# Nucleophilic Displacement of the Methoxy Group in Abnormal Fischer Indolization of 2-Methoxyphenylhydrazones

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In 1883, Fischer et al.[1] found that pyruvic acid 1-methylphenylhydrazone gave 1-methylindole-2-carboxylic acid when treated with dilute hydrogen chloride (eq 1). More recently, the reaction has become
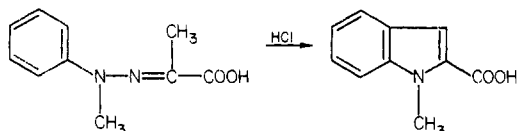
well-known as the Fischer indolization.[2] Since arylhydrazones can be easily prepared from aryldiazonium salts and active methine compounds via the Japp–Klingemann reaction,[3] Fischer indolization becomes a versatile method for the preparation of indole derivatives.

During the development of the chemistry of Fischer indolization, several tentative reaction pathways were proposed. In 1918, Robinson et al.[4] proposed a plausible mechanism[5] which has been widely accepted. The mechanism comprises the following steps in a modern sense: (i) Initially, the phenylhydrazone (1) is isomerized to the enehydrazine (2) by an acid catalyst (see Scheme I). (ii) At the second stage, intramolecular C–C bond formation takes place by an attack of the enehydrazine moiety on the phenyl ring. Earlier there were many arguments concerning the mode of this step, but now a [3,3]sigmatropic shift process has been widely accepted in spite of the absence of conclusive proof. (iii) Attack of the aryl nitrogen (N_A) at the carbon of a side chain iminium group followed by loss of ammonia provides the indole product (3).

In the Robinson proposal, the C–C bond formation step was viewed as analogous to the *o*-benzidine rearrangement,[4] but there remained a question why the para rearrangement did not take place during Fischer indolization, in spite of the fact that an *o*-benzidine rearrangement[6] generally accompanies the para rearrangement. In 1948, Carlin et al.[7] treated the 2,6-dichlorophenylhydrazone (4) of acetophenone with zinc chloride in order to obtain conclusive evidence relating to this problem and obtained a rearrangement product, 5,7-dichloro-2-phenylindole (5), as shown in Scheme II. This was the first finding of migration of an ortho substituent of the starting phenylhydrazone during Fischer indolization.

Since this result was somewhat similar to that of the ortho-Claisen rearrangement[8] of 2,6-disubstituted phenyl allyl ether, the step involving C–C bond formation was recognized as an analogue of the ortho-Claisen rearrangement. Carlin et al.[9] also tried the

cyclization of 2,6-dimethylphenylhydrazone derivatives and obtained products in which 1,2 or 1,4 migration of an *o*-methyl group took place. Similar kinds of experiment are still being continued by several groups[10] for the purpose of elucidation of the mechanism of Fischer indolization.

In a classic sense, the Robinson mechanism suggested that the cyclization took place by electrophilic substitution of the enehydrazine group on the phenyl ring. In fact, a superficial survey in *Chemical Abstracts* of reported conditions used for various Fischer indolizations seems to indicate that cyclization can take place under fairly mild conditions (e.g., use of a protic acid at room temperature) in the case of a phenylhydrazone bearing an electron-donating group on the benzene ring, while relatively stronger conditions, such as employment of a Lewis acid under reflux, are required for the cyclization of a phenylhydrazone having an electron-attracting group. These conclusions seem to support the classic interpretation of the Fischer indolization. In other words, Fischer indolization would seem best adapted for the synthesis of indoles having an electron-donating group such as a methoxy group.

However, the preparation of many methoxyindoles involving the total syntheses of indole alkaloids has been achieved by other methods, while there are many reports on the application of the method to the preparation of indoles having an electron-attracting substituent such as a nitro group. These facts allude to the presence of some problems to be solved in the Fischer indolization of methoxyphenylhydrazones. In fact, in 1958 Pappalardo et al.[11] reported the formation of an undefined indole, mp 168 °C, on treatment of ethyl pyruvate 2-methoxyphenylhydrazone (6) with ethanolic hydrogen chloride, whereas the expected 7-methoxyindole product (7), mp 117 °C, was produced when the

(1) E. Fischer and F. Jourdan, *Ber.*, **16**, 2241 (1883).
(2) For a review of normal Fischer indolization, see B. Robinson, *Chem. Rev.*, **63**, 373 (1963); **69**, 227 (1969); W. A. Remers and R. K. Brown in "Indole", W. J. Houlihan, Ed., Wiley-Interscience, New York, 1972, pp 232–317.
(3) R. R. Phillips, *Org. React.*, **10**, 143 (1959).
(4) G. M. Robinson and R. Robinson, *J. Chem. Soc.*, **113**, 639 (1918); **125**, 827 (1924).
(5) This mechanism has been generally called the Robinson mechanism. However, essentially the same mechanism had been proposed by K. Brunner [*Ber.*, **31**, 1943 (1898)] 20 years before the Robinson proposal.
(6) For a review of the benzidine rearrangement, see "Aromatic Rearrangement", H. J. Hine, Elsevier, Amsterdam, 1967, pp 126–179.
(7) (a) R. B. Carlin and E. E. Fischer, *J. Am. Chem. Soc.*, **70**, 3421 (1948); (b) R. B. Carlin, J. G. Wallace, and E. E. Fischer, *ibid.*, **74**, 990 (1952); (c) R. B. Carlin and G. W. Larson, *ibid.*, **79**, 934 (1957).
(8) D. S. Tarbell, *Chem.. Rev.*, **27**, 495 (1940); D. S. Tarbell and J. W. Wilson, *J. Am. Chem. Soc.*, **64**, 1066 (1942).
(9) See, for example, R. B. Carlin and D. P. Carlson, *J. Am. Chem. Soc.*, **79**, 3605 (1957); R. B. Carlin and J. W. Harrison, *J. Org. Chem.*, **30**, 563 (1965).
(10) See, for example, R. Fusco and F. Sannicolô, *Tetrahedron*, **36**, 161 (1980); B. Miller and E. R. Matjeka, *J. Am. Chem. Soc.*, **102**, 4772 (1980).
(11) G. Pappalardo and T. Vitali, *Gazz. Chim. Ital.*, **88**, 574 (1958).

