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The Mode of Cyclisation of the Arylhydrazones and *O*-Phenyl Ethers of the Oximes of Asymmetric Ketones Under the Conditions of the Fischer Reaction

I.I.Grandberg and V.I.Sorokin

Both the Fischer synthesis of indoles and the recently discovered rearrangement of *O*-phenyl ethers of oximes, which takes place under similar conditions and leads to the formation of benzofurans, are assessed in the review from the same standpoint. A number of studies published recently altered the ideas held for a long time concerning the mode of cyclisation of the arylhydrazones of asymmetric ketones into indoles. It was believed previously that CH_3, CH_2, and CH groups in the α-position in the carbonyl fragment constitute a series in which the capacity for cyclisation increases. However, it has been found that the acidity of the medium plays a very significant role in determining the mode of cyclisation and can actually reverse it. The concepts put forward to account for this finding are examined critically and general ideas are developed which, in the author's view, explain satisfactorily the influence of the pH of the medium and of certain other factors on the mode of cyclisation of both arylhydrazones and *O*-aryloximes.
The bibliography includes 109 references.

CONTENTS

1. General postulates of the mechanism of the Fischer reaction 115
2. The mode of cyclisation of arylhydrazones of asymmetric ketones 119
3. The mode of rearrangement of *O*-phenyl ethers of the oximes of asymmetric ketones 123
4. Factors determining the mode of cyclisation 123

1. GENERAL POSTULATES OF THE MECHANISM OF THE FISCHER REACTION

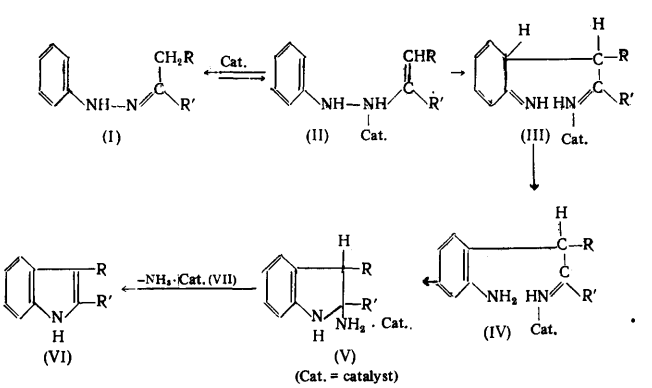
The cyclisation of arylhydrazones into indole derivatives in acid media, discovered by Fischer in 1883,[1] still continues to attract attention. This reaction has become the basis for a general, convenient, and easy preparative method for synthesising a wide variety of indole derivatives. Several mechanisms have been proposed at different times for this reaction, but those put forward by Reddelin[2] and Wieland[3], Bamberger and Landau[4], Neber et al.,[5] and Pausacker and Schubert[6] failed to pass experimental tests.

The generally accepted mechanism of the Fischer indole synthesis, to which a number of reviews have been devoted[7-12], is now that proposed by G. M. and R. Robinson[13,14] supplemented and additionally elucidated by Allen and Wilson[15], Carlin and Fischer[16], Arbuzov and Kitaev[17], and Suvorov et al.[18]

The elucidation of the mechanism of the synthesis of tryptamines from arylhydrazones and γ-chloroketones in a number of studies by Grandberg and coworkers[19-22] also made a definite contribution to the Robinson mechanism.

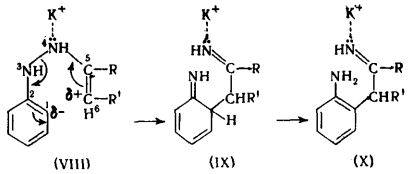
According to the Robinson mechanism, the reaction proceeds via the following main stages: (1) tautomeric conversion of the hydrazone (I) into the enehydrazine (II); (2) formation of a new C–C bond [(II) → (III)]; (3) cyclisation with subsequent elimination of an ammonia molecule and the formation of the indole structure [(III) → (IV) → (V) → (VI)].

The first and second stages of the reaction [(I) → (II) and (II) → (III)] are of greatest theoretical interest, while the last stage [(III) → (IV)] permits different ways of indole ring closure, depending on the conditions under which the indole is formed.



The most important stage of the process—the formation of a new C–C bond [(II) → (III)]—was regarded until recently as involving intramolecular electrophilic attack by the ene fragment on the aromatic ring[9-12]. On the basis of the concepts of the general theory of conjugation[23,24], Arbuzov and Kitaev[17] suggested that this stage be regarded as an intramolecular rearrangement of the activated 1,6-conjugated system. In an acid medium or on formation of a complex with the catalyst, this conjugated system is activated: bond polarisation is enhanced as a result of which the atoms in the 1- and 6-positions receive excess charges which are of opposite sign. When these atoms are in significantly close proximity, the formation of a bond between them, leading to a redistribution of

electron density in the system and the rearrangement (VIII) → (X) with dissociation of the 3–4 linkage, becomes quite probable.

