Fischer Indolisation and Related Compounds. Part 21.[1] Direction on the Cyclisation in the Fischer Indolisation of Ethyl Pyruvate 2-(*p*- or *m*-Substituted Phenyl)phenylhydrazones

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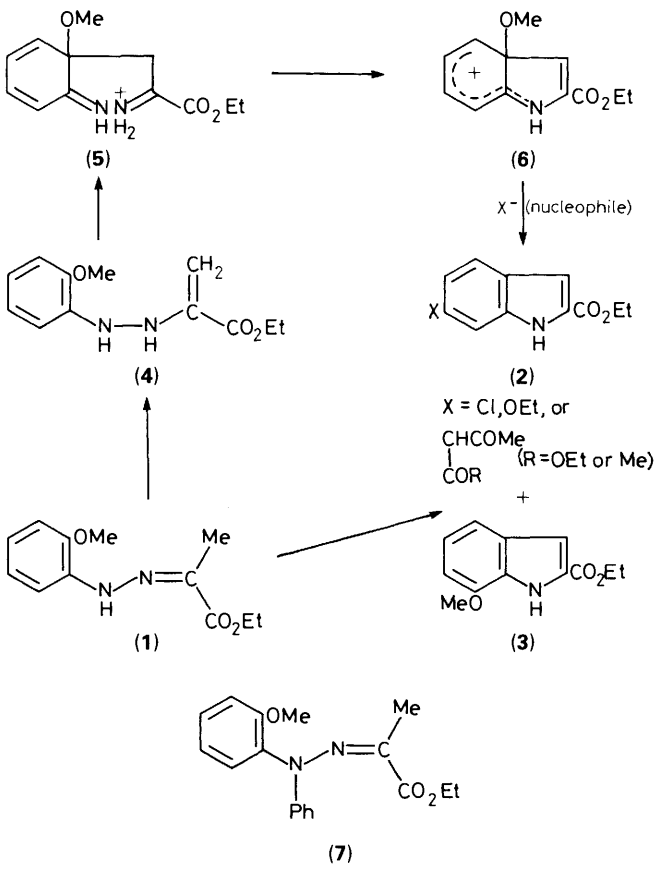
The Fischer indolisation of three kinds of ethyl pyruvate 2-(*p*- or *m*-substituted phenyl)phenylhydrazones (**8a—c**) was carried out with hydrogen chloride in ethanol or under sigmatropic conditions, in order to clarify chemically the mechanism of the first cyclisation step of Fischer indolisation. The reaction under acidic conditions took place predominantly on the electron-enriched benzene nucleus whereas the reaction under sigmatropic conditions took place with lower regioselectivity and in lower yield than the former. These results indicate to us that Fischer indolisation is catalysed by acid and proceeds by electrophilic attack of the enehydrazine entity on the aromatic nucleus.

In previous papers, we reported[2] that treatment of ethyl pyruvate 2-(2-methoxyphenyl)hydrazone (**1**) with ethanolic hydrogen chloride or with toluene-*p*-sulphonic acid (TsOH) in benzene containing an enolisable β-dicarbonyl compound gave the 6-substituted indole derivatives (**2**), products of *ortho*-C-6 abnormal Fischer indolisation, as a major product together with a small amount of the normally expected ethyl 7-methoxyindole-2-carboxylate (**3**). Formation of the 6-substituted indoles, which were unexpected in the normal chemical sense, is explicable in terms of a mechanism (Scheme 1) whereby the enehydrazine entity of (**4**), a tautomer of the phenylhydrazone (**1**), attacks the methoxy substituted *ortho* position rather than the normal unsubstituted one.

Thus, Fischer indolisation of phenylhydrazones having a variety of functional groups at one of the *ortho* positions was systematically studied[3] under relatively weak acid conditions (ethanolic hydrogen chloride), and under relatively strong acid conditions (zinc chloride in acetic acid). These studies showed that, activating groups (MeO, AcNH) facilitated abnormal Fischer indolisation in the presence of ethanolic hydrogen chloride, while, weakly deactivating groups (halogen) gave rise to abnormal Fischer indolisation only in the presence of zinc chloride in acetic acid. Furthermore, treatment of phenylhydrazones bearing a strongly deactivating *ortho* group (CF_3) with zinc chloride in acetic acid gave only the normal Fischer indolisation product. These experimental results prompted us to examine the direction of indolisation for *o*-methoxy substituted diphenylhydrazones (**7**).

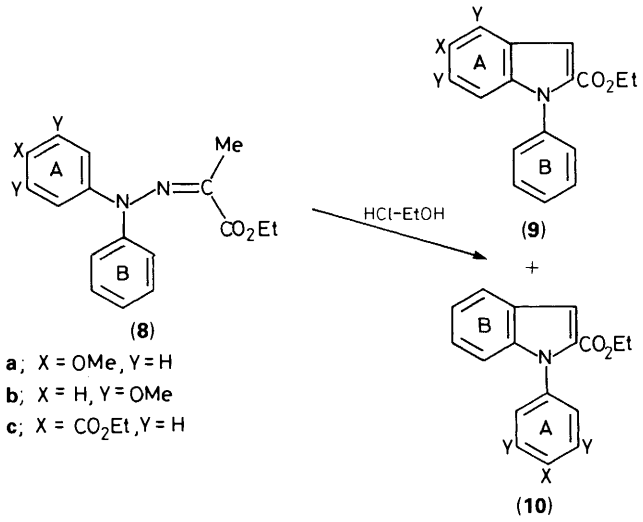
In general, Fischer indolisation itself is believed to proceed through 3,3-sigmatropic rearrangement[4] in the enehydrazine form (**4**). However, as described above, Fischer indolisation of simple phenylhydrazones was significantly affected by the degree of electron density on the benzene ring of the starting phenylhydrazones. Thus, in order to examine the general features of the Fischer indolisation of diarylhydrazones, product analyses of Fischer indolisations of ethyl pyruvate 2-(substituted phenyl)phenylhydrazones (**8a—c**), in which all four *ortho* positions of the aromatic rings are unsubstituted, was conducted with ethanolic hydrogen chloride. Here, we describe our results.

The three starting diaryl hydrazones (**8a—c**) were synthesized as shown in Scheme 3. Diphenylamine derivatives (**11**) were treated with sodium nitrite in acidic media to give the corresponding *N*-nitroso compounds† (**12**), which were reduced with zinc in acetic acid to the hydrazines (**13**). Treatment of the latter with ethyl pyruvate gave the desired hydrazones (**8a—c**).

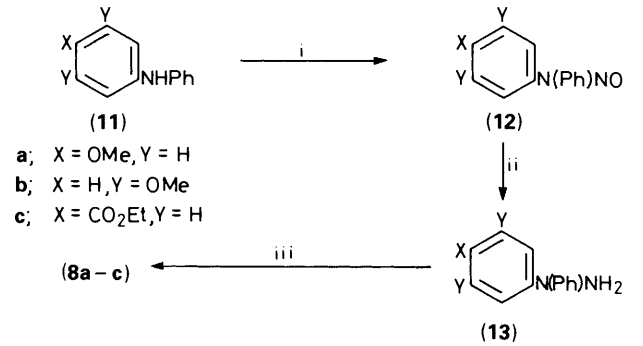


Scheme 1.