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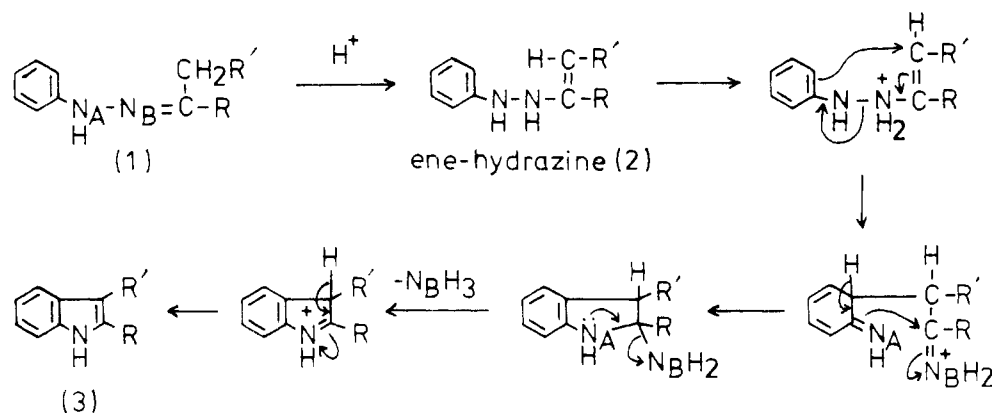
Table I

6^a
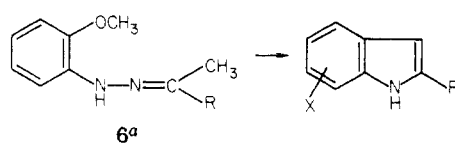
	% products, X =								
reagents	7-OCH$_3$, (7)	7-OEt	6-Cl (8)	6-OEt (10)	4-OCH$_3$ (12)	3-,4-,5-Cl mixture	H	dimer	
3 N HCl-EtOH	16	1	10	5	1	12			
sat. HCl-EtOH (ours)	4	2	35	0.3		8		Cl (+) 0.6	
sat. HCl-EtOH[14] (Gannon's)	(+) TLC		36	(+) mass spectrum		3-Cl (13) 1		CH$_3$O (+) 0.1	
HCl-AcOH	17		21			6			
H$_2$SO$_4$-EtOH	13			2			0.2		

reagents	7-OCH$_3$ (7)	5-Cl	5-OCH$_3$ (14)	4-OCH$_3$ (12)	H
ZnCl$_2$-AcOH	18	1.5	0.7	0.3	1
BF$_3$-AcOH	14		0.9		2
BF$_3$-AcOEt	15		5		3
H$_2$SO$_4$-AcOH	5		0.3		0.2

^{a} R = CO$_2$Et.

Scheme I

Scheme II
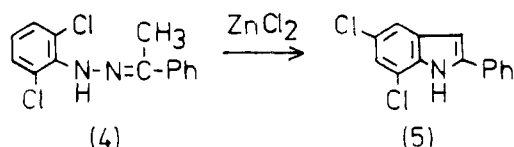
same hydrazone (6) was treated with a mixture of sulfuric and acetic acids (see Table Ia). Their finding stimulated our interest in reexamination of their experiments.

The Ortho-C-6 and Ortho-C-5 Abnormal Fischer Indolizations

Fischer indolization of 6 under various conditions gave a variety of unexpected indole products together with the normally expected 7-methoxyindole (7). These abnormal reactions can be classified into two major categories, ortho-C-6[12] or ortho-C-5[13] abnormal Fischer indolization, according to whether the product is a 6-substituted or a 5-substituted indole (Table I[12,13]).
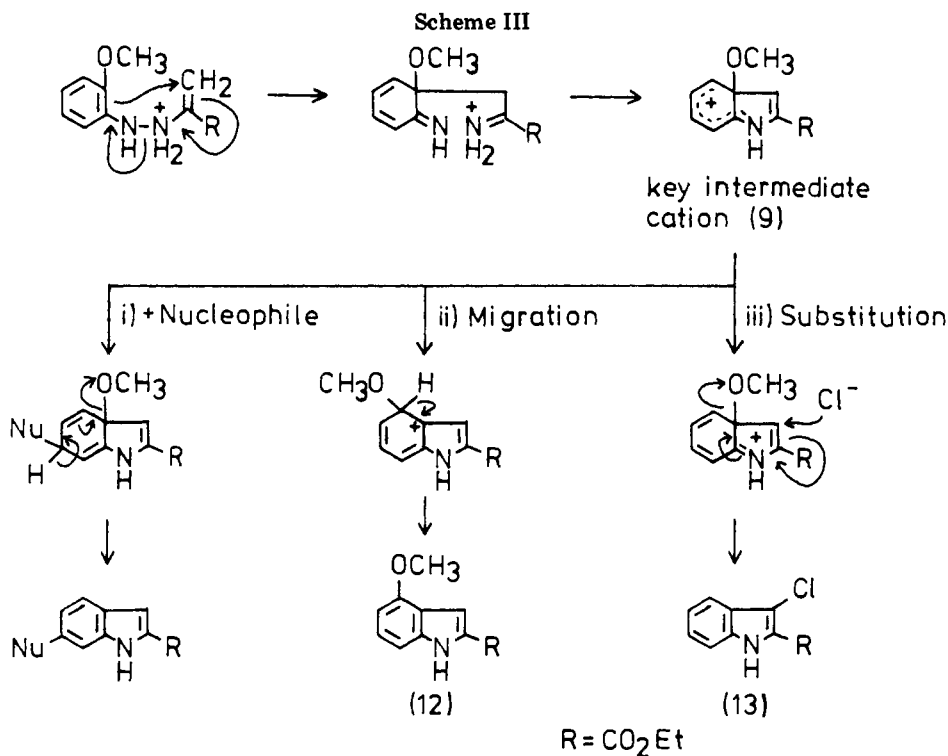
(12) H. Ishii, Y. Murakami, K. Hosoya, H. Takeda, Y. Suzuki, and N. Ikeda, *Chem. Pharm. Bull.*, 21, 1481 (1973).
(13) H. Ishii, Y. Murakami, T. Furuse, K. Hosoya, and N. Ikeda, *Chem. Pharm. Bull.*, 21, 1495 (1973).

In this Account, we begin with a discussion of the ortho-C-6 abnormal Fischer indolization.[12] This is represented by the formation of ethyl 6-chloroindole-2-carboxylate (8) on treatment of 6 with ethanolic hydrogen chloride. It should be noted here that Gannon et al.[14] reported almost the same experiment and obtained essentially the same result. This unexpected reaction could be rationalized by expansion of the Robinson mechanism as shown in Scheme III. Let us suppose that C–C bond formation by the enehydrazine intermediate takes place at the ortho position occupied by the methoxy group, thereby forming an intermediate with the methoxy group on a tertiary carbon. This would be transformed into the key intermediate cation (9) by attack of the ring imino nitrogen on the side-chain iminium carbon and expulsion of an ammonia molecule.[15] This key intermediate cation (9) plays important roles in both the ortho-C-6 and ortho-C-5

(14) W. F. Gannon, J. D. Benigni, D. E. Dickson, and R. L. Minnis, *J. Org. Chem.*, 34, 3002 (1969).
(15) Gannon et al.[14] claimed that the cyclization is caused by protonation at the opposite imino group. Their mechanism leads to the conclusion that the indole product should be formed by loss of the N$_A$ nitrogen. However, Gannon's pathway is not the primary one at least, because we[12] obtained a relatively large quantity of a mixture of N$_A$-methylindole derivatives in the Fischer indolization of ethyl pyruvate N$_A$-methyl-2-methoxyphenylhydrazone.