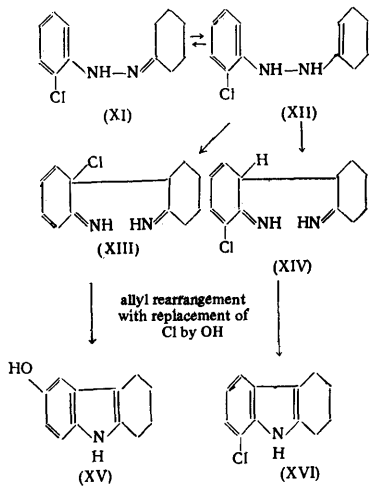


(VIII) (IX) (X)

However, it is noteworthy that there is virtually no direct experimental evidence for the electrophilic attack.

The evidence supporting the electrophilic attack, which explains the influence of substituents in the aromatic ring of arylhydrazones on the reaction, quoted by a number of workers[25–28] is based on two unproved hypotheses, namely that the stage involving the formation of a new C–C bond [(II) → (III)] determines the rate of the entire reaction and that the yield of the indole derivative is directly proportional to the rate of the stage. Moreover, the ideas according to which the formation of the C–C bond involves a carbon atom in the aromatic ring already occupied by a substituent are inconsistent with the general theory of electrophilic substitution. It is well known that as a rule an electrophilic species is directed to the position without a substituent even in those cases where the substituent is an electron-donating group. This is because the abstraction of a proton from the resulting σ-complex is more favourable on energy grounds than the abstraction of another positively charged group. Exceptions are observed only in the case of non-concerted orientation, severe process conditions, and marked electrophilicity of the attacking species (NO_2^+, SO_3H^+).[29]

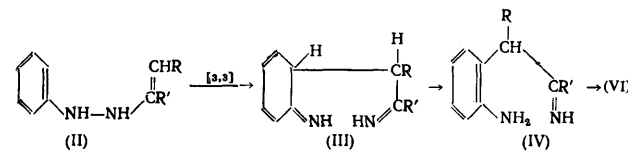
As an example one may quote the data of Barnes et al.,[30] who observed the formation of a mixture of two products [(XV) and (XVI)] on conversion of the *o*-chlorophenylhydrazone of cyclohexanone (XI) into an indole derivative. It was found that, together with the normal product 8-hydroxytetrahydrocarbazole (XVII), the reaction involves also the formation of 6-hydroxytetrahydrocarbazole (XVI), the structure of which was subsequently proved[31], i.e. the formation of the C–C bond involves also a position occupied by a substituent even though a free position is present in the aromatic ring.



(XI) (XII) (XIII) (XIV) (XV) (XVI)

Indole structure syntheses of this kind, in which the C–C bond is formed with a carbon atom of the aromatic ring occupied by a substituent with subsequent migration or elimination of the substituent, are fairly numerous[16,32–42]. These results led to doubts being cast in one of the recent studies on the electrophilic mechanism of the formation of the C–C bond in the second reaction stage[43] and it was suggested that the formation of the C–C bond in the Fischer reaction occurs as a result of a sigmatropic [3,3] rearrangement.

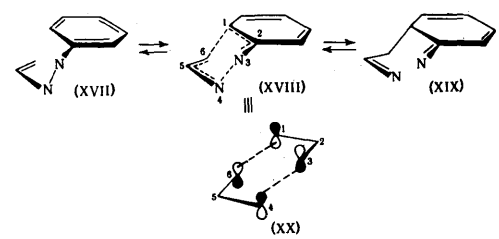
A similar approach was previously justified in the discussion of the mechanism of the Claisen rearrangement[44,45]. Other reactions related to the Fischer indole synthesis (for example the benzidine rearrangements) were also regarded in the above study as sigmatropic rearrangements[43].



(II) (III) (IV) (VI)

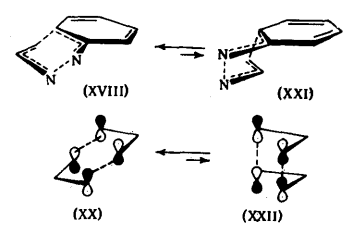
Cautious attempts to regard the Fischer reaction as a sigmatropic rearrangement were described in the literature even earlier. Thus Schmid and coworkers[46] suggested that the acid-catalysed Fischer reaction may be a sigmatropic process and Robinson suggested, using a more cautious form of words[10], that a process of this kind is possible only in the thermal indole-formation reaction.

In the study quoted above[43] an attempt was made to explain the available experimental literature data for the Fischer reaction and similar processes from the standpoint of the principle of the conservation of orbital symmetry. In this treatment the formation of a new C–C bond in the reaction proceeds via a four-centre transition state [the chair conformation (XVIII)], which consists of two highest occupied molecular orbitals of allyl radicals in which the 3–4 linkage has still not been finally ruptured and the 1–6 linkage has not been finally formed [formula (XX)].



(XVII) (XVIII) (XIX) (XX)

The interaction of the central parts of the