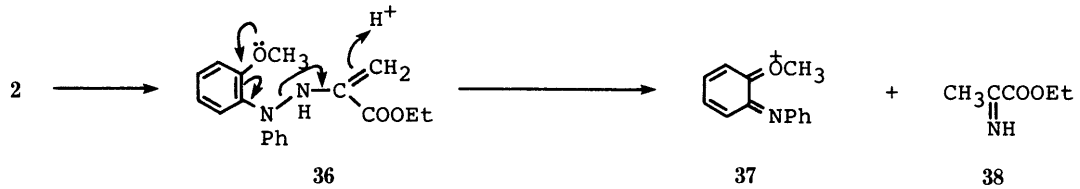


Chart 5



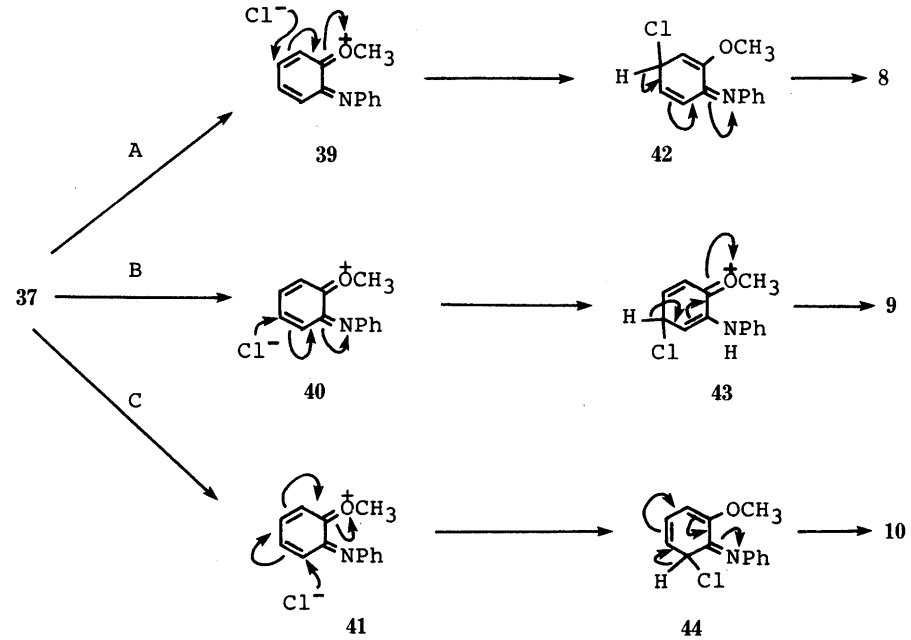


Chart 6

methoxy group.[2)]

Discussion

Cyclization Direction The result of the Fischer indolization of ethyl pyruvate 2-(2-methoxyphenyl)phenylhydrazone (**2**) is summarized in the table of Chart 3. Among the indolic products, the *N*-(2-methoxyphenyl)indole (**13**) is formed by cyclization toward the B-nucleus of the hydrazone (**2**). Other indoles (**11**, **12**, and **14**) should result from the cyclization toward the A-nucleus. The total amount of indoles obtained from the electron-poorer B-nucleus cyclization is much greater than that from the electron-richer A-nucleus cyclization. This tendency is common to the two reactions with hydrochloric acid in ethanol and zinc chloride in acetic acid. The present result is inconsistent with the previous finding[1,4)] that Fischer indolization proceeds through the electrophilic attack of the enhydrazine moiety on the aromatic nucleus. We cannot have any idea to explain all these results at this time. In order to obtain further information, we intend to carry out the Fischer indolization of the diarylhydrazone having an electron-attracting group at the 2-position on one of two nuclei.

Chlorinated Diphenylamines The formation mechanism of the chlorinated diphenylamines (**8**—**10**) could be as shown in Chart 6 on the basis of reported examples.[1,4)] The hydrazone (**2**) reacted with a proton and cleavage occurred at the nitrogen–nitrogen bond to generate an activated *o*-quinone imine intermediate (**37**) and pyruvate derivative (**38**). The quinone imine (**37**) reacted with chloride anion at the *meta* positions to the charged methoxy group to form the 4- or 6-chlorinated diphenylamine (**8** and **10**) in the same manner as reported,[1,4)] through route A or C. The formation of the 5-chlorodiphenylamine (**9**) was slightly different. The position of chlorine was *para* to the methoxy group. A chloride anion would react at the *meta* position to the imine moiety in the common intermediate (**37**) as shown by route B and would be aromatized to give the product (**9**). The formation of **9** would be consistent with the presence of the quinone imine intermediate (**37**).