Scheme III

OCH3 → CH2 → R → OCH3 R → OCH3 R

key intermediate
cation (9)

i) +Nucleophile   ii) Migration   iii) Substitution

OCH3
Nu · · · R
H   N
     H

CH3O H
R
N
H

OCH3 Cl−
R
N
H

Nu R
N
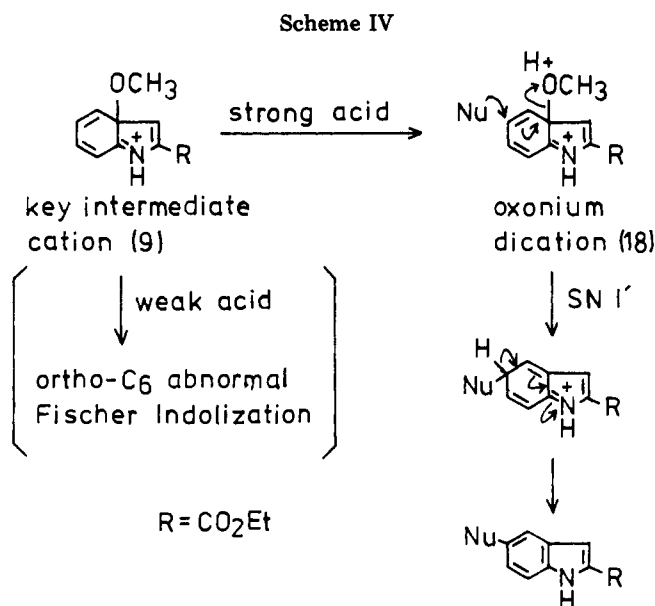H

OCH3
R
N
H
(12)

Cl
R
N
H
(13)

R = CO2Et

abnormal Fischer indolizations as shown in Schemes III and IV. We visualize the complicated transformation of 9 into unexpected indole products by the three pathways shown in Scheme III.

In pathway i, the key intermediate cation (9) experiences attachment of a nucleophile such as a chloride anion and/or an ethanol molecule (used as a solvent) to the C-6 or C-4 position. (Attachment at C-4 is not shown.) Elimination of a methanol molecule provides the 6-chloro- (8), 6-ethoxy- (10), or 4-chloroindole (11) derivatives. This deduction is supported by the fact that the yield of 8 depends upon the concentration of hydrogen chloride. Moreover, such a concept gives a clue to the formation of a dimeric indole product, because the indole products formed during the reaction have a nucleophilic center at the C-3 position (vide infra).

In pathway ii, the formation of 4-methoxyindole (12) is rationalized by assuming 1,2 migration of the tertiary methoxy group of 9 followed by aromatization. Although several research groups have reported 1,2 migration of an alkyl group[9,10] in the Fischer indolization of o-alkylphenylhydrazones, such a migration of a methoxy group has remained unknown until now.

In pathway iii, the formation of the 3-chloroindole (13) is explainable by supposing attachment of chloride anion at the C-3 position of 9 accompanied by loss of the methoxy group. On the other hand, when zinc chloride in acetic acid, instead of ethanolic hydrogen chloride, was used as a reagent in the Fischer indolization of the same 2-methoxyphenylhydrazone (6), small amounts of 5-substituted indole products were obtained along with the expected 7-methoxyindole (7). In this experiment, no 6-substituted indole derivative could be found even on careful examination of the crude reaction mixture by TLC and GLC. This type of reaction is designated as ortho-C-5 abnormal Fischer indolization.[13] It should be noted here that the formation of the 5-methoxyindole (14) is fundamental because it

Scheme IV

OCH3
R
N
H

key intermediate
cation (9)

strong acid →

H+ OCH3
Nu R
N
H

oxonium
dication (18)

weak acid ↓

ortho-C6 abnormal
Fischer Indolization

SN 1' ↓

H
Nu R
N
H

↓

Nu R
N
H

R = CO2Et

could be obtained also by treatment of the same hydrazone (6) with boron trifluoride. Such 1,3 migration of a methoxy group is quite new. Moreover, Carlin's discovery[7b,c] of the formation of 5,7-dihaloindoles from 2,6-dihalophenylhydrazone derivatives with zinc chloride falls within this category. In Scheme IV, the probable mechanism of ortho-C-5 abnormal Fischer indolization is depicted.

From comparison of representative examples described above, one gathers that the nature of the reagent is the factor determining the mode of abnormal Fischer indolization, but this deduction is refuted by the fact[13] that treatment of the 2,6-dimethoxyphenylhydrazone (15) with either zinc chloride in acetic acid or ethanolic hydrogen chloride provides the 5-chloroindole product (16) (see Scheme V). Moreover, though predicted to be the main product because ethanolic hydrogen chlo-
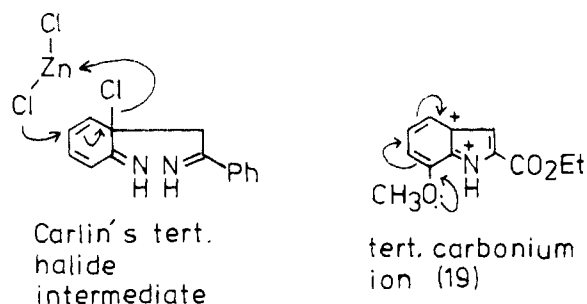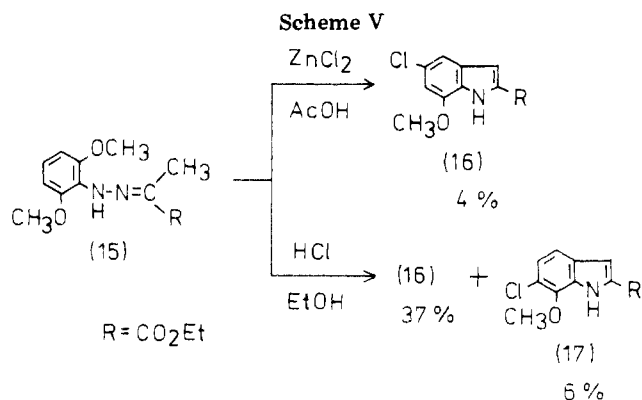
Cl
|
Zn
Cl

N N
H H
Ph

Carlin's tert. halide intermediate

N CO2Et
CH3O H

tert. carbonium ion (19)

Figure 1.

Scheme V

OCH3
CH3O
N-N=C
H
CH3
R

(15)

R = CO2Et

ZnCl2
AcOH

Cl
CH3O
N
H
R

(16)

4 %

HCl
EtOH

(16) + Cl
37 % CH3O
N
H
R

(17)

5 %

ride was used as a reagent, the 6-chloroindole (17) is actually a minor product in the latter case.

Carlin et al.[7c] explained their results by an attractive mechanism in which the tertiary halide intermediate reacts with zinc chloride via a cyclic transition state (Figure 1). Their mechanism, however, cannot explain the formation of the 5-chloroindole (16) from the 2,6-dimethoxyphenylhydrazone (15) when the reagent is ethanolic hydrogen chloride. In abnormal Fischer indolization of 2-methoxyphenylhydrazone derivatives, it is probable that differences of the relative acid strengths of the reagents toward the tertiary methoxy group of 9 cause various indole products to be formed. When the acid strength of a reagent is sufficient to cause protonation of the tertiary methoxy group, the resulting oxonium dication (18) would be subject to S_N1' displacement with a nucleophile present in the reaction mixture at the C-5 position of the indole skeleton to give the ortho-C-5 abnormal product, as shown in Scheme IV. In contrast, when the acid strength is not sufficient, these nucleophiles would add to the key intermediate cation (9) at the C-6 position to give a neutral intermediate (see pathway i, Scheme III). This would be followed by elimination of a methanol molecule under the acidic conditions, resulting in the formation of the ortho-C-6 abnormal product.