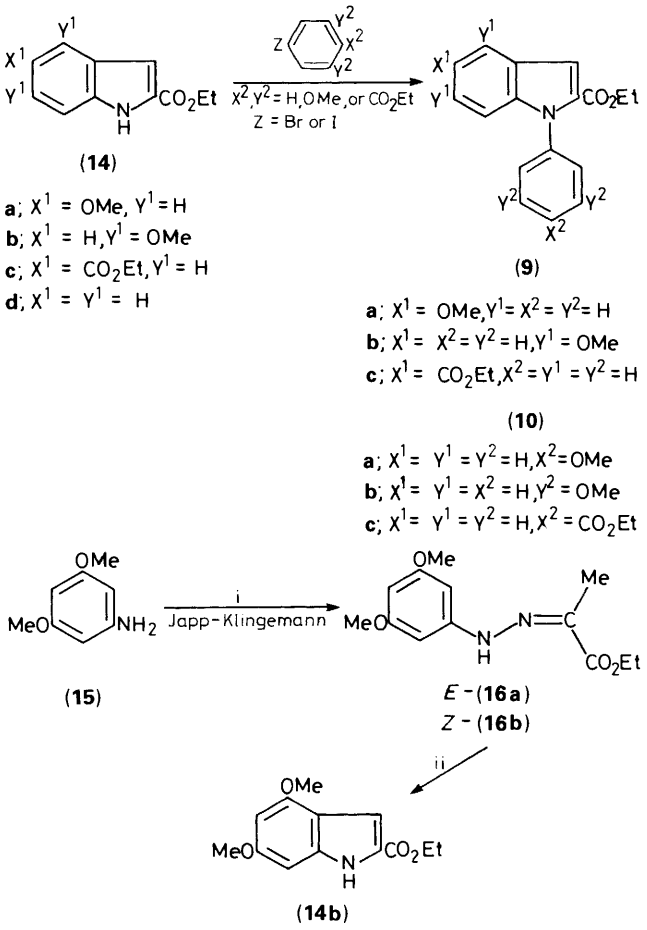
* In their mass spectra, none of the nitroso compounds described in the present paper show an M^+ ion. The highest ion was observed at m/z $M^+ - 29$, which can be explained by elimination of NO˙, followed by addition of H˙.



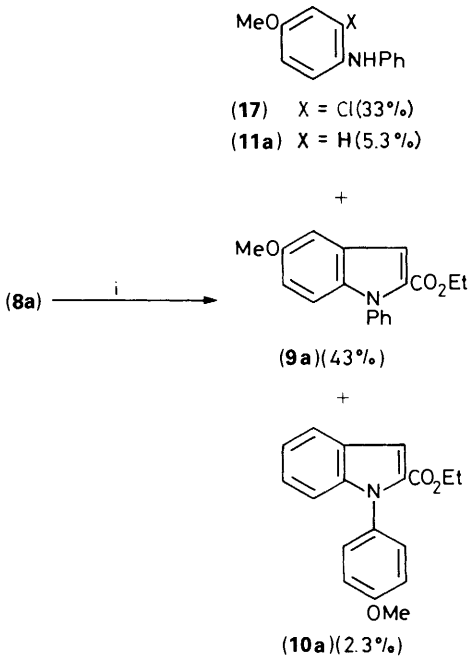
Scheme 2.



Scheme 3. *Reagents:* i, $NaNO_2$, HCl aq., EtOH; ii, Zn, AcOH; iii, $MeCOCO_2Et$



Scheme 4. *Reagents:* i, (a) HClaq, $NaNO_2$; (b) KOH, $MeCOCH(Me)CO_2Et$; ii, $ZnCl_2$, AcOH



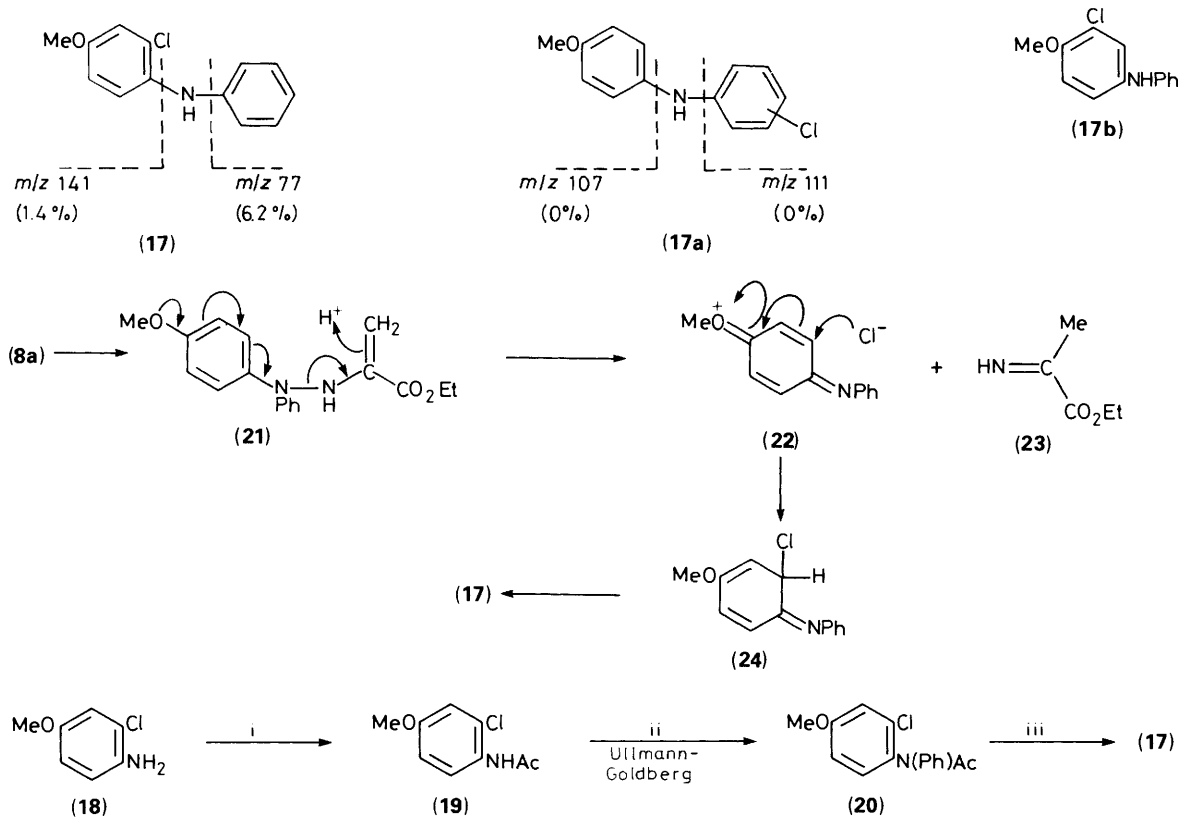
Scheme 5. *Reagent:* i, HCl, EtOH

For the purpose of identification, the six *N*-arylindole products, (**9**) and (**10**), which should result from Fischer indolisation of the diarylhydrazones (**8a—c**), were prepared by Ullmann–Goldberg reactions of the corresponding 1*H*-indoles (**14**) with halogenobenzene derivatives (Scheme 4). The unknown 1*H*-indole, ethyl 4,6-dimethoxyindole-2-carboxylate (**14b**), was prepared from 3,5-dimethoxyaniline (**15**) (Scheme 4).

Initially, Fischer indolisation of ethyl pyruvate 2-(4-methoxyphenyl)phenylhydrazone (**8a**) was examined. Treatment of the 4-methoxyphenylhydrazone (**8a**) with saturated hydrogen chloride in ethanol gave four products, (**17**), (**11**), (**9a**), and (**10a**) in 33, 5.3, 43, and 2.3% yields, respectively (Scheme 5).

The molecular formula $C_{13}H_{12}ClNO$ of the first compound (**17**) (m.p. 51—52.5 °C) was established on the basis of its elemental analysis and mass spectrum [*m/z* 233 (M^+) and 235 ($M^+ + 2$, 36% intensity of M^+)]. In its i.r. spectrum, it showed NH absorption at 3 402 cm^{-1} and in its ^1H n.m.r. spectrum, there appeared a methoxy signal at δ 3.74, and eight ArH signals at δ 6.66—7.32. These data demonstrated that compound, (**17**), was the chloro analogue of the diphenylamine (**11a**). These experimental results led us to adopt three structures (**17**), (**17a**), and (**17b**) (see Scheme 6) as candidates for the first compound. On the other hand, in its mass spectrum, compound (**17**) exhibits two characteristic fragmentation ions explicable in terms of fragmentations of structures (**17**) and (**17b**) [*m/z* 141 (C_7H_6ClO): 1.4% and *m/z* 77 (C_6H_5): 6.2%)], but not those by the formula (**17a**) at *m/z* 107 (C_7H_7O) and *m/z* 111 (C_6H_4Cl). This spectral evidence allowed us to exclude formula (**17a**) from our structural consideration of the first compound.