Experimental

All melting points were measured on a micro melting point hot stage (Yanagimoto) and are uncorrected. IR spectra were recorded in Nujol mulls (unless otherwise stated) on Hitachi EPI-G3 and Shimadzu IR 400 instruments. ^{1}H-NMR spectra were recorded in $CDCl_3$ (unless otherwise stated) on JEOL JMN-4H-100 (100 MHz) and Hitachi R-24B (60 MHz) spectrometers. In the ^{1}H-NMR spectrum, chemical shifts are given in δ-values referred to internal tetramethylsilane, and the assignment of all NH and OH signals was confirmed by the disappearance of their signals after addition of D_2O. MS were measured by using the direct inlet system on a JEOL JMS-01-SG-2 spectrometer. For column chromatography, silicic acid (SiO_2) (100 mesh, Millinckrodt Chemical Works) and silica gel (Kiesel gel 60, 70—230 mesh, Merck), and for preparative thin layer chromatography (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. Distillation for elemental analysis of oily compounds was performed by using a micro distillation and sublimation apparatus (Miyamoto Riken Ind. Co., Ltd., Japan).

***N*-Phenyl-*o*-acetanisidide (4) General Procedure for Ullmann–Goldberg Reaction**[1,4)] A mixture of *o*-acetanisidide[8)] (**3**) (15.0 g), bromobenzene (19.5 ml), anhydrous K_2CO_3 (8.0 g), Cu powder (0.8 g), and a catalytic amount of I_2 in nitrobenzene (85 ml) was refluxed for 34 h under an Ar atmosphere. The reaction mixture was poured into H_2O, and steam distilled. The residue was extracted with Et_2O, then the extract was dried over anhydrous K_2CO_3, and evaporated to dryness *in vacuo*. The residue (25.0 g) was chromatographed over silicic acid using benzene, followed by AcOEt–benzene (1 : 8), to give a solid (17.66 g, 81%). Recrystallization from hexane–benzene gave pale brown plates (15.68 g), mp 108—109.5 °C. *Anal.* Calcd for $C_{15}H_{15}NO_2$: C, 74.66; H, 6.27; N, 5.81. Found: C, 74.93; H, 6.45; N, 5.76. IR ν_{max} cm^{-1}: 1665 (C=O). ^{1}H-NMR δ: 1.99 (3H, dif s, $COCH_3$), 3.85 (3H, s, OCH_3), 6.83—7.40 (9H, m, arom H). MS *m/z*: 241 (M^+).

***N*-Phenyl-*o*-anisidine (5)** A suspension of *N*-phenyl-*o*-acetanisidide (**4**) (15.676 g) in 40% H_2SO_4 (140 ml) was refluxed for 10 h under an Ar atmosphere. The reaction mixture was poured into H_2O, and extracted with Et_2O, then the extract was washed with 5% $NaHCO_3$, and dried over anhydrous K_2CO_3. Removal of the solvent *in vacuo* gave the residue (12.93 g), which was chromatographed over silicic acid using benzene to give a solid (12.09 g, 97%). Recrystallizations from hexane gave colorless plates, mp 36—37 °C [lit.,[9)] bp 158—160 °C (2 mmHg)]. *Anal.* Calcd for $C_{13}H_{13}NO$: C, 78.36; H, 6.58; N, 7.03. Found: C, 78.18; H, 6.74; N, 6.73. IR ν_{max} cm^{-1}: 3405 (NH). ^{1}H-NMR δ: 3.85 (3H, s, OCH_3), 5.60 (1H, br s, NH), 6.82—7.75 (9H, m, arom H). MS *m/z*: 199 (M^+).

***N*-Nitroso-*N*-phenyl-*o*-anisidine (6)** A solution of $NaNO_2$ (459 mg) in H_2O (2.5 ml) was added dropwise to a solution of *N*-phenyl-*o*-anisidine (**5**) (1.00 g) containing concentrated HCl (0.5 ml) at 0—4 °C, and the whole was stirred for 1 h. Then the reaction mixture was poured into H_2O, and extracted with Et_2O. The extract was washed with H_2O, dried over $MgSO_4$ and evaporated *in vacuo*. The residue (1.18 g) was chromatographed over silicic acid using benzene to give a solid (1.13 g). Recrystallizations from cyclohexane gave yellow needles (992 mg, 93%), mp 66—68 °C. *Anal.* Calcd for $C_{13}H_{12}N_2O$: C, 68.41; H, 5.30; N, 12.27. Found: C, 68.02; H, 5.33; N, 12.08. IR: no NH. ^{1}H-NMR δ: 3.72 (3H, s, OCH_3), 7.00—7.51 (9H, m, arom H). MS *m/z*: 199 ($M^+ - 29$).[4)]