In the case of the 2,6-dimethoxyphenylhydrazone (15), we may assume that an additional methoxy group situated at the C-7 position of an indole nucleus stabilizes the tertiary carbonium ion (19), formation of which is the rate-determining step in the S_N1' reaction for ortho-C-5 abnormal Fischer indolization. This assumption furnishes a plausible and reasonable explanation for the formation of the 5-chloroindole (16) from 15 on treatment even with ethanolic hydrogen chloride. In summary, the abnormal Fischer indolization favors formation of the ortho-C-5 abnormal product under stronger acidic conditions but the ortho-C-6 product under less acidic conditions.

Furthermore, it is of interest that introduction[12] of a methyl group on an N_A nitrogen of a starting phenylhydrazone remarkably accelerates Fischer indolization itself for an ambiguous reason. For example, treatment of pyruvic acid 2-chlorophenylhydrazone under reflux with saturated ethanolic hydrogen chloride gave only the ethyl ester of the starting hydrazone (in good yield[16]), but not any indole product. Thus, when treated with ethanolic hydrogen chloride, the ester remained unchanged, while treatment of the same ester with zinc chloride produced the 5-chloroindole corresponding to ortho-C-5 abnormal Fischer indolization. In contrast, the N_A-methyl derivative of the ester gave the 6-chloroindole derivative even on treatment with ethanolic hydrogen chloride. These results suggest to us some contribution of Carlin's cyclic mechanism when zinc chloride was used as a reagent. If not, the formation of at least some of the 5-chloroindole would be expected when ethanolic HCl is used, inasmuch as the acid strength of the reagent would not be expected to have a significant effect on the formation of the tertiary carbonium ion (19) in the case of the 2-chlorophenylhydrazone compared with the case of the 2-methoxyphenylhydrazone (6). Moreover, the formation of only the 6-chloroindole in the latter case is explicable by supposing that addition of a chloride anion to the tertiary chloro intermediate preceded the formation of the tertiary carbonium ion (19), since there are no reasons for it to be stabilized.

Finally, it is known that Fischer indolization of several ortho-substituted phenylhydrazones under some specific conditions[10] provides an indole product in which the ortho substituent is removed. A series of our experiments seems to suggest that the use of relatively strong acid which produces the ortho-C-5 abnormal product also causes the formation of the indole in which an ortho substituent group of the starting phenylhydrazone is removed. However, the precise mechanism of this process is obscure.

Application of the Ortho-C-6 Abnormal Fischer Indolization to the Syntheses of the Naturally Occurring 6-Substituted Indoles

In the ortho-C-6 abnormal Fischer indolization, the *o*-methoxy group of a phenylhydrazone is subject to nucleophilic replacement by nucleophiles present in the reaction mixture (see pathway i, Scheme III). In other words, if we can find organic molecules with nucleophilicity sufficient to serve as an acceptor of the key intermediate cation (9) in acidic media, ortho-C-6 abnormal Fischer indolization can be developed to provide a methods for synthesis of indole derivatives having a unique side chain at the C-6 position.

Initially, insertion of an active methylene group into the C-6 position of an indole nucleus was undertaken.[17] Enolizable dicarbonyl compounds were chosen as acceptors of the key intermediate cation (9), with the expectation that they would behave as nucleophiles even under the acidic conditions of Fischer indolization (see Scheme VI). *p*-Toluenesulfonic acid would be used as a catalyst for cyclization, inasmuch as the *p*-toluenesulfonate ion is not sufficiently nucleophilic to

(16) J. T. Hewitt, *J. Chem. Soc.*, **59**, 209 (1881); H. N. Rydon and J. Tweddle, *ibid.*, 3499 (1955).

(17) H. Ishii, Y. Murakami, T. Furuse, K. Hosoya, H. Takeda, and N. Ikeda, *Tetrahedron*, **29**, 1991 (1973).

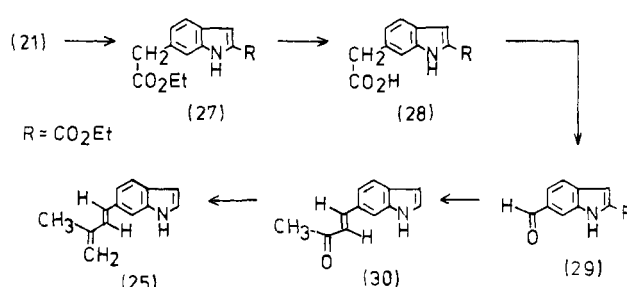Scheme VI

Scheme VII

Scheme VIII
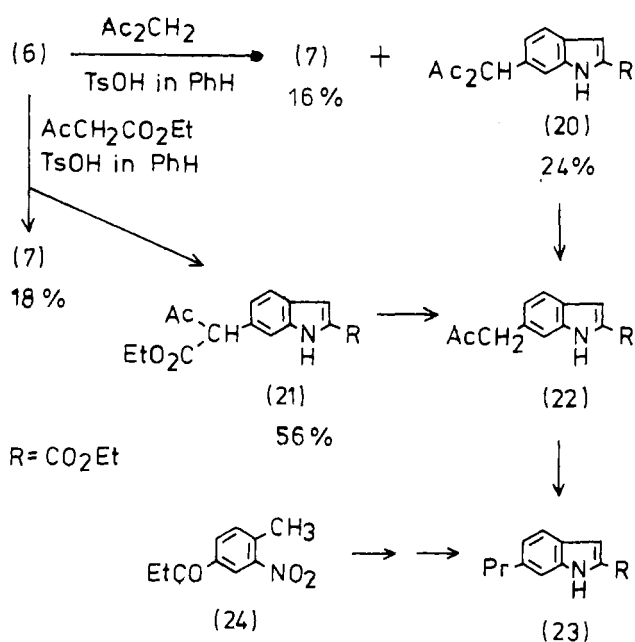
react with the intermediate cation (9) itself. Benzene would be the reaction solvent.

Treatment of 6 in benzene with *p*-toluenesulfonic acid in the presence of an excess amount of either acetyl-acetone or ethyl acetoacetate gave the desired 6-substituted indole, 20 or 21, respectively.[17] The structures were established decisively by the following chemical means. The indole product (21) having an ethyl acetoacetate group was treated with the mixed sulfuric and acetic acids to give the acetonyl product (22) which was also obtained from 20 by treatment[18] with sodium hydroxide. Treatment of 22 with ethanedithiol followed by desulfurization with Raney Ni and by esterification gave the 6-*n*-propylindole derivative (23) which was independently prepared from 4-methyl-3-nitropropiophenone (24) via Reissert's method.[19] We call this useful method for synthesis of 6-substituted indoles the "advanced" Fischer indolization in order to distinguish it from other abnormal Fischer indolizations.