Compound (**17b**), however, is a known compound[5] the m.p. of which (m.p. 100.5—101 °C) differs from that of the first compound (m.p. 51—52.5 °C). Thus, it is established that the first compound is (**17**); this was confirmed by an independent



Scheme 6. *Reagents:* i, Ac_2O; ii, PhBr, K_2CO_3, Cu_2Br_2, pyridine; iii, KOH, EtOH

Table. Results of Fischer indolisation of ethyl pyruvate 2-(*p*- or *m*-substituted phenyl)phenylhydrazones (**8a**—**c**)

Hydrazone	Reagent or solvent	Yield (%) (9)	Yield (%) (10)	Ratio of indoles	By-products
(**8a**)	HCl–EtOH	43	2.3	19:1 (23:1)[a]	(**11a**) 5.3%
(**8b**)	HCl–EtOH	43	17	2.6:1 (3.3:1)[a]	(**17**) 33%
(**8c**)	HCl–EtOH	11	67	1:6.1 (1:6.8)[a]	(**13c**) 17%
(**8a**)	Ethylene glycol	10[b]		(3.7:1)[a]	(**11a**) 69%
(**8b**)	Diethylene glycol	12[b]		(1.9:1)[a]	(**11b**) 52%
(**8c**)	Ethylene glycol	15[b]		(1:2.5)[a]	(**11c**) 39%

[a] Determined from ^1H n.m.r. spectrum. [b] Total yields of indoles (**9**) and (**10**)

synthesis of it from 2-chloro-4-methoxyaniline (**18**) (see Scheme 6).

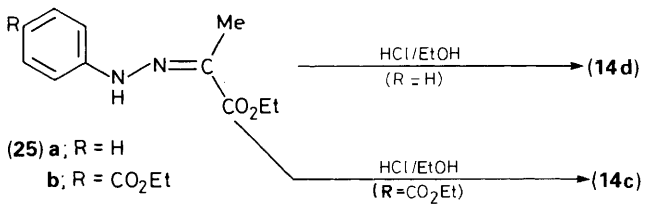
The mechanism of formation of (**17**) in the Fischer indolisation of the 4-methoxyphenylhydrazone (**8a**) can be rationalised as follows (see Scheme 6): (i) the quinone imine (**22**) was formed by proton attack on the enehydrazine form (**21**) of (**8a**), followed by cleavage of the N–N bond; (ii) attack of a chloride anion on the quinone imine (**22**) then gave product (**17**). It should be emphasised here that the *para*-methoxy group in the hydrazone (**8a**) is essential for formation of the chlorinated product (**17**), since related compounds without such a group, (**8b**) and (**8c**), failed to give products corresponding to (**17**) *vide infra*. The reaction which leads to the by-product (**17**) can be classified as a nucleophilic aromatic substitution reaction in acidic media, and thus seems to belong to the same category as the phenol–benzene coupling reaction described by Shudo and co-workers,[6] and the acid-catalysed nucleophilic rearrangements reported by Kikugawa and co-workers.[7]

The second compound was found to be *N*-phenyl-*p*-anisidine (**11a**), which was supposed to be formed by reductive N–N bond fission of the hydrazone (**8a**) by an unknown mechanism. Formation of such by-products (**17**) and (**11a**) is common in the Fischer indolisation of ethyl pyruvate 2-(4-methoxyphenyl)-(**8a**) or 2-(2-methoxyphenyl)*-phenylhydrazone.

The third (m.p. 57.5—60.5 °C) and the fourth (m.p. 114—116 °C) products were identical with authentic samples of ethyl 5-methoxy-1-phenylindole-2-carboxylate (**9a**) and ethyl 1-(4-methoxyphenyl)indole-2-carboxylate (**10a**). Thus the ratio of (**9a**) and (**10a**) is 19:1 (Table 1). In their ^1H n.m.r. spectra, each product showed methoxy signals at δ_H 3.79 and 3.83. After addition of a shift reagent, tris(dipivaloylmethanato)europium [Eu(dpm)$_3$], these signals shifted to δ_H 4.13 and 4.25, respectively. In order to obtain the exact product ratio of indolic products, the intensities of these methoxy signals were measured in the ^1H n.m.r. spectrum of the indolic mixture, which was isolated from the reaction mixture, in the presence of shift reagent. The spectral experiment showed that ethyl 5-methoxy-1-phenylindole-2-carboxylate (**9a**) is formed by a factor of 23 to ethyl 1-(4-methoxyphenyl)indole-2-carboxylate (**10a**) in the Fischer indolisation of the 4-methoxyphenylhydrazone (**8a**).

The result obtained from the above mentioned cyclisation of the 4-methoxyphenylhydrazone (**8a**) seemed to lead to the clear conclusion that Fischer indolisation of diarylhydrazones proceeds toward the nucleus bearing an activating group. However the experiments described were carried out on the basis that the

* Unpublished results.



Scheme 7.

total electron density of a benzene nucleus is increased by the presence of a methoxy group. However, since the cyclised position was *meta* to the methoxy group, the σ-value for which in the *meta* position in the Hammett equation is positive, doubts arose as to our interpretation of this experiment. In order to resolve this doubt we subjected to Fischer indolisation another diphenylhydrazone, (**8b**), having on one of the benzene nuclei two methoxy groups symmetrically situated at *meta* positions to the hydrazone nitrogen.

The reaction of the phenylhydrazone (**8b**) with hydrogen chloride in ethanol gave the two readily identifiable and separable indoles (**9b**) (43%) and (**10b**) (17%) in the ratio 2.6:1 (see Table). In the indolic mixture, the ratio of (**9b**):(**10b**) was 3.3:1 (1H n.m.r.). Although the ratio is rather small, this result confirms that the direction of cyclisation obtained for Fischer indolisation of 4-methoxyphenylhydrazone (**8a**). The fact that the ratio of (**9b**):(**10b**) is closer to unity than that of (**9a**):(**10a**) in (**8a**) is explicable only if, in addition to the electronic effect of the methoxy groups, their steric effects are taken into account.

In order to obtain further information about the direction of cyclisation in the Fischer indolisation of diarylhydrazones, the phenylhydrazone (**8c**) was treated with hydrochloric acid in ethanol. The Fischer indolisation[3b] of ethyl pyruvate 2-phenylhydrazone (**25a**) with hydrochloric acid in ethanol gave ethyl indole-2-carboxylate (**14d**) although the reaction proceeded only partially [11% yield of (**14d**) and 48% recovery of (**25a**)], whereas ethyl pyruvate 2-(4-ethoxycarbonyl)phenylhydrazone (**25b**) was reported[8] not to give the corresponding ethyl 5-ethoxycarbonylindole-2-carboxylate (**14c**) with the same reagent. In view of this, we expected the indolisation of (**8c**) to be completely in favour of cyclisation to the unsubstituted phenyl nucleus.

In fact, the Fischer indolisation of (**8c**) gave three compounds, (**9c**), (11%), (**10c**), (67%), and (**13c**), (17%) (see Table). The first two indolic compounds, identical with authentic specimens, were obtained in a ratio of 1:6.1 [a ratio of 1:6.8 was obtained by integration of OCH_2Me in a mixture of them from the Eu(dpm)$_3$-induced ^{1}H n.m.r. spectrum]. This showed that cyclisation also occurred on the less deactivating nucleus. Although this result was unexpected, it confirms those obtained from the Fischer indolisation of the 4-methoxy- and the 3,5-dimethoxy-phenylhydrazones (**8a, b**).

The third compound was found to be ethyl 4-(1-phenylhydrazino)benzoate (**13c**), which was probably formed by ethanolysis of the hydrazone (**8c**) before cyclisation. It is noteworthy that no abnormal by-products such as diphenylamines, (**11a**) and (**17**), obtained in the Fischer indolisation of the 4-methoxyphenylhydrazone (**8a**) were formed. Such results support the mechanism for formation of the chlorinated diphenylamine (**17**) shown in Scheme 6. The fact that the 4-methoxyphenylhydrazone (**8a**) gave by-products in considerable yields suggests that 4-methoxy-1H-phenylhydrazones in general would suffer the same side reaction, thus resulting in lower than expected yields of indoles.

A sigmatropic mechanism has been claimed[4] for thermal Fischer indolisation in the absence of an acid catalyst. This, together with the report[10] that substituents in the aromatic nucleus have little affect on the Claisen rearrangement, a typical sigmatropic reaction, led us to investigate the differences in substituent effect for thermal and the acid-catalysed Fischer indolisations. Thus, we found that refluxing the diarylhydrazones (**8a—c**) in ethylene glycol or in diethylene glycol without acid gave the corresponding indoles: (**9a**) and (**10a**) for the hydrazone (**8a**), (**9b**) and (**10b**) for the hydrazone (**8b**), and (**9c**) and (**10c**) for the hydrazone (**8c**). The yields were much lower than the corresponding reactions under acidic conditions, and far more diarylamines, (**11a**) and (**11b**), were formed as by-products (see Table). The major indoles formed in each case were the same as under acid condition, although the ratios were found to be closer to unity. Glycols have generally been used for thermal indolisation as neutral solvents, although being apparently protic, some protonation of the aryl hydrazones might occur. In view of this we subjected the hydrazone (**8b**) to thermal Fischer indolisation in an aprotic solvent, Dowtherm A.[11] This reaction gave only decomposition products and no indoles.