Ethyl Pyruvate 2-(2-Methoxyphenyl)phenylhydrazone (2) Zn powder (12 g) was added portionwise to a solution of *N*-nitroso-*N*-phenyl-*o*-anisidine (**6**) (6.30 g) in a mixture of AcOH (35 ml) and H_2O (14 ml) under ice cooling, and the whole was stirred for 10 h. Then the reaction mixture was poured into H_2O, and filtered with suction to remove the unreacted Zn powder. The filtrate was basified with 10% NaOH, extracted with Et_2O. The extract was washed with H_2O, dried over anhydrous K_2CO_3, and evaporated to dryness. The residue (5.955 g), a crude 1-(2-methoxyphenyl)-1-phenylhydrazine (**7**), was dissolved in EtOH (30 ml). Ethyl pyruvate (2.26 g) and one drop of AcOH were added to this solution, and the whole was refluxed for 5 min. The reaction mixture was concentrated to dryness *in vacuo*. The residue (8.116 g) was chromatographed over silicic acid using benzene to give a solid (4.91 g). Recrystallizations from hexane gave pale yellow prisms (3.838 g, 45%), mp 102—103.5 °C. *Anal.* Calcd for $C_{18}H_{20}N_2O_3$: C, 69.21; H, 6.45; N, 8.97. Found: C, 69.13; H, 6.49; N, 8.95. IR ν_{max} cm^{-1}: 1690 (C=O). ^{1}H-NMR δ: 1.38 (3H, t, J=7.5 Hz, $CH_2\underline{CH}_3$), 1.52 (3H, s, CCH_3), 3.76 (3H, s, OCH_3), 4.31 (2H, q, J=7.5 Hz, $O\underline{CH}_2CH_3$), 6.95—7.50 (9H, m, arom H). MS *m/z*: 312 (M^+).

Fischer Indolization of Ethyl Pyruvate 2-(2-Methoxyphenyl)phenylhydrazone (2) with Saturated HCl in EtOH Ethyl pyruvate 2-(2-methoxyphenyl)phenylhydrazone (**2**) (1.801 g) was dissolved in absolute EtOH (90 ml) saturated with dry HCl gas and the whole was stirred at room temperature for 40 min. Then the reaction mixture was poured into H_2O, and extracted with Et_2O. The extract was washed with diluted $NaHCO_3$, and dried over anhydrous K_2CO_3. Removal of the solvent *in vacuo* gave the residue (1.44 g), which was chromatographed over silica gel using benzene to give the amine fraction (390 mg), and the indole fraction (707 mg) in that order of elution.

The amine fraction was repeatedly chromatographed over silica gel using benzene–hexane (1 : 1) to give three eluates, a mixture of **8** and **9**, **5**, and **10** in that order of elution. The mixture of **8** and **9** was separated into the two components by column chromatography over silica gel using Et_2O–hexane (1 : 10).

a) 4-Chloro-*N*-phenyl-*o*-anisidine (**8**): 96 mg (7.1%) yield. Oily compound. IR ν_{max}^{neat} cm^{-1}: 3420 (NH). MS *m/z*: 235 (M^+ + 2, 34%, intensity of M^+), 233 (M^+, base peak). *N*-Acetyl derivative (**19**) of the amine (**8**): prepared by reaction with Ac_2O–pyridine (75% yield). Colorless columns from hexane–benzene, mp 103—105 °C. This compound was identical with an authentic sample, whose preparation is described later.

b) 5-Chloro-*N*-phenyl-*o*-anisidine (**9**): 188 mg (14.0%) yield. Oily compound. IR ν_{max}^{neat} cm^{-1}: 3400 (NH). MS *m/z*: 235 (M^+ + 2, 35% intensity of M^+), 233 (M^+, base peak). *N*-Acetyl derivative (**21**) of the amine (**9**): prepared by the reaction with Ac_2O–pyridine (78% yield). Colorless prisms from benzene–hexane, mp 121—123 °C. This compound was identical with an authentic sample, whose preparation is described later.

c) *N*-Phenyl-*o*-anisidine (**5**): 17 mg (1.5%) yield. Colorless plates from

pentane, mp 36—37 °C. This compound was identical with an authentic sample.

d) 6-Chloro-*N*-phenyl-*o*-anisidine (**10**): 34 mg (2.5%) yield. Oily compound. IR ν_{max}^{neat} cm^{-1}: 3400 (NH). MS *m/z*: 235 ($M^+ + 2$, 37% intensity of M^+), 233 (M^+). This compound was identical with an authentic sample, whose preparation is described later.

The indole fraction was repeatedly chromatographed over silica gel using benzene–hexane (1 : 1) to give three indoles, **11**, **12**, and **13**, in that order of elution.

e) Ethyl 6-Chloro-1-phenylindole-2-carboxylate (**11**): 23 mg (1.3%) yield. Colorless prisms from pentane, mp 57.5—59 °C. IR ν_{max} cm^{-1}: 1710 (C=O). MS *m/z*: 301 ($M^+ + 2$, 36% intensity of M^+), 299 (M^+, base peak). This compound was identical with an authentic sample, whose preparation is described later.

f) Ethyl 7-Methoxy-1-phenylindole-2-carboxylate (**12**): 36 mg (2.8%) yield. Colorless needles from hexane, mp 58—60 °C. IR ν_{max} cm^{-1}: 1725 (C=O). MS *m/z*: 295 (M^+, base peak). This compound was identical with an authentic sample, whose preparation is described later.

g) Ethyl 1-(2-Methoxyphenyl)indole-2-carboxylate (**13**): 588 mg (34%) yield. Colorless prisms from hexane, mp 71—73.5 °C. IR ν_{max} cm^{-1}: 1710 (C=O). MS *m/z*: 295 (M^+, base peak). This compound was identical with an authentic sample, whose preparation is described later.