In 1972, Taylor et al.[20] isolated the 6-substituted indole 6-(3-methylbuta-1,3-dienyl)indole (25), from *Monodora tenuifolia* (*Annonaceae*). In 1969, Sorm et al.[21] isolated another 6-substituted indole, 6-(3-methyl-2-butenyl)indole (26), from *Riccardia sinuata* (Hook.) Trev. (*Hepaticae*). Since it seemed that both alkaloids having an isoprene unit at the C-6 position of an indole nucleus could be synthesized easily from 21, the synthesis of these 6-substituted indole alkaloids was undertaken.[18]

In the synthesis of 21, the yield should, theoretically, be affected by the molar equivalents of the nucleophile used. In fact, when 10 equiv of ethyl acetoacetate was used, 21 was obtained in 20% yield,[17] while, with 15 equiv the yield increased to 56%.[18] Degradation of 21 with base followed by esterification with diazoethane
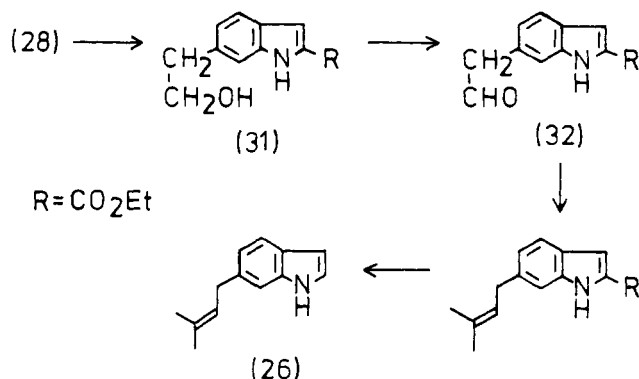
gave the 6-indolyl acetate 27 (see Scheme VII). The required monoacid (28), which was a common intermediate in our synthetic approaches, was prepared by partial hydrolysis of 27 with concentrated hydrogen chloride in acetic acid.

For the purpose of synthesis of Taylor's base (25), 28 was oxidized with pyridine *N*-oxide[22] to give the 6-indolyl aldehyde 29. Treatment of 29 with acetone followed by hydrolysis furnished the acid, which was decarboxylated by treatment with copper chromite[23] to give the α,β-unsaturated ketone (30). Wittig reaction of 30 with methylenetriphenylphosphorane provided Taylor's base (25) (Scheme VII).

For the purpose of the synthesis of Šorm's base (26), it was necessary to convert the carboxyl group of 28 to an aldehyde group without reduction of the ester group at the C-2 position. Since Borwn et al.[24] reported that an acid group was subject to reduction with diborane more easily than an ester to give a primary alcohol, this method was applied to 28. Subsequent oxidation of the alcohol (31) with Collins' reagent[25] provided the desired aldehyde (32) in reasonable yield. Treatment of 32 with isopropylidenetriphenylphosphorane followed by hydrolysis and decarboxylation gave Šorm's base (26) (Scheme VIII).

These successful trials show the usefulness of "advanced" Fischer indolization. The cyclization[26] of 6 in the presence of an excess amount of diethyl malonate, malononitrile, ethyl cyanoacetate, or barbituric acid under the same conditions as those used with di-

(18) H. Ishii and Y. Murakami, *Tetrahedron*, 31, 933 (1975).
(19) For a general review of the chemistry of indoles, see "The Chemistry of Indoles", R. J. Sundberg, Academic Press, New York, 1970.
(20) M. N. Nwaji, S. O. Onyiriuka, and D. A. H. Taylor, *J. Chem. Soc., Chem. Commun.*, 327 (1972).
(21) Isolation: V. Benešová, Z. Samek, V. Herout, and F. Šorm, *Collect. Czech. Chem. Commun.*, 34, 1807 (1969). Synthesis: H. Plieninger and H. Sirowej, *Chem. Ber.*, 104, 2027 (1971).

(22) C. Rüchardt, S. Eichler, and O. Krätz, *Tetrahedron Lett.*, 233 (1965); T. Cohen, I. W. Song, and J. H. Fager, *ibid.*, 237 (1965).
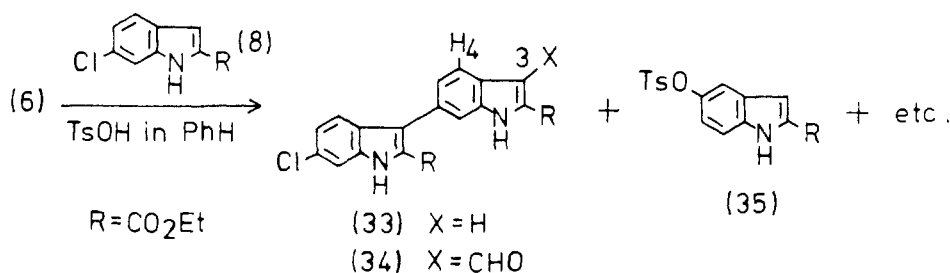(23) W. A. Lazier and H. R. Arnold, "Organic Syntheses", Collect. Vol. II, Wiley, New York, 1943, p 142.
(24) H. C. Brown, "Boranes in Organic Chemistry", Cornell University Press, New York, 1972, p 230; H. C. Brown and B. C. Subba Rao, *J. Org. Chem.*, 22, 1136 (1957).
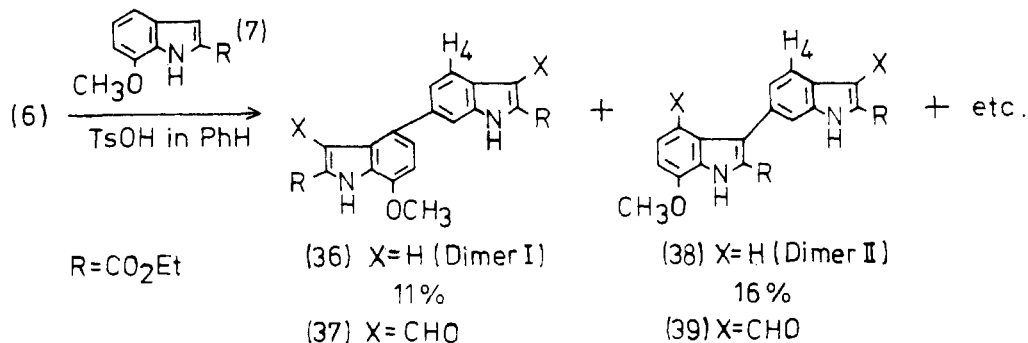(25) J. C. Collins, W. W. Hess, and F. J. Frank, *Tetrahedron Lett.*, 3363 (1968); R. Ratcliffe and R. Rodehorst, *J. Org. Chem.*, 35, 4000 (1970).
(26) H. Ishii, T. Ishikawa, H. Takeda, and M. Ueda, unpublished results.

Scheme IX

$$ (6) \xrightarrow[\text{TsOH in PhH}]{} $$

R = CO₂Et

(33) X = H
(34) X = CHO

(35)

Scheme X

$$ (6) \xrightarrow[\text{TsOH in PhH}]{} $$

R = CO₂Et

(36) X = H (Dimer I)
11%
(37) X = CHO

(38) X = H (Dimer II)
16%
(39) X = CHO

ethyl malonate and ethyl acetoacetate was attempted in order to examine the availability of other dicarbonyl compounds as reagents for "advanced" Fischer indolization. Unfortunately, no indole having a desired side chain at the C-6 position could be obtained from these reaction mixtures.