After completion[1] of our present work, Przheval'skii reported[12] the Fischer indolisation of some cyclohexanone diarylhydrazones for purposes similar to our own, claiming that the reaction proceeds *via* a [3,3]-sigmatropic rearrangement, on the basis of the observation that the two expected indoles were formed, under both acid-catalysed and thermal conditions, in a ratio near to unity regardless of substituents on the benzene nucleus. Our results contrast with those, leading us to claim that acid-catalysed Fischer indolisation proceeds by electrophilic attack of the enehydrazine entity on the benzene nucleus as suggested by Robinson.[4]

Finally it should be emphasised that a phenyl (or generally an aryl) group on the 1-position of arylhydrazones was found to facilitate indolisation compared with the corresponding 1*H*-arylhydrazone. This is supported by (i) the fact that in the indolisation of 4-ethoxycarbonylphenylhydrazone (**8c**) cyclisation occurred on both the deactivated and activated sites and (ii) the report[13a] that the Fischer indolisation of a 1-phenyl derivative (**8**; X=Y=H) of ethyl pyruvate 2-phenylhydrazone (**25a**) with hydrochloric acid in ethanol gave smoothly the expected ethyl 1-phenylindole-2-carboxylate (**9**; X=Y=H) in a good yield (75.5%), in contrast to our already described result[3b] of the reaction of the corresponding 1*H*-hydrazone (**25a**). The same accelerating effect of 1-alkyl group of arylhydrazones is already known.[13b]

Experimental

M.p.s were determined on a Yanagimoto micro-melting hot-stage apparatus and are uncorrected. I.r. spectra were recorded in Nujol mulls (unless otherwise stated) on a Hitachi EPI-G3 spectrometer. ^{1}H N.m.r. spectra were recorded in $CDCl_3$ (unless otherwise stated) on a JEOL JNM-4H-100 spectrometer with tetramethylsilane as an internal reference. Mass spectra were recorded with Hitachi RMU-6E and high resolution mass spectra were recorded with JEOL JMS-01SG-2 spectrometers. Silicic acid (100 mesh, Mallinckrodt Chemical Works) and silica gel (Kieselgel 60, 70-230 mesh ASTM, Merck) were used for column chromatography, and Kieselgel GF_{254} nach Stahl (Merck) for preparative thin layer chromatography (t.l.c.).

Synthesis of Ethyl Pyruvate 2-(4-Methoxyphenyl)phenylhydrazone (**8a**).—(a) N-*Nitroso*-N-*phenyl*-p-*anisidine* (**12a**). A solution of $NaNO_2$ (1.75 g) in water (6.4 ml) was added dropwise to a stirred solution of *N*-phenyl-*p*-anisidine[14] (**11a**) (4.00 g) in a mixture of EtOH (30 ml) and concentrated HCl (2.0 ml) at 0—3 °C, and the mixture was stirred for 40 min at the same temperature. The reaction mixture was poured into water and extracted with Et_2O, and the extract was washed with water, dried (K_2CO_3), and evaporated under reduced pressure to give

crude product (5.59 g) as brown rods, which was recrystallised from hexane to give the nitroso compound (**12a**) as pale yellow rods (4.15 g, 91%), m.p. 80—83 °C (lit.,[15] m.p. 81—82 °C) (Found: C, 78.0; H, 6.5; N, 7.2. Calc. for $C_{13}H_{13}NO$: C, 78.35; H, 6.6; N, 7.05%); $\nu_{max.}$ 3 365 (NH) cm^{-1}; $\delta_H(CCl_4)$ 3.73 (3 H, s, OMe), 5.15 (1 H, br s, NH), and 6.60—7.20 (9 H, m, ArH); *m/z* 199 ($M^+ - 29$).

(b) 1-(4-*Methoxyphenyl*)-1-*phenylhydrazine* (**13a**). A solution of the nitroso compound (**12a**) (1.67 g) in AcOH (8 ml) was added to a suspension of Zn powder (2.0 g) in water (3 ml) at 3—7 °C with stirring. After all the nitroso compound (**12a**) had been consumed (checked by t.l.c.) the reaction mixture was poured into water and filtered to remove the insoluble material, which was then washed with Et_2O. The combined filtrate and washings were basified with 10% aqueous NaOH and extracted with Et_2O, and the extract was dried (K_2CO_3) and evaporated under reduced pressure to give the crude product as yellow crystals. Recrystallisation of the latter from cyclohexane gave the pure hydrazine (**13a**) (527 mg, 34%), m.p. 69—71 °C (lit.,[15] m.p. 58—60 °C) (Found: C, 72.75; H, 6.55; N, 13.05. Calc. for $C_{13}H_{14}N_2O$: C, 72.85; H, 6.6; N, 13.1%); $\nu_{max.}$ 3 332 (NH) cm^{-1}; δ_H (CCl_4) 3.75 (3 H, s, OMe), 3.83 (2 H, br s, NH_2), and 6.61—7.20 (9 H, m, ArH); *m/z* 214 (M^+).

(c) *Ethyl pyruvate* 2-(4-*methoxyphenyl*)*phenylhydrazone* (**8a**). Ethyl pyruvate (108 mg) and one drop of acetic acid was added to a solution of the hydrazine (**13a**) (100 mg) in dry EtOH (10 ml) and the mixture was refluxed for 5 min. It was then evaporated under reduced pressure to give a solid (140 mg), which was recrystallised from hexane to give yellow prisms (81 mg, 56%), m.p. 80—81 °C (Found: C, 69.1; H, 6.45; N, 8.9. $C_{18}H_{20}N_2O_3$ requires C, 69.2; H, 6.45; N, 8.95%); $\nu_{max.}$ 1 696 (ester) cm^{-1}; $\delta_H(CCl_4)$ 1.37 (3 H, t, *J* 7.5 Hz, CMe), 1.56 (3 H, s, =CMe), 3.80 (3 H, s, OMe), 4.25 (2 H, q, *J* 7.5 Hz, OCH_2), and 6.68—7.31 (9 H, m, ArH); *m/z* 312 (M^+).

Synthesis of Ethyl Pyruvate 2-(3,5-*Dimethoxyphenyl*)*phenylhydrazone* (**8b**).—(a) N-*Nitroso*-N-*phenyl*-3,5-*dimethoxyaniline* (**12b**). Concentrated HCl (0.5 ml) and then a solution of $NaNO_2$ (160 mg) in water (1 ml) was added dropwise to a solution of *N*-phenyl-3,5-dimethoxyaniline[16] (**11b**) (500 mg) in EtOH (10 ml) at 0—4 °C with stirring. Stirring was continued for 1 h, after which the mixture was poured into water and extracted with Et_2O, and the extract dried (K_2CO_3) and evaporated. The residue (501 mg) was chromatographed over silicic acid using benzene as an eluant to give a crystalline product (480 mg) which was recrystallised from cyclohexane to afford yellow prisms (438 mg), m.p. 66.5—68.5 °C (Found: C, 65.0; H, 5.45; N, 10.55. $C_{14}H_{14}N_2O_3$ requires C, 65.1; H, 5.45; N, 10.85%); $\nu_{max.}$ no NH.