Fischer Indolization of Ethyl Pyruvate 2-(2-Methoxyphenyl)phenylhydrazone (2) with $ZnCl_2$–AcOH The hydrazone (**2**) (1.50 g) was added to a solution of anhydrous $ZnCl_2$ (1.18 g) in AcOH (15 ml) and the whole was refluxed for 35 min. The reaction mixture was poured into ice-water, and extracted with Et_2O, then the extract was washed with H_2O and 5% $NaHCO_3$, and dried over $MgSO_4$. Removal of the solvent *in vacuo* gave a crystalline residue (1.465 g). Column chromatography over silicic acid using benzene gave four eluates, A, B, C, D in that order of elution.

a) *N*-Phenyl-*o*-anisidine (**5**): A solid (20 mg) obtained from eluate A was recrystallized from pentane to give colorless plates (18.4 mg, 4.8%), mp 36—37.5 °C. IR ν_{max} cm^{-1}: 3400 (NH). This compound was identical with an authentic sample.

b) Ethyl 1-Phenylindole-2-carboxylate (**14**): A solid (5 mg) obtained from eluate B was recrystallized from pentane to give colorless plates (4 mg, 0.8%), mp 62.5—65.5 °C. IR ν_{max} cm^{-1}: 1710 (C=O). MS *m/z*: 265 (M^+, base peak). This compound was identical with an authentic sample, whose preparation is described later.

c) Ethyl 7-Methoxy-1-phenylindole-2-carboxylate (**12**): A solid (21 mg) obtained from eluate C was recrystallized from pentane to give colorless columns (21 mg, 3.6%), mp 58—60 °C. IR ν_{max} cm^{-1}: 1725 (C=O). This compound was identical with an authentic sample, whose preparation is described later.

d) Ethyl 1-(2-Methoxyphenyl)indole-2-carboxylate (**13**): A solid (148 mg) obtained from eluate D was recrystallized from pentane to give colorless prisms (145 mg, 25.5%), mp 66.5—67.5 °C. This compound was identical with an authentic sample, whose preparation is described later.

Preparation of Authentic 4'-Chloro-*N*-phenyl-*o*-acetanisidide (19) i) Ethyl 4-Chloro-2-methoxycarbanilate (**16**): DPPA[10] (3.46 ml) and Et_3N (3.0 ml) was added to a solution of commercial (Aldrich) 4-chloro-2-methoxybenzoic acid (**15**) (2.00 g) in dry dioxane (30 ml) and the mixture was refluxed for 4 h. Then absolute EtOH (5 ml) was added to it and the whole was refluxed for a further 6 h. After the reaction was over, the reaction mixture was concentrated to dryness *in vacuo* and the residue was dissolved in benzene. The organic layer was successively washed with 5% citric acid, H_2O, 5% $NaHCO_3$, and saturated NaCl, and dried over $MgSO_4$. Removal of the solvent *in vacuo* gave a pale yellow solid (2.64 g), which was chromatographed over silica gel using benzene, followed by benzene–AcOEt (10 : 1), to give colorless crystals (1.78 g, 72%). Recrystallization from Et_2O–hexane gave colorless prisms, mp 84—86 °C. *Anal.* Calcd for $C_{10}H_{12}ClNO_3$: C, 52.29; H, 5.27; N, 6.10. Found: C, 52.45; H, 5.26; N, 5.99. IR ν_{max} cm^{-1}: 3260 (NH), 1700 (C=O). ^{1}H-NMR δ: 1.31 (3H, t, J=8.0 Hz, $CH_2\underline{CH}_3$), 3.83 (3H, s, OCH_3), 4.21 (2H, q, J=8.0 Hz, $OC\underline{H}_2CH_3$), 6.79 (1H, d, J=2.0 Hz, C_3-H), 6.87 (1H, dd, J=8.0, 2.0 Hz, C_6-H), 7.08 (1H, br s, NH), 7.97 (1H, d, J=8.0 Hz, C_5-H). MS *m/z*: 231 ($M^+ + 2$, 41% intensity of M^+), 229 (M^+, base peak).