The 3,6′-Biindole

In the Fischer indolization of 6 with saturated ethanolic hydrogen chloride, we isolated a minute amount of a chlorine containing indolic dimer, mp 236–240 °C (C₂₂H₁₉O₄N₂Cl), while Gannon et al.[14] reported the isolation of another indolic dimer, mp 233–235 °C, bearing a methoxy group. Taking into account the chemical evidence[19] that indole derivatives are susceptible to electrophilic substitution such as by the Vilsmeier reagent at the C-3 position, one can reasonably assume that nucleophilic addition of the 6-chloroindole (8), the main product of the experiment, at its C-3 position to the C-6 position of the key intermediate cation (9) gave the 6-chloro-3,6′-biindole derivative. The "advanced" Fischer indolization[19] of 6 using an excess amount of 8 gave two new indole products. As expected, one of the two was identical with a specimen of our dimer.

The structural confirmation of the dimer 33 came from the inspection of its ¹H NMR spectral data. In the ¹H NMR spectrum, 33 shows signals due to H-3 (δ 7.00) and two NH protons (δ 11.82 and 11.95). The fact that 33 lacks one H-3 signal means that one of its two indolic units is linked with the benzene portion of the other indolic unit at the C-3 position. Information about the other side of the linkage was obtained from comparison of the signal due to H-4 of 33 with that of the corresponding formyl derivative (34). Formylation of 33 with the Vilsmeier reagent gave a product possessing one formyl group. The ¹H NMR spectrum of 34 shows two NH signals (δ 11.98 and 12.78) but no signal due to H-3, indicating that the formylation took place at the C-3 position. The formyl derivative (34) has a 1 H doublet (J = 8.5 Hz) at δ 8.27 shifted by

60–130 Hz from the signals due to the aromatic protons of the starting dimer (33). Since it is known that introduction of a formyl group into the C-3 position of an indole derivative causes the signal due to H-4, which is situated at a position peri to the formyl group, to shift downfield by 60–100 Hz through the anisotropic effect of the carbonyl group, the signal could be assigned to the H-4 of the formylated indole unit.[17] Irradiation at δ 8.27 changed the splitting pattern of the signal at δ 7.25 from a quartet (J = 8.5 and 2.0 Hz) to a doublet (J = 2.0 Hz) and vice versa. These spectral data show the existence of protons at the C-5 and C-7 positions of the formylated indole unit, indicating that the formylated indole unit is linked to the other indole unit of the dimer at the C-6 position. This evidence established the structure of the original dimer (33) as the 6-chloro-3,6′-biindole (Scheme IX).

The second and minor indole product (35) of the "advanced" Fischer indolization using 8 contained a tosyloxy substituent. Consideration of the mechanisms proposed for abnormal Fischer indolizations gave a clue as to the position of the tosyloxy group. As a tosylate ion is well-known to be a fairly weak nucleophile, it could not add to the key intermediate cation (9) at the C-6 position, but would be subject to an Sₙ1′ reaction with a methoxy group of the key intermediate cation (9) at the C-5 position to give the ortho-C-5 abnormal product. This assumption was confirmed by the fact that this product (35) could be obtained by tosylation of the reported 5-hydroxyindole derivative[27] (Scheme IX).

By analogy with our dimer, we supposed Gannon's dimer[14] to be the ortho-C-6 abnormal product formed with the 7-methoxyindole (7), the normally expected product. However, treatment of a mixture of 6 and 7 in benzene with p-toluenesulfonic acid produced a mixture of two dimeric indoles in yields of 11% (dimer I) and 16% (dimer II) (see Scheme X). Both of them

(27) E. F. Alvarez, M. Lora-Tamayo and T. Monge, *Bull. Soc. Chim. Fr.*, 1932 (1969).

have the same empirical formula, $C_{23}H_{22}O_5N_2$. Dimer I (36), mp 234–236 °C, has the same melting point as that reported by Gannon et al.,[14] mp 233 °C. But 36 is clearly no a 3,6'-biindole, because its ^1H NMR spectrum shows two NH (δ 11.82 and 11.98) and two H-3 signals (δ 7.17 and 7.24). Since it is well-known that 7-methoxyindole derivatives are susceptible to electrophilic attack at C-4 and C-6 besides C-3, the structure of 36 was presumed to be the 7-methoxy-4,6'- or -6,6'-biindole. Conclusive evidence for the 4,6'-biindole structure was obtained by inspection of the ^1H NMR spectrum of the diformyl dimer I (37) which was prepared by treatment of 36 with the Vilsmeier reagent. The diformyl derivative (37) shows two aldehydic (δ 9.94 and 10.62) and two NH (δ 12.68 and 12.91) protons, but no signal due to H-3. These data indicate that formyl groups were introduced into both of the two C-3 positions of 36. Furthermore, in the ^1H NMR spectrum of 37, there is only one aromatic proton shifted downfield as a doublet (δ 8.19, J = 8.4 Hz) when compared with the signals due to the aromatic protons of 36. This spectral evidence shows that 37 has only one H-4, indicating that one indole unit is linked to the other indole unit at the C-4 position. Decoupling experiments on the aromatic protons of the latter indole unit with H-4 as a starting point disclosed that the C-5 and the C-7 positions are occupied by protons [δ 7.24 (quartet, J_1 = 8.4 Hz, J_2 = 1.5 Hz) and 7.45 (doublet, J = 1.5 Hz)]. These spectral evidences are enough to establish the structure of the original dimer (36) as the 7-methoxy-4,6'-biindole derivative.

The structural assignment of dimer II (38) was made as follows: In the ^1H NMR spectrum, 38 shows two NH (δ 11.68 and 11.82) and one C_3-H (δ 7.17), suggesting that 38 is a 3,6'-biindole derivative. Formylation of 38 also furnished a diformyl derivative (39). In the ^1H NMR spectrum, 39 shows H-4 at δ 8.19 as a doublet (J = 8.4 Hz). Decoupling experiments with the guidance of H-4 revealed that the C-3-formylated indole unit has three benzenoid protons at the 4-, 5-, and 7-positions. Besides these three aromatic protons, 38 shows a pair of two doublets due to two aromatic protons at δ 7.71 (J = 8.2 Hz) and 7.03 (J = 8.2 Hz). Although the coupling constant indicates that these two protons are located vicinally, whether they are H-4 and H-5 or H-5 and H-6 remains obscure from the data available so far. However, tentatively, the second formyl group could be assigned to the C-4 position, since the formation of dimer I (36) suggested that electrophilic attack of the 7-methoxyindole (7) occurs at the C-4 position in preference to the C-6 position. These considerations lead us to the deduction that dimer II (38) is the 3,6'-biindole.

In 1949, Pausacker et al.[28] reported that Fischer indolization of cyclohexanone 2-methoxyphenylhydrazone (40) in dilute sulfuric acid gave a byproduct containing a methoxy group, together with the expected 8-methoxy-1,2,3,4-tetrahydrocarbazole (see Scheme XI). From its weak basicity and the formation of 1-methoxy-carbazole on dehydrogenation with chloranil, they claimed that the byproduct was 5,6,7,8-tetrahydro-4a-methoxy-4aH-carbazole [described as 12-methoxy-1,2,3,4-tetrahydroisocarbazole in their report[28]] (41).