(b) *Ethyl pyruvate* 2-(3,5-*dimethoxyphenyl*)*phenylhydrazone* (**8b**). Zn powder (312 mg) was added portionwise to a suspension of nitroso compound (**12b**) (200 mg) in AcOH (2 ml), water (0.6 ml), and EtOH (4 ml) at 0 °C and the mixture was stirred for 2 h. After the reaction was complete, the reaction mixture was poured into water and the precipitate filtered off. The filtrate was basified with 10% aqueous NaOH and extracted with Et_2O, and the extract was washed with water, dried (K_2CO_3), and evaporated to give oily 1-(3,5-dimethoxyphenyl)-1-phenylhydrazine (**13b**) (109 mg). This, without purification, was refluxed with ethyl pyruvate (76 mg) in EtOH (1 ml) for 10 min. The mixture was then evaporated under reduced pressure and the residue purified by column chromatography over silicic acid using Et_2O-cyclohexane (1:1) as an eluant to give a pale yellow oil [87 mg, based on the nitroso compound (**12b**), 33%]; $\nu_{max.}$(neat) 1 702 cm^{-1} (ester); δ_H 1.38 (3 H, t, *J* 7.5 Hz, CMe), 1.62 (3 H, s, =CMe), 3.72 (6 H, s, 2 × OMe), 4.31 (2 H, q, *J* 7.5 Hz, OCH_2), 6.28 (3 H, m, 2-, 4-, and 6-H), and 7.15 (5 H, m, ArH); (Found; M^+, 342.1552. $C_{19}H_{22}N_2O_4$ requires 342.1581).

Synthesis of 2-(4-*Ethoxycarbonylphenyl*)*phenylhydrazone* (**8c**). —(a) *Ethyl* 4-*anilinobenzoate* (**11c**). A solution of 4-anilinobenzoic acid[17] (4.00 g) in dry EtOH (143 ml) saturated with dry HCl gas was refluxed for 8 h. The reaction mixture was then concentrated under reduced pressure to *ca.* 50 ml and poured into ice–water. The latter was basified with 5% aqueous $NaHCO_3$ and extracted with Et_2O and the extract was washed with water, dried ($MgSO_4$), and evaporated under reduced pressure to give a brown solid (4.24 g, 94%), m.p. 109.5—111 °C. Recrystallisation of this from cyclohexane gave pale yellow prisms (4.00 g, 89%), m.p. 111—112 °C (Found: C, 74.5; H, 6.35; N, 5.55. $C_{15}H_{15}NO_2$ requires C, 74.65; H, 6.25; N, 5.8%); $\nu_{max.}$ 3 365, 3 340 (NH), 1 695, and 1 684 cm^{-1} (ester); $\delta_H(CCl_4)$ 1.35 (3 H, t, *J* 7.5 Hz, CMe), 4.26 (2 H, q, *J* 7.5 Hz, OCH_2), 6.17 (1 H, br s, NH), and 6.77—7.90 (9 H, m, ArH); *m/z* 241 (M^+).

(b) *Ethyl* 4-(N-*nitrosoanilino*)*benzoate* (**12c**). A solution of $NaNO_2$ (2.20 g) in water (1.6 ml) was added to a stirred solution of the benzoate (**11c**) (3.00 g) in a mixture of EtOH (990 ml) and concentrated HCl (2.4 ml) at 2 °C during 7.5 h. The reaction mixture was poured into ice–water and extracted with Et_2O, and the extract was washed with water, dried ($MgSO_4$), and evaporated under reduced pressure to give yellow crystals (3.35 g, 100%), m.p. 57–69.5 °C. Recrystallisation of the latter from hexane gave yellow prisms (3.01 g, 90%), m.p. 68—71 °C (Found: C, 66.65; H, 5.2; N, 10.1. $C_{15}H_{14}N_2O_3$ requires C, 66.65; H, 5.2; N, 10.35%); $\nu_{max.}$ 1 714 (ester) and 1 474 cm^{-1} (NO); $\delta_H(CCl_4)$ 1.39 (3 H, t, *J* 7.5 Hz, CMe), 4.33 (2 H, dif q, *J* 7.5 Hz, OCH_2), and 6.85—8.16 (9 H, m, ArH); *m/z* 241 ($M^+ - 29$).

(c) *Ethyl* 4-(1-*phenylhydrazino*)*benzoate* (**13c**). A solution of the nitroso compound (**12c**) (3.37 g) in AcOH (16 ml) was added to a suspension of Zn powder (3.37 g) in water (50 ml) at −5 to 2 °C with stirring. After being stirred at −2 to 0 °C for 4.5 h, the reaction mixture was filtered to remove the insoluble material, and the latter washed with Et_2O and water. The combined filtrate and washings were extracted with Et_2O and the extract was washed with 5% aqueous $NaHCO_3$ and water, dried ($MgSO_4$), and evaporated under reduced pressure to give an oily residue (3.10 g). Chromatography of the latter over silicic acid using benzene gave two eluates.

The less polar eluate gave yellow prisms (414 mg, 14%), m.p. 111—112.5 °C, which was identical with the starting ethyl 4-anilinobenzoate (**11c**).

The more polar eluate with $CHCl_3$ gave ethyl 4-(1-phenylhydrazino)benzoate (**13c**) (2.53 g, 79%), which was distilled at 200—205 °C (1.2 mmHg) to give an analytical sample as a pale yellow oil (Found: C, 70.1; H, 6.25; N, 10.8. $C_{15}H_{16}N_2O_2$ requires C, 70.3; H, 6.3; N, 10.95%); $\nu_{max.}$($CHCl_3$) 3 360 (NH) and 1 700 cm^{-1} (ester); δ_H 1.36 (3 H, t, *J* 7.5 Hz, CMe), 4.11 (1 H, br s, NH), 4.32 (2 H, q, *J* 7.5 Hz, OCH_2), and 6.97—7.95 (9 H, m, ArH); *m/z* 256 (M^+).

(d) *Ethyl pyruvate* 2-(4-*ethoxycarbonylphenyl*)*phenylhydrazone* (**8c**). Ethyl pyruvate (1.20 g) and two drops of AcOH were added to a solution of the hydrazine (**13c**) (2.10 g) in EtOH) (4 ml). The reaction mixture was refluxed for 20 min, after which it was cooled and evaporated under reduced pressure to give a yellow solid (3.53 g), m.p. 55—62.5 °C. Recrystallisation of the latter from hexane–Et_2O gave yellow prisms (2.65 g, 91%), m.p. 60—63 °C (Found: C, 67.8; H, 6.35; N, 7.8. $C_{20}H_{22}N_2O_4$ requires C, 67.8; H, 6.25; N, 7.9%); $\nu_{max.}$ 1 713 and 1 700 cm^{-1} (ester); δ_H 1.37 (3 H, t, *J* 7.5 Hz, CMe), 1.39 (3 H, t, *J* 7.5 Hz, CMe), 1.63 (3 H, s, =CMe), 4.34 (4 H, q, *J* 7.5 Hz, 2 × OCH_2), and 7.00—8.00 (9 H, m, ArH); *m/z* 354 (M^+).

Syntheses of Authentic N-*Arylindole Derivatives* (**9**) *and* (**10**).—(a) *General procedure for the Ullmann–Goldberg reaction.*[18a] The method was based on reference 18*b*. A mixture of 1*H*-indole (**14**) (1.06 mmol), anhydrous K_2CO_3 (1.52 mmol), Cu_2Br_2(0.14 mmol), and bromo- or iodo-benzene (2.00 mmol) in

nitrobenzene (0.6 ml) and pyridine (0.2 ml) was heated at 180 °C for several hours. The mixture was then cooled, poured into water, and extracted with Et_2O. The organic layer was washed with 5% aqueous HCl and water, dried (K_2CO_3), and evaporated to dryness under reduced pressure to give the crude product. This was purified by column chromatography over silicic acid using benzene or benzene–cyclohexane as an eluant.

(b) *Ethyl 5-methoxy-1-phenylindole-2-carboxylate* (**9a**). Ethyl 5-methoxyindole-2-carboxylate[2,19] (**14a**) (232 mg) was treated with bromobenzene under Ullmann–Goldberg conditions for 10 h. The product (91 mg, 29%) was recrystallised from pentane to give colourless prisms, m.p. 59—62 °C (Found: C, 73.2; H, 5.7; N, 4.8. $C_{18}H_{17}NO_2$ requires C, 73.2; H, 5.8; N, 4.75%); $\nu_{max.}$ 1 720 cm^{-1} (ester); $\delta_H(CCl_4)$ 1.19 (3 H, t, *J* 7.5 Hz, CMe), 3.79 (3 H, s, OMe), 4.14 (2 H, q, *J* 7.5 Hz, OCH_2), and 6.69—7.52 (9 H, m, ArH); *m/z* 295 (M^+).