ii) 4'-Chloro-*o*-acetanisidide (**18**): A mixture of ethyl 4-chloro-2-methoxycarbanilate (**16**) (700 mg) and KOH (1.05 g) in ethylene glycol (7 ml) was heated at 160 °C (bath temperature) for 1.5 h. The reaction mixture was poured into H_2O, extracted with Et_2O. The extract was washed with saturated NaCl, and dried over anhydrous K_2CO_3. Removal of the solvent *in vacuo* gave 4-chloro-*o*-anisidine (**17**) (450 mg, 94%), mp 45—49 °C, which was recrystallized from EtOH–H_2O to give colorless needles, mp 48.5—49 °C (lit.,[11] mp 52 °C). A solution of the amine (**17**) (400 mg) in Ac_2O (2.0 ml) was stirred at room temperature for 1 h. The reaction mixture was poured into H_2O and basified with 28% NH_4OH. Precipitated crystals were collected with suction and air-dried to give colorless plates (495 mg, 98%), mp 147—151 °C. A part of this compound was recrystallized from H_2O–EtOH to give colorless plates, mp 149.5—150.5 °C (lit.,[11] mp 150 °C). IR ν_{max} cm^{-1}: 3270 (NH), 1660 (C=O). ^{1}H-NMR δ: 2.17 (3H, s, $COCH_3$), 3.84 (3H, s, OCH_3), 6.79 (1H, d, J=2.0 Hz, C_3-H), 6.87 (1H, dd, J=9.0, 2.0 Hz, C_5-H), 7.62 (1H, br s, NH), 8.24 (1H, d, J=9.0 Hz, C_6-H).

iii) 4'-Chloro-*N*-phenyl-*o*-acetanisidide (**19**): A mixture of 4'-chloro-*o*-acetanisidide (**18**) (200 mg), anhydrous K_2CO_3 (150 mg), and Cu_2Br_2 (37 mg) in bromobenzene (2 ml) was heated at 180—190 °C (bath temperature) under an Ar atmosphere for 5 h. The reaction mixture was worked up according to the general procedure of the Ullmann–Goldberg reaction. The crude product (279 mg) was recrystallized from benzene–hexane to give colorless prisms (217 mg, 79%), mp 103—105 °C. *Anal.* Calcd for $C_{15}H_{14}ClNO_2$: C, 65.34; H, 5.12; N, 5.08. Found: C, 65.68; H, 5.02; N, 5.11. IR ν_{max} cm^{-1}: 1670 (C=O). ^{1}H-NMR δ: 2.00 (3H, s, $COCH_3$), 3.83 (3H, s, OCH_3), 6.77—7.45 (8H, m, arom H).

Preparation of Authentic 5'-Chloro-*N*-phenyl-*o*-acetanisidide (21) A mixture of 5'-chloro-*o*-acetanisidide[12] (**20**) (500 mg), anhydrous K_2CO_3 (382 mg), Cu_2Br_2 (93 mg), and bromobenzene (5 ml) was heated at 180—190 °C (bath temperature) under an Ar atmosphere for 11 h. The reaction mixture was worked up according to the general procedure of the Ullmann–Goldberg reaction. The crude product (716 mg) was chromatographed over silica gel using benzene–AcOEt (10 : 1) to give a colorless solid (626 mg, 91%), mp 118—121 °C. Recrystallization from benzene–hexane gave colorless prisms, mp 119—121 °C. *Anal.* Calcd for $C_{15}H_{14}ClNO_2$: C, 65.34; H, 5.12; N, 5.08. Found: C, 65.51; H, 5.03; N, 5.16. IR ν_{max} cm^{-1}: 1670 (C=O). ^{1}H-NMR δ: 2.02 (3H, s, $COCH_3$), 3.85 (3H, s, OCH_3), 6.77—7.47 (8H, m, arom H).

Preparation of Authentic 6-Chloro-*N*-phenyl-*o*-anisidine (10) i) 6'-Chloro-(α-methylthio)-*o*-acetotoluidide (**24**): A solution of 6-chloro-(α-methylthio)-*o*-toluidine (**23**) (7.939 g), prepared from *o*-chloroaniline (**22**) according to Claus *et al.*'s method,[5] in Ac_2O (64 ml) was stirred at room temperature for 4 h. Then the reaction mixture was poured into H_2O, basified with NH_4OH, and extracted with AcOEt. The extract was washed with H_2O, and dried over anhydrous K_2CO_3. Removal of the solvent *in vacuo* gave a pale yellow solid (9.484 g, 87%), mp 119—121 °C. Recrystallization from benzene gave colorless leaflets (9.127 g, 83%), mp 123—124 °C. *Anal.* Calcd for $C_{10}H_{12}ClNOS$: C, 52.28; H, 5.27; N, 6.10. Found: C, 52.36; H, 5.21; N, 6.21. IR ν_{max} cm^{-1}: 3320 (NH), 1670 (C=O). ^{1}H-NMR δ: 1.96 (3H, s, SCH_3), 2.20 (3H, s, $COCH_3$), 3.64 (2H, s, CH_2S), 7.10—7.50 (4H, m, arom H and NH).