(28) C. S. Barnes, K. H. Pausacker, and C. I. Schubert, *J. Chem. Soc.*, 1381 (1949).

Scheme XI
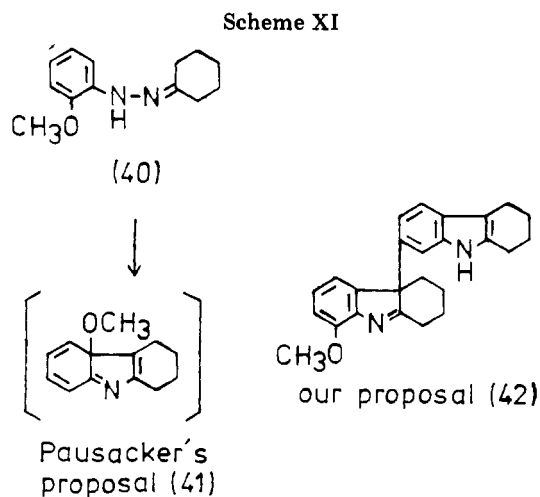
Later, Tomlinson et al.[29] examined Pausacker's procedure[28] as applied to cyclohexanone 2-hydroxyphenylhydrazone and cast doubt on Pausacker's structural assignment. On the other hand, Gannon et al.[14] repeated Pausacker's experiment with cyclohexanone 2-methoxyphenylhydrazone (40) itself and indeed obtained a material having almost the same melting point, mp 152–155 °C, as that reported, mp 145–146 °C. Their reported data[14] for the characterization of the product, however, are as follows: Elemental analyses are consistent with $C_{25}H_{26}ON_2$; in the mass spectrum, the molecular ion was observed at m/z 370; and its ^1H NMR spectrum exhibits one NH, one OCH_3 and six or seven aromatic protons in a complex system. In connection with our studies on ortho-C-6 abnormal Fischer indolization, we propose the new dimeric structure[17] (42) for Pausacker's product.

Fischer Indolization of Phenylhydrazones Bearing Various Kinds of Substituents at the Ortho Position

In connection with the unexpected results in the case of the 2-methoxyphenylhydrazone derivatives, Fischer indolizations of phenylhydrazones bearing various kinds of a substituent at the ortho position, other than a methoxy group, were examined.

The Methylthio Group.[30]   The 2-(methylthio)-phenylhydrazone 43 gave three products, a relatively simple result, on treatment with zinc chloride in acetic acid, while treatment of the same hydrazone with ethanolic hydrogen chloride resulted in formation of many indolic products as shown in Scheme XII. Though expected by analogy with the behavior of 2-methoxy-phenylhydrazone (6), 5- and 6-substituted indole products could not be detected in the reaction mixture, regardless of the reagent used. In contrast, the 3-(methylthio)indole (48) was a common and characteristic abnormal product in both experiments. It is thus clear that the direction of abnormal Fischer indolization depends upon the identity of the substituent situated at the ortho position. The formation of 3-(methyl-thio)indole (48) is also rationalized to occur via the tertiary methylthio intermediate 49. Moreover, the incorporation of a chlorine atom into the C-3 position

(29) A. H. Milne and M. L. Tomlinson, *J. Chem. Soc.*, 2789 (1952).
(30) H. Ishii, H. Atoda (née Tatsuno), T. Tohjo, Y. Kondo, and Y. Murakami, Abstracts of Papers, 11th Congress of Heterocyclic Chemistry, Kanazawa, Japan, 1978, p 41.
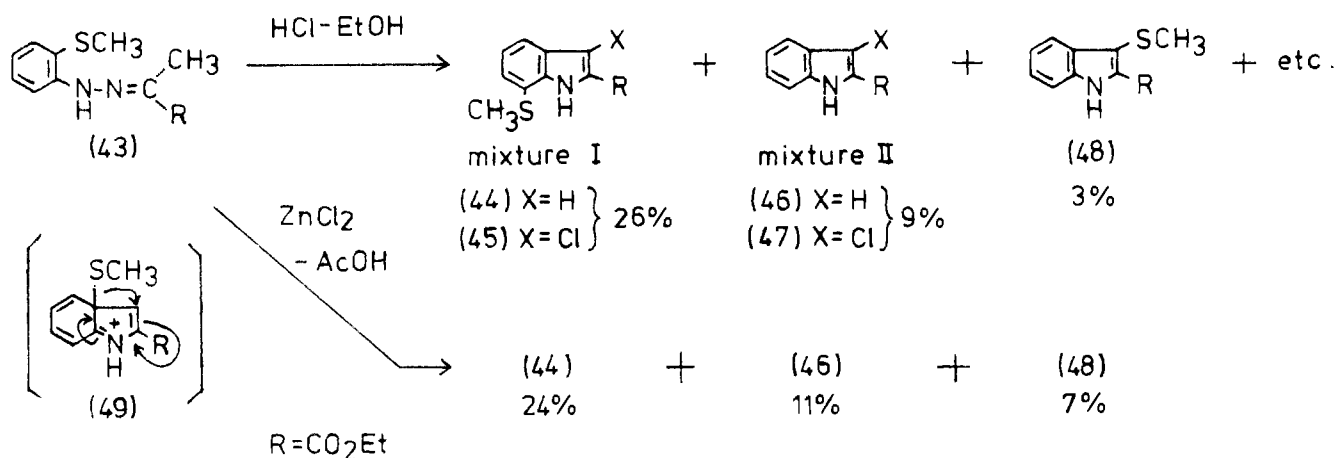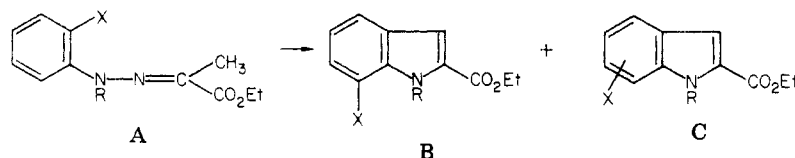
Scheme XII

Table II

starting material (A)	reaction condition	ref	normal product (B) (7-sub)	abnormal indolic byproduct (C)			
				4-sub.	5-sub.	6-sub.	others
X = CH$_3$, R = H (50)	ZnCl$_2$	31a	as a sole product	–	–	–	–
	polyphosphoric acid	31b	51 (++)	4- (52) or 5- (53)	–	–	
	HCl–EtOH	30	51 (++)	4- (52) or 5- (53) with others			
X = Ph, R = H (56)	ZnCl$_2$–AcOH	30	57 (61%)	58 (21%)	–	–	–
X = CF$_3$, R = H (59)	ZnCl$_2$–AcOH	30	60 (25%)	–	–	–	–

of some indolic products occurs to some extent during Fischer indolization of the 2-methylthiophenyl-hydrazone (43) with ethanolic hydrogen chloride; thus 45 and 47 are formed in low yields. However, the mechanism of this process remains obscure.