(c) *Ethyl 1-(4-methoxyphenyl)indole-2-carboxylate* (**10a**). Ethyl indole-2-carboxylate[2,20] (**14d**) (200 mg) was allowed to react with *p*-bromoanisole under Ullmann–Goldberg conditions for 14.5 h. The product (190 mg) was recrystallised from cyclohexane to give colourless needles, m.p. 114—116 °C (Found: C, 72.95; H, 5.8; N, 4.65. $C_{18}H_{17}NO_3$ requires C, 73.2; H, 5.8; N, 4.75%); $\nu_{max.}$ 1 713 cm^{-1} (ester); $\delta_H(CCl_4)$ 1.22 (3 H, t, *J* 7.5 Hz, CMe), 3.83 (3 H, s, OMe), 4.14 (2 H, q, *J* 7.5 Hz, OCH_2), 6.80—7.32 (8 H, m, ArH), and 7.57 (1 H, m, ArH); *m/z* 295 (M^+).

(d) *Ethyl 4,6-dimethoxy-1-phenylindole-2-carboxylate* (**9b**). (i) Ethyl pyruvate 2-(3,5-dimethoxyphenyl)hydrazone (**16**). A solution of $NaNO_2$ (2.963 g) in water (12 ml) was added to a stirred solution of 3,5-dimethoxyaniline[21] (5.455 g) in concentrated HCl (7.1 ml) and water (28 ml) at 0—4 °C to give a diazonium salt solution. This was added dropwise to a solution of ethyl α-methylacetoacetate[22] (5.293 g) in EtOH (40 ml) containing 50% aqueous KOH (6.1 ml) at 4 °C or below. The whole was stirred at the same temperature for 1.5 h and then at room temperature for further 1 h. The reaction mixture was poured into ice–water, extracted with benzene, and the extract washed with water, dried ($MgSO_4$), and evaporated under reduced pressure to give a red oil (7.54 g). This was chromatographed over silicic acid with benzene as an eluant to give two hydrazones, *Z*-(**16a**) and *E*-(**16b**) in order of the elution.

(ii) (*Z*)-Ethyl pyruvate 2-(3,5-dimethoxyphenyl)hydrazone (**16a**). The first eluate (285 mg, 3.0%) was recrystallised from hexane to give (**16a**) as pale orange prisms, m.p. 76—77 °C (Found: C, 58.6; H, 6.9; N, 10.45. $C_{13}H_{18}N_2O_4$ requires C, 58.65; H, 6.8; N, 10.5%); $\nu_{max.}$ 3 220 (NH) and 1 668 cm^{-1} (ester); $\delta_H(CCl_4)$ 1.33 (3 H, t, *J* 7.0 Hz, CMe), 2.10 (3 H, s, =CMe), 3.73 (6 H, s, 2 × OMe), 4.22 (2 H, q, *J* 7.0 Hz, OCH_2), 5.89 (1 H, t, *J* 2.2 Hz, 4-H), and 6.19 (2 H, d, *J* 2.2 Hz, 2- and 6-H).

(iii) (*E*)-Ethyl pyruvate 2-(3,5-dimethoxyphenyl)hydrazone (**16b**). The second eluate (3.37 g, 35%) was recrystallised from hexane to give (**16b**) as pale yellow needles, m.p. 105.5—107.5 °C (Found: C, 58.6; H, 6.85; N, 10.6. $C_{13}H_{18}N_2O_4$ requires C, 58.65; H, 6.8; N, 10.5%); $\nu_{max.}$ 3 265 (NH) and 1 694 cm^{-1} (ester); $\delta_H(CCl_4)$ 1.32 (3 H, t, *J* 7.0 Hz, CMe), 1.98 (3 H, s, =CMe), 3.69 (6 H, s, 2 × OMe), 4.22 (2 H, q, *J* 7.0 Hz, OCH_2), 5.90 (1 H, t, *J* 2.2 Hz, 4-H), 6.22 (2 H, d, *J* 2.2 Hz, 2- and 6-H), and 7.75 (1 H, br s, NH).

(iv) Ethyl 4,6-dimethoxyindole-2-carboxylate (**14b**). Anhydrous $ZnCl_2$ (520 mg) was added to a solution of the (*E*)-hydrazone (**16b**) (504 mg) in AcOH (7 ml) and the whole was refluxed for 3 h. After cooling, the reaction mixture was poured into water, extracted with Et_2O, and the extract washed with 5% aqueous $NaHCO_3$ and water, dried ($MgSO_4$), and evaporated. The residue (337 mg) was purified with column chromatography over silicic acid with benzene–$CHCl_3$ (5:1) as an eluant to give crystals (175 mg, 37%), m.p. 142—143 °C. Recrystallisation of the latter from cyclohexane–benzene gave colourless needles, m.p. 143—144 °C (Found: C, 62.5; H, 6.05; N, 5.65. $C_{13}H_{15}NO_4$ requires C, 62.65; H, 6.05; N, 5.6%); $\nu_{max.}$ 3 335 (NH) and 1 668 cm^{-1} (ester); $\delta_H(CCl_4)$ 1.40 (3 H, t, *J* 7.0 Hz, CMe), 3.76 (3 H, s, 4-OMe), 3.88 (3 H, s, 6-OMe), 4.36 (2 H, q, *J* 7.0 Hz, OCH_2), 6.01 (1 H, d, *J* 2.0 Hz, 5- or 7-H), 6.31 (1 H, d, *J* 2.0 Hz, 7- or 5-H), 7.13 (1 H, d, *J* 2.0 Hz, 3-H), and 9.34 (1 H, br s, NH).

(v) Ethyl 4,6-dimethoxy-1-phenylindole-2-carboxylate (**9b**). A mixture of the 1*H*-indole (**14b**) (100 mg), Cu_2Br_2 (20 mg), and powdered anhydrous K_2CO_3 (111 mg) in bromobenzene (2 ml) and pyridine (1 ml) was heated at 150 °C for 4 h under argon. Work-up, according to the general procedure for the Ullmann–Goldberg reaction, gave (**9b**) as crystals (124 mg, 95%), which were recrystallised from benzene–hexane to afford colourless prisms, m.p. 122.5–124 °C (Found: C, 70.3; H, 5.9; N, 4.2. $C_{19}H_{19}NO_4$ requires C, 70.15; H, 5.9; N, 4.3%); $\nu_{max.}$ 1 710 cm^{-1} (ester); δ_H 1.19 (3 H, t, *J* 7.5 Hz, CMe), 3.66 (3 H, s, OMe), 3.92 (3 H, s, OMe), 4.12 (2 H, q, *J* 7.5 Hz, OCH_2), 6.02 (1 H, d, *J* 2.0 Hz, 5- or 7-H), 6.18 (1 H, d, *J* 2.0 Hz, 7- or 5-H), and 7.21—7.47 (6 H, m, 3-H and other ArH).

(e) *Ethyl 1-(3,5-dimethoxyphenyl)indole-2-carboxylate* (**10b**). A mixture of ethyl indole-2-carboxylate[2,20] (**14d**) (100 mg), 3,5-dimethoxybromobenzene[21] (344 mg), powdered anhydrous K_2CO_3 (146 mg), and Cu_2Br_2 (20 mg) in pyridine (0.5 ml) and nitrobenzene (2 ml) was heated at 160—170 °C for 4.5 h under argon. Work-up according to the general procedure for the Ullman–Goldberg reaction gave a solid (147 mg, 86%) which was recrystallised from benzene–hexane to afford colourless rods, m.p. 79—81.5 °C (Found: C, 70.25; H, 5.85; N, 4.3. $C_{19}H_{19}NO_4$ requires C, 70.15; H, 5.9; N, 4.3%); $\nu_{max.}$ 1 713 cm^{-1} (ester); δ_H 1.25 (3 H, t, *J* 7.5 Hz, CMe), 3.80 (6 H, s, 2 × OMe), 4.24 (2 H, q, *J* 7.5 Hz, OCH_2), 6.51 (2 H, dif d, *J* 2.0 Hz, 2′- and 6′-H), 6.57 (1 H, dif d, *J* 2.0 Hz, 4′-H), 7.23 (3 H, m, 5-, 6-, and 7-H), 7.44 (1 H, s, 3-H), and 7.72 (1 H, m, 4-H); *m/z* 325 (M^+, base peak).