ii) 6'-Chloro-*N*-phenyl-(α-methylthio)-*o*-acetotoluidide (**25**): A mixture of 6'-chloro-(α-methylthio)-*o*-acetotoluidide (**24**) (101 mg), powdered anhydrous K_2CO_3 (67 mg), Cu_2Br_2 (6 mg), and bromobenzene (0.82 ml) was heated at 150—155 °C (bath temperature) under an Ar atmosphere for 2.5 h. The reaction mixture was worked up according to the general method of the Ullmann–Goldberg reaction. The crude product (128 mg) was recrystallized from benzene–hexane to give colorless prisms (114 mg, 85%), mp 131—134 °C. *Anal.* Calcd for $C_{16}H_{16}NOS$: C, 62.83; H, 5.27; N, 4.58. Found: C, 62.92; H, 5.16; N, 4.52. IR ν_{max} cm^{-1}: 1682 (C=O), no NH. ^{1}H-NMR δ: 1.90 (3H, s, SCH_3), 2.03 (3H, br s, $COCH_3$), 3.40, 3.57 (each 1H, d, J=14.0 Hz, $ArC\underline{H}_2S$), 6.98—7.66 (8H, m, arom H).

iii) (a) *N*-Acetyl-3-chloro-*N*-phenylanthranilaldehyde (**26**): A solution of SO_2Cl_2 (1.60 ml) in absolute CH_2Cl_2 (1.60 ml) was added to a solution of 6'-chloro-*N*-phenyl-(α-methylthio)-*o*-acetotoluidide (**25**) (5.436 g) in absolute CH_2Cl_2 (30 ml), and the whole was refluxed for 1 h. The reaction mixture was quenched with H_2O (50 ml), stirred at room temperature for 1 h, and extracted with $CHCl_3$. The organic layer was washed with H_2O, dried over $MgSO_4$, and evaporated to dryness *in vacuo*. The residue (6.265 g) was chromatographed over silica gel using benzene followed by benzene–AcOEt (10 : 1) to give two eluates, I (1.883 g, 30%) and II (3.290 g, 68%), in that order of elution.

Eluate II was recrystallized from benzene–hexane to give *N*-acetyl-3-chloro-*N*-phenylanthranilaldehyde (**26**) as colorless prisms, mp 92—94 °C. *Anal.* Calcd for $C_{15}H_{12}ClNO_2$: C, 65.82; H, 4.42; N, 5.12. Found: C, 65.94; H, 4.35; N, 5.18. IR ν_{max} cm^{-1}: 1670 (C=O). ^{1}H-NMR δ: 2.15 (3H, s, $COCH_3$), 7.07—7.99 (8H, m, arom H), 10.19 (1H, s, CHO). MS *m/z*: 275 ($M^+ + 2$, 41% intensity of M^+), 273 (M^+), 202 (base peak).

(b) 6'-Chloro-bis(α-methylthio)-*N*-phenyl-*o*-acetotoluidide (**27**): Eluate I was recrystallized from benzene–hexane to give colorless prisms, mp 116—118 °C. *Anal.* Calcd for $C_{17}H_{18}ClNOS_2$: C, 58.02; H, 5.16; Cl, 10.10; N, 3.98; S, 18.22. Found: C, 58.13; H, 5.10; Cl, 10.22; N, 4.05; S, 18.12.

IR ν_{max} cm^{-1}: 1685 (C=O). ^{1}H-NMR δ: 1.45 (3H, s, $COCH_3$), 2.10 (3H, s, SCH_3), 2.18 (3H, s, SCH_3), 4.89 (1H, s, CH(S)S), 7.00—7.80 (8H, s, arom H). MS *m/z*: 353 (M^++2, 43% intensity of M^+), 351 (M^+), 214 (base peak).

(c) Conversion of 6'-Chloro-bis(α-methylthio)-*N*-phenyl-*o*-acetotoluidide (**27**) to *N*-Acetyl-3-chloro-*N*-phenylanthranilaldehyde (**26**): The procedure followed that reported.[13] A solution of SO_2Cl_2 (0.04 ml) in CH_2Cl_2 (1 ml) was added dropwise to a mixture of 6'-chloro-bis(α-methylthio)-*N*-phenyl-*o*-acetotoluidide (**27**) (154 mg) and wet silica gel [a mixture of silica gel (0.2 g) and H_2O (0.2 g)] in CH_2Cl_2 (2 ml) under ice-cooling, and the whole was stirred at room temperature for 3 h. Powdered anhydrous K_2CO_3 (0.4 g) was added, and the reaction mixture was stirred for 5 min, then filtered. The filtrate was evaporated to dryness *in vacuo*. The oily residue (139 mg) was chromatographed over silica gel using benzene–AcOEt (10:1) to give two eluates.