The Methyl Group.[30] Fischer indolization of ethyl pyruvate 2-methylphenylhydrazone (50) had already been examined by several groups.[31] Since, however, they reported different results, the hydrazone 50 was treated with ethanolic hydrogen chloride to give the 4-(52) and/or 5-methylindole (53) product along with the normally expected 7-methylindole (51) (see Table II). Unfortunately, a precise assignment of the structure of the abnormal product could not be achieved, because samples of the 4- (52) and 5-methylindoles (53) which were prepared by alternative routes show the same behavior on TLC, GLC, and HPLC.

The Phenyl Group.[30] In 1976, Fusco et al.[32] reported the formation of the 1,2-migration product (55) from the phenylhydrazone derivative (54) (see Scheme XIII). Since, however, substituents already occupied both positions *ortho* to nitrogen, their result could not apply immediately to our discussion. Therefore, Fischer indolization of a hydrazone bearing a phenyl at the ortho position was examined. When treated with zinc chloride in acetic acid, the hydrazone 56 smoothly gave a 1,2-migration product, 4-phenylindole (58), with the normally expected 7-phenylindole (57) in 21% and 61%

(31) (a) R. B. Carlin, W. O. Henley, and D. P. Carlson, *J. Am. Chem. Soc.*, 79, 5712 (1957); (b) B. Heath-Brown and P. G. Philpott, *J. Chem. Soc.*, 7185 (1965).
(32) R. Fusco and F. Sannicolò, *Gazz. Chim. Ital.*, 106, 85 (1976).

Scheme XIII
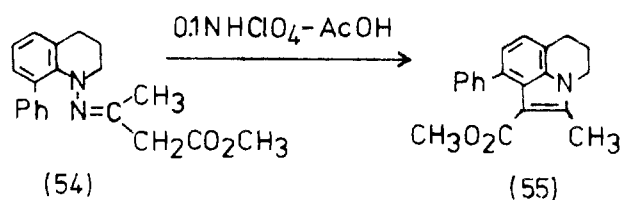
yields, respectively (see Table II). On the other hand, treatment of the same hydrazone (56) with ethanolic hydrogen chloride gave an inseparable mixture which shows on TLC many spots, including spots corresponding to the 7- (57) and 4-phenylindoles (58).

The Trifluoromethyl Group.[30] Strongly acidic conditions are needed to cyclize a phenylhydrazone bearing an electron-attractive group on a phenyl ring, as described above. Since a trifluoromethyl group is an electron-attractive group, Fischer indolization of the 2-trifluoromethylphenylhydrazone (59) was examined to see whether an abnormal product could be formed or not. As expected, ethanolic hydrogen chloride did not work to cyclize the hydrazone 59, but, when the hydrazone was treated with a large amount of zinc chloride in acetic acid, the normally expected indole product (60) was obtained together with substantial recovery of the starting material (59). No abnormal product was detected in this reaction mixture.

The N$_A$–C-3 Abnormal Fischer Indolization

During our studies of Fischer indolization of *o*-chlorophenylhydrazone derivatives, we occasionally

Scheme XIV

(61)

R = CO₂Et

(62) X=Cl
82%

(63) X=OAc
1%

(64)
1%

(65)

(66)
5%

(67)
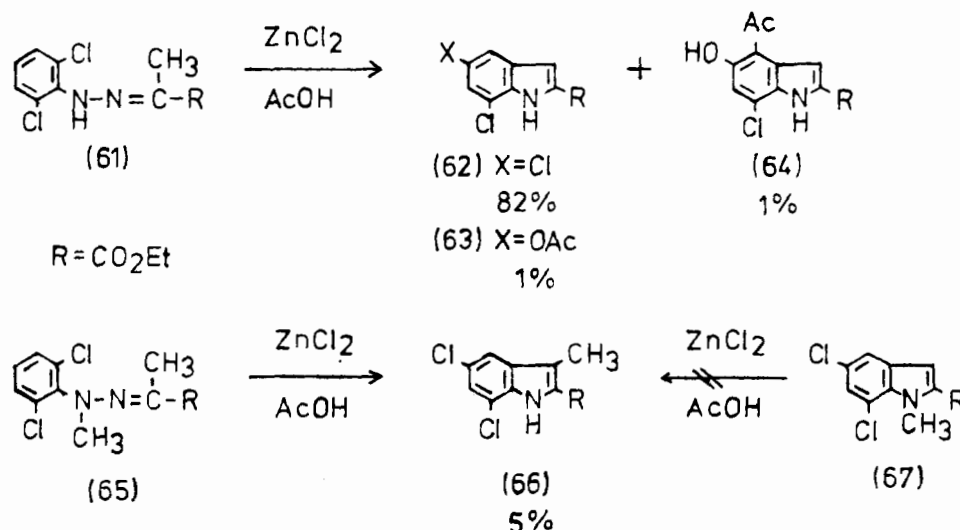
found that introduction of a methyl group onto the N_A nitrogen of a starting 2-chlorophenylhydrazone accelerates Fischer indolization to give the ortho-C-5 abnormal product, as described above. In contrast, the same modification of the 2,6-dichlorophenylhydrazone (61) caused retardation of Fischer indolization and a new type of migration reaction to occur.[33]

Treatment of the 2,6-dichlorophenylhydrazone (61) with zinc chloride in acetic acid afforded three ortho-C-5 abnormal products (62–64), shown in Scheme XIV. Among them, the 4,5,7-trisubstituted indole (64) was rationalized as a Fries rearrangement product derived from the ortho-C-5 abnormal product (63). On the other hand, treatment of the N_A-methyl derivative (65) of 61 provided a striking migration product, 5,7-dichloro-3-methylindole (66), whose structure was confirmed by comparison with a sample prepared via an alternative route. It should be concluded that the migration of a methyl group from the N_A nitrogen to the C-3 position takes place during Fischer indolization because the N-methyl-5,7-dichloroindole (67) was recovered unchanged from treatment under the same conditions as that of the above experiment. However, the precise mechanism is still unknown.

(33) H. Ishii, T. Hagiwara, T. Ishikawa, N. Ikeda, and Y. Murakami, Abstracts of Papers, 7th Congress of Heterocyclic Chemistry, Chiba, Japan, 1974, p 70.

Concluding Remarks

Our initial objective was elucidation of the formation of abnormal products during the Fischer indolization of *o*-methoxyphenylhydrazones. As a consequence of the insight obtained, we were able to develop the ortho-C-6 abnormal Fischer indolization to provide a new method for synthesis of 6-substituted indole derivatives. In the course of these studies, several new migration reactions were occasionally found, for example, the formation of 2,5-dimethoxy-*p*-phenylenediamine from a 2,5-dimethoxyphenylhydrazone derivative,[34] and the formation of a new indole trimer[35] on treatment of indole itself with *p*-toluenesulfonic acid in benzene. The mechanisms of several abnormal reactions which we observed to take place during Fischer indolization remain to be elucidated. We believe that elucidation of them may shed some light on the limitations of Fischer indolization. Thus, studies of Fischer indolization leave many problems yet to be solved, in spite of the substantial contributions of many workers in this field.

(34) H. Ishii, Y. Murakami, S. Tani, K. Abe, and N. Ikeda, *Yakugaku Zasshi*, 90, 724 (1970).
(35) H. Ishii, K. Murakami, Y. Murakami, and K. Hosoya, *Chem. Pharm. Bull.*, 25, 3122 (1977).