(f) *Diethyl 1-phenylindole-2,5-dicarboxylate* (**9c**). Diethyl indole-2,5-dicarboxylate[8] (**14c**) (101 mg) was allowed to react with iodobenzene under Ullmann–Goldberg conditions for 3 h. The product (86 mg, 66%) was recrystallised from hexane–benzene to give colourless scales, m.p. 129—130.5 °C (Found: C, 71.2; H, 5.65; N, 4.15. $C_{20}H_{19}NO_4$ requires C, 71.2; H, 5.7; N, 4.15%); $\nu_{max.}$ 1 732 and 1 708 cm^{-1} (C=O); δ_H 1.22 (3 H, t, *J* 7.5 Hz, CMe), 1.41 (3 H, t, *J* 7.5 Hz, CMe), 4.21 (2 H, q, *J* 7.5 Hz, OCH_2), 4.39 (2 H, q, *J* 7.5 Hz, OCH_2), 7.06 (1 H, d, *J* 8.0 Hz, 7-H), 7.20—7.59 (6 H, m, ArH), 7.91 (1 H, dd, *J* 8.0 and 2.0 Hz, 6-H), and 8.47 (1 H, d, *J* 2.0 Hz, 4-H); *m/z* 337 (M^+).

(g) *Ethyl 1-(4-ethoxycarbonylphenyl)indole-2-carboxylate* (**10c**). Ethyl indole-2-carboxylate[2,20] (300 mg) was allowed to react with ethyl *p*-bromobenzoate under Ullmann–Goldberg conditions for 12.5 h. The product (329 mg, 75%) was recrystallised from hexane to give colourless prisms, m.p. 113—114 °C (Found: C, 71.05; H, 5.7; N, 4.0. $C_{20}H_{19}NO_4$ requires C, 71.2; H, 5.7; N, 4.15%); $\nu_{max.}$ 1 717 cm^{-1} (ester); δ_H 1.23 (3 H, t, *J* 7.5 Hz, CMe), 1.41 (3 H, t, *J* 7.5 Hz, CMe), 4.22 (2 H, q, *J* 7.5 Hz, OCH_2), 4.41 (2 H, q, *J* 7.5 Hz, OCH_2), 7.00—7.77 (7 H, m, ArH), and 8.17 (2 H, d, *J* 8.0 Hz, 3′- and 5′-H); *m/z* 337 (M^+).

Fischer Indolisation of Ethyl Pyruvate 2-(4-Methoxyphenyl)-phenylhydrazone (**8a**).—A solution of the hydrazone (**8a**) (2.00 g) in dry EtOH (80 ml) saturated with dry HCl gas was stirred at room temperature for 2.5 h. The reaction mixture was poured into ice–water and extracted with Et_2O, and the extract was washed with 5% aqueous $NaHCO_3$, dried (K_2CO_3), and evaporated to afford a residue (1.69 g), which was chromatographed over silicic acid using benzene–cyclohexane as eluant to provide three eluates (I—III) in order of the elution.

(a) *2-Chloro-N-phenyl-p-anisidine* (**17**). Eluate I gave solid (497 mg, 33%), m.p. 43—48 °C, which was recrystallised from

hexane to give colourless prisms, m.p. 51—52.5 °C (Found: C, 67.1; H, 5.05; N, 6.15. $C_{13}H_{12}ClNO$ requires C, 66.8; H, 5.2; N, 6.0%); $\nu_{max.}$ 3 402 cm^{-1} (NH); $\delta_H(CCl_4)$ 3.74 (2 H, s, OMe), 5.62 (1 H, br s, NH), 6.66 (1 H, dd, *J* 9.4 and *J* 3.2 Hz, 5-H), and 6.78—7.32 (7 H, m, ArH); *m/z* 235 (M^+ + 2, 36% of M^+) and 233 (M^+).

(b) N-*Phenyl*-p-*anisidine*[14] (**11a**). Eluate II gave the title compound as colourless rods (68 mg, 5.3%), m.p. 104—106 °C; it was identical with an authentic sample.

Eluate III afforded a colourless oil (897 mg, 48%), which was submitted to preparative t.l.c. over silica gel using hexane–Et_2O (5:1) as an eluant to give two fractions.

(c) *Ethyl* 5-*methoxy*-1-*phenylindole*-2-*carboxylate* (**9a**). The less polar fraction of eluate III gave colourless prisms (803 mg, 42.5%), m.p. 57.5—60.5 °C, which was recrystallised from hexane–Et_2O to give the title compound. This was identical in all respects including mixed m.p. with an authentic sample prepared from ethyl 5-methoxyindole-2-carboxylate (**14a**).

(d) *Ethyl* 1-(4-*methoxyphenyl*)*indole*-2-*carboxylate* (**10a**). The more polar fraction of eluate III gave colourless needles (44 mg, 2.3%), m.p. 114—116 °C, which was recrystallised from cyclohexane. This was identical in all respects including mixed m.p. with the authentic sample prepared from ethyl indole-2-carboxylate (**14d**).

(e) *Determination of the ratio of indole components* (**9a**) *and* (**10a**) *from the* ^1H *n.m.r. spectrum of eluate III.* $Eu(dpm)_3$ (60 mg, 0.085 mmol) was added to a solution of eluate III (50 mg, 0.170 mmol) in $CDCl_3$ (0.5 ml). Intensities of the shifted signals at δ_H 4.13 [s, 5-OMe of (**9a**)] and 4.25 [s, 4′-OMe of (**10a**)] were observed in the ratio 23:1.

Alternative Synthesis of 2-*Chloro*-N-*phenyl*-p-*anisidine* (**17**).—(a) N-*Acetyl*-2-*chloro*-p-*anisidine* (**19**). 2-Chloro-*p*-anisidine[23] (8.511 g) in Ac_2O (36 ml) was stirred at room temperature for 1.5 h after which the reaction mixture was poured into ice–water. The mixture was basified with concentrated NH_4OH and extracted with $CHCl_3$ and the extract was dried (K_2CO_3), and evaporated to dryness under reduced pressure. The residue (9.846 g) was recrystallised from benzene to give colourless needles (9.146 g), m.p. 114—117 °C (lit.,[24] m.p. 114 °C) (Found: C, 54.25; H, 4.9; N, 7.15. Calc. for $C_9H_{10}ClNO_2$: C, 54.15; H, 5.05; N, 7.0%); $\nu_{max.}$ 3 310 (NH) and 1 650 cm^{-1} (C=O); δ_H 2.19 (3 H, s, COMe), 3.79 (3 H, s, OMe), 6.80 (1 H, dd, *J* 3.0 and 9.0 Hz, 5′-H), 6.91 (1 H, d, *J* 3.0 Hz, 3′-H), 7.41 (1 H, br s, NH), and 8.11 (1 H, d, *J* 9.0 Hz, 6′-H).

(b) N-*Acetyl*-2-*chloro*-N-*phenyl*-p-*anisidine* (**20**). A mixture of *N*-acetyl-2-chloro-*p*-anisidine (**19**) (0.307 g), anhydrous K_2CO_3 (229 mg), and Cu_2Br_2 (20 mg) in bromobenzene (3 ml) was refluxed for 3.5 h under argon and then poured into water and extracted with Et_2O. The organic layer was dried (K_2CO_3), and evaporated to dryness under reduced pressure to give a residue (470 mg). Purification of the latter by column chromatography over silicic acid using benzene–AcOEt (3:1) as eluant gave an oil (404 mg), b.p. 140 °C (0.0002 mmHg) (Found: C, 64.9; H, 5.05; N, 5.0. $C_{15}H_{14}ClNO_2$ requires C, 65.35; H, 5.1; N, 5.1%); $\nu_{max.}(CHCl_3)$ 1 660 cm^{-1} (CO); δ_H 2.01 (3 H, s, COMe), 3.78 (3 H, s, OMe), 6.80 (1 H, dd, *J* 9.0 and 3.0 Hz, 5′-H), 7.00 (1 H, d, *J* 3.0 Hz, 3′-H), and 7.10—7.44 (6 H, m, ArH).

(c) 2-*Chloro*-N-*phenyl*-p-*anisidine* (**17**). A solution of *N*-acetyl-2-chloro-*N*-phenyl-*p*-anisidide (**20**) (496 mg) in 10% alcoholic KOH (2.8 ml) was refluxed for 1 h under argon. The reaction mixture was poured into water and extracted with Et_2O and the extract was washed with water, dried (K_2CO_3), and evaporated to dryness. The residue was chromatographed over silicic acid using benzene–hexane (3:1) as eluant and recrystallised to give colourless prisms (196 mg), m.p. 51.5—52 °C. The product, identical (i.r. and mixed m.p.) with the Fischer product, was dimorphic, m.p. 46.5—47 °C and 51.5—52 °C, the two forms being interconvertible with cross-seeding.