The first eluate (53 mg, 34%) was found to be the starting thioacetal (**27**). The second eluate (79 mg, 66%) was recrystallized from benzene–hexane to give colorless prisms, mp 90—94 °C, this product was identical with *N*-acetyl-3-chloro-*N*-phenylanthranilaldehyde (**26**).

iv) 2'-Chloro-6'-hydroxy-*N*-phenylacetanilide (**28**): Pertrifluoroacetic acid was prepared by adding trifluoroacetic anhydride (2.3 ml, 16.3 mmol) to a suspension of 30% H_2O_2 (0.28 ml, 2.7 mmol) in CH_2Cl_2 (1 ml) under ice-cooling. This peracid solution was added dropwise to a solution of *N*-acetyl-3-chloro-*N*-phenylanthranilaldehyde (**26**) (500 mg, 1.8 mmol) in CH_2Cl_2 (3 ml) under ice-cooling, and the whole was stirred at room temperature for 2 h. The reaction was quenched with H_2O (1 ml) and Na_2SO_3 (1.1 g), and the reaction mixture was extracted with $CHCl_3$, washed with H_2O, and dried over $MgSO_4$. Removal of the solvent *in vacuo* left an oily residue (519 mg), which was chromatographed over silica gel using benzene–AcOEt (6:1) followed by $CHCl_3$–MeOH (10:1) to give two eluates.

The first eluate (341 mg, 71%) was recrystallized from MeOH–$CHCl_3$ to give colorless prisms of 2'-chloro-6'-hydroxy-*N*-phenylacetanilide (**28**), mp 185—187 °C. *Anal.* Calcd for $C_{14}H_{12}ClNO_2$: C, 64.25; H, 4.62; N, 5.35. Found: C, 64.24; H, 4.52; N, 5.55. IR ν_{max} cm^{-1}: 3125 (OH), 1645 (C=O). ^{1}H-NMR δ: 1.93 (3H, s, $COCH_3$), 6.60—7.55 (8H, m, arom H), 8.25 (1H, br s, OH). MS *m/z*: 263 (M^++2, 38% intensity of M^+), 261 (M^+), 219 (base peak).

The second eluate (127 mg, 24%) was recrystallized from benzene–MeOH to give colorless prisms, mp 157—160 °C, and this product was found to be *N*-acetyl-3-chloro-*N*-phenylanthranilic acid (**29**), based on the following spectral data. IR ν_{max} cm^{-1}: 1705 (CO_2H), 1630 ($NCOCH_3$). ^{1}H-NMR δ: 2.02, 2.19 (totally 3H, each s, $COCH_3$), 6.95—7.91 (8H, m, arom H), 9.07 (1H, br s, CO_2H). MS *m/z*: 291 (M^++2, 30% intensity of M^+), 289 (M^+), 247 (base peak).

v) 6'-Chloro-*N*-phenyl-*o*-acetanisidide (**30**): Dimethyl sulfate (0.28 ml) was added to suspension of 2'-chloro-6'-hydroxy-*N*-phenylacetanilide (**28**) (0.340 g) and K_2CO_3 (0.285 g) in xylene (7 ml) at 140 °C (bath temperature), and the whole was refluxed for 1 h. Then the reaction mixture was quenched with 5% NaOH (10 ml), stirred at room temperature for 1 h, and extracted with Et_2O. The ethereal layer was washed, dried over anhydrous K_2CO_3, and evaporated to dryness *in vacuo*. A crystalline residue (0.336 g) was recrystallized from benzene–hexane to give colorless prisms (0.312 g, 87%), mp 118—120 °C. *Anal.* Calcd for $C_{15}H_{14}ClNO_2$: C, 65.34; H, 5.12; N, 5.08. Found: C, 65.28; H, 5.12; N, 4.78. IR ν_{max} cm^{-1}: 1680 (C=O). ^{1}H-NMR δ: 1.98 (3H, dif s, $COCH_3$), 3.82 (3H, s, OCH_3), 6.60—7.55 (8H, m, arom H). MS *m/z*: 277 (M^++2, 31% intensity of M^+), 275 (M^+), 233 (base peak).

vi) Authentic 6-Chloro-*N*-phenyl-*o*-anisidine (**10**): A mixture of 6'-chloro-*N*-phenyl-*o*-acetanisidide (**30**) (101 mg) and powdered KOH (251 mg) in ethylene glycol (2 ml) was heated at 140 °C for 1 h under an Ar atmosphere. Then the reaction mixture was poured into H_2O, and extracted with Et_2O. The extract was washed with H_2O, and dried over $MgSO_4$. Removal of the solvent *in vacuo* left an oily residue (84 mg), which was chromatographed over silica gel using benzene–AcOEt (10:1) to give a colorless oil (84 mg, 98%), bp 115—120 °C (1 mmHg). *Anal.* Calcd for $C_{13}H_{12}ClNO$: C, 66.81; H, 5.12; N, 5.99. Found: C, 66.76; H, 5.18; N, 5.83. IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 3400 (NH). ^{1}H-NMR δ: 3.77 (3H, s, OCH_3), 4.75 (1H, br s, NH), 6.58—7.41 (8H, m, arom H). MS *m/z*: 235 (M^++2, 34% intensity of M^+), 233 (M^+, base peak).

Preparation of Authentic *N*-Arylindoles by Ullmann–Goldberg Reaction

i) Ethyl 6-Chloro-1-phenylindole-2-carboxylate (**11**): A mixture of ethyl 6-chloroindole-2-carboxylate[3] (**33**) (200 mg), iodobenzene (0.2 ml), anhydrous K_2CO_3 (200 mg), Cu_2Br_2 (20 mg), and pyridine (0.4 ml) in nitrobenzene (2 ml) was refluxed for 9 h under an Ar atmosphere. The reaction mixture was worked up according to the general procedure. The crude product (308 mg) was chromatographed over silicic acid using benzene to give a solid (182 mg). Recrystallization from hexane–benzene gave colorless prisms (160 mg, 62%), mp 55—57.5 °C. *Anal.* Calcd for $C_{17}H_{14}ClNO_2$: C, 68.12; H, 4.71; N, 4.67. Found: C, 68.24; H, 4.64; N, 4.64. IR ν_{max} cm^{-1}: 1710 (C=O). ^{1}H-NMR δ: 1.15 (3H, t, J=7.5 Hz, $CH_2\underline{CH}_3$), 4.16 (2H, q, J=7.5 Hz, $OC\underline{H}_2CH_3$), 7.00—7.68 (9H, m, arom H).

ii) Ethyl 7-Methoxy-1-phenylindole-2-carboxylate (**12**): A mixture of ethyl 7-methoxyindole-2-carboxylate (**34**) (100 mg), bromobenzene (216 mg), anhydrous K_2CO_3 (100 mg), Cu_2Br_2 (10 mg), and pyridine (0.2 ml) in nitrobenzene (1 ml) was refluxed for 10 h under an Ar atmosphere. The reaction mixture was worked up according to the general procedure. The residue (265 mg) was chromatographed over silicic acid using benzene to give a solid (220 mg). Recrystallization from pentane gave colorless columns (130 mg, 49%), mp 58—59.5 °C. *Anal.* Calcd for $C_{18}H_{17}NO_3$: C, 73.20: H, 5.80; N, 4.74. Found: C, 73.34; H, 5.85; N, 4.75. IR ν_{max} cm^{-1}: 1725 (C=O). ^{1}H-NMR δ: 1.16 (3H, t, J=7.5 Hz, $CH_2\underline{CH}_3$), 3.52 (3H, s, OCH_3), 4.16 (2H, q, J=7.5 Hz, $OC\underline{H}_2CH_3$), 6.66 (1H, dd, J=7.5, 1.5 Hz, C_6-H), 7.07 (1H, t, J=7.5 Hz, C_5-H), 7.26—7.60 (7H, m, arom H).

iii) Ethyl 1-(2-Methoxyphenyl)indole-2-carboxylate (**13**): A mixture of ethyl indole-2-carboxylate[14] (**35**) (200 mg), 2-bromoanisole (800 mg), anhydrous K_2CO_3 (200 mg), Cu_2Br_2 (20 mg), and pyridine (0.4 ml) in nitrobenzene (2 ml) was refluxed for 12 h under an Ar atmosphere. The reaction mixture was worked up according to the general procedure. The residue (324 mg) was chromatographed over silicic acid using benzene to give a solid (240 mg). Recrystallization from pentane gave colorless prisms (123 mg, 39%), mp 66—68 °C. *Anal.* Calcd for $C_{18}H_{17}NO_3$: C, 73.20; H, 5.80; N, 4.74. Found; C, 72.99; H, 5.74; N, 4.89. IR ν_{max} cm^{-1}: 1710 (C=O). ^{1}H-NMR δ: 1.16 (3H, t, J=7.5 Hz, $CH_2\underline{CH}_3$), 3.65 (3H, s, OCH_3), 4.18 (2H, q, J=7.5 Hz, $OC\underline{H}_2CH_3$), 6.94—7.55 (8H, m, arom H), 7.69 (1H, dd, J=7.5, 2.0 Hz, C_4-H).

iv) Ethyl 1-Phenylindole-2-carboxylate (**14**): A mixture of ethyl indole-2-carboxylate (**35**) (300 mg), bromobenzene (750 mg), anhydrous K_2CO_3 (300 mg), Cu_2Br_2 (30 mg), and pyridine (0.6 ml) in nitrobenzene (3 ml) was refluxed for 15 h under an Ar atmosphere. The reaction mixture was worked up according to the general procedure. The residue (398 mg) was chromatographed over silicic acid using benzene to give a solid (67 mg). Recrystallization from pentane gave colorless plates (54 mg, 13%), mp 62.5—65.5 °C. *Anal.* Calcd for $C_{17}H_{15}NO_2$: C, 76.96; H, 5.70; N, 5.28. Found: C, 76.86; H, 5.67; N, 5.13. IR ν_{max} cm^{-1}: 1710 (C=O). ^{1}H-NMR δ: 1.16 (3H, t, J=7.5 Hz, $CH_2\underline{CH}_3$), 4.16 (2H, q, J=7.5 Hz, $OC\underline{H}_2CH_3$), 7.00—7.68 (10H, m, arom H).

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