Fischer Indolisation of Ethyl Pyruvate 2-(3,5-*Dimethoxyphenyl*)*phenylhydrazone* (**8b**).—The hydrazone (**8b**) (802 mg), dissolved in dry EtOH (30 ml) saturated with dry HCl gas, was stirred at 60 °C for 40 min. The mixture was then poured into water and extracted with Et_2O, and the extract washed with 5% aqueous $NaHCO_3$, dried ($MgSO_4$), and evaporated to give a solid (641 mg). This was purified by short column chromatography over silicic acid with benzene as an eluant to give crystals (465 mg, 61%) of the two indoles, ethyl 4,6-dimethoxyindole-2-carboxylate (**9b**) and ethyl 1-(3,5-dimethoxyphenyl)-indole-2-carboxylate (**10b**).

(a) *Ethyl* 4,6-*dimethoxy*-1-*phenylindole*-2-*carboxylate* (**9b**). Fractional recrystallisation of the crystals from hexane gave (**9b**) (236 mg). The mother liquor was evaporated and chromatographed several times over silicic acid using benzene as an eluant to give two fractions. The less-polar fraction gave a further crop of (**9b**) (88 mg, total 324 mg, 43%). Recrystallisation from hexane gave a pure sample of (**9b**) as colourless prisms, m.p. 121.5—123 °C (Found: C, 70.3; H, 5.9; N, 4.35. $C_{19}H_{19}NO_4$ requires C, 70.15; H, 5.7; N, 4.3%). This compound was identical with an authentic sample.

(b) *Ethyl* 1-(3,5-*dimethoxyphenyl*)*indole*-2-*carboxylate* (**10b**). The more polar fraction gave (**10b**) (127 mg, 17%) which was recrystallised from hexane to afford colourless rods, m.p. 80—82 °C. This compound was identical with an authentic sample.

(c) *Determination of the ratio of indole components* (**9b**) *and* (**10b**) *by* ^1H *n.m.r. spectrometry.* Intensities of singlet methoxy signals at δ_H 3.66 [a methoxy group of (**9b**)] and 3.80 [two methoxy groups of (**10b**)] were observed in the ratio of 1.65:1. Thus the ratio of (**9b**) and (**10b**) was 3.3:1.

Fischer Indolisation of Ethyl Pyruvate 2-(4-*Ethoxycarbonyl*)-*phenylhydrazone* (**8c**).—A solution of the hydrazone (**8c**) (1.00 g) in dry EtOH (50 ml) saturated with dry HCl gas was refluxed for 30 min. The mixture was then cooled, concentrated under reduced pressure to half under volume, and poured into ice–water. The latter was then extracted with Et_2O and the extract washed with 5% aqueous $NaHCO_3$ and water, dried ($MgSO_4$), and evaporated to give a yellow solid (940 mg). This was chromatographed on silicic acid using benzene as eluant, followed by $CHCl_3$ to give two eluates, I and II.

(a) *Ethyl* 1-(4-*ethoxycarbonylphenyl*)*indole*-2-*carboxylate* (**10c**). Recrystallisation of eluate I (760 mg) from hexane–benzene gave (**10c**) as colourless prisms (421 mg), m.p. 114.5—116 °C, as relatively insoluble product (Found: C, 71.25; H, 5.7; N, 4.1. $C_{20}H_{19}NO_4$ requires C, 71.2; H, 5.6; N, 4.15%). This compound was identical in all respects including mixed m.p. with an authentic sample.

(b) *Diethyl* 1-*phenylindole*-2,5-*dicarboxylate* (**9c**). Recrystallisation of the mother liquor of the indole (**10c**) from benzene–hexane gave (**9c**) as colourless prisms (32 mg), m.p. 129.5—131 °C. This compound was identical with an authentic sample in all respects including mixed m.p.

The mother liquor of the indole (**9c**) was submitted to preparative t.l.c. over silica gel using hexane–Et_2O (5:1) as a developing solvent to give further crops of the indoles, ethyl 1-(4-ethoxycarbonylphenyl)indole-2-carboxylate (**10c**) [214 mg, total 635 mg (67%)] and ethyl 1-phenylindole-3,5-dicarboxylate (**9c**) [77 mg, total 109 mg (11%)].

(c) *Determination of the ratio of indole components* (**9c**) *and* (**10c**) by ^1H *n.m.r. spectrometry.* $Eu(dpm)_3$ (12.5 mg, 0.018 mmol) was added to solution of eluate I (30 mg, 0.089 mmol) in $CDCl_3$ (0.5 ml). The intensities of the methylene signals for the shifted ethoxy group at δ_H 6.53 [q, 5-CO_2CH_2 of (**9c**)] and 6.03 [q, 4′-CO_2CH_2 of (**10c**)] were observed in the ratio of 1:6.8.

(d) *Ethyl* 4-(1-*phenylhydrazino*)*benzoate* (**13c**). Rechro-

matography of eluate II (121 mg, 17%) over silicic acid with benzene gave pure (**13c**) as a yellow oil, which was identical with an authentic sample.

Thermal Fischer Indolisation of Ethyl Pyruvate 2-(4-*Methoxyphenyl*)*phenylhydrazone* (**8a**).—A solution of the hydrazone (**8a**) (1.04 g) in ethylene glycol (10 ml) was refluxed for 1 h after which it was cooled, poured into water, and extracted with Et_2O. The extract was washed with water, dried ($MgSO_4$), and evaporated under reduced pressure to give a residue (702 mg). This was chromatographed over silicic acid using benzene–cyclohexane (1:1) as eluant to give two eluates (I and II). Eluate I gave colourless needles (457 mg, 69%), m.p. 104—106 °C, which were identical with those of an authentic *N*-phenyl-*p*-anisidine (**11a**).

Eluate II was evaporated under reduced pressure to give a colourless oil (100 mg, 10%), which was found to be a mixture of two indoles (**9a**) and (**10a**) in the ratio 3.7:1 [Eu(dpm)$_3$-induced ^{1}H n.m.r. spectrum].

Thermal Fischer Indolisation of Ethyl Pyruvate 2-(3,5-*Dimethoxyphenyl*)*phenylhydrazone* (**8b**).—(a) *In diethylene glycol.* A solution of the hydrazone (**8b**) (1.379 g) in diethylene glycol (10 ml) was heated at 240 °C (bath) for 30 min and then worked-up as for the hydrazone (**8a**). The resulting residue (860 mg) was chromatographed over silicic acid and eluted with benzene to give two eluates. The first eluate gave *N*-phenyl-3,5-dimethoxyaniline (**11b**) (481 mg, 52%), m.p. 69—71 °C, which was identical with an authentic sample. The second eluate gave a mixture (90 mg, 12%) of two indoles (**9b**) and (**10b**), in the ratio 1.9:1 (^{1}H n.m.r. spectrum).

(b) *In Dowtherm A.* The hydrazone (**8b**) (506 mg) was added in Dowtherm A[11] (5 ml) and the whole was heated at 240 °C (bath) for 45 min. The solvent was removed under reduced pressure and the residue was chromatographed over silicic acid using benzene as an eluant to give the amine (**11b**) (198 mg, 58%), which was identical with an authentic sample.

Thermal Fischer Indolisation of Ethyl Pyruvate 2-(4-*Ethoxycarbonylphenyl*)*phenylhydrazone* (**8c**).—A solution of the hydrazone (**8c**) (500 mg) in ethylene glycol (5 ml) was refluxed for 2 h and worked-up as for the hydrazone (**8a**). The resulting residue was chromatographed over silicic acid using benzene as eluant to give two eluates (I and II). Eluate I gave colourless prisms (132 mg, 39%), m.p. 110—111 °C, which were found to be identical with those of an authentic sample of ethyl 4-anilinobenzoate (**11c**). Eluate II was evaporated under reduced pressure to give a colourless solid (70 mg, 15%), which was found to be a mixture of the indoles (**9c**) and (**10c**) in the ratio 1:2.5 [Eu(dpm)$_3$-induced ^{1}H n.m.r. spectrum].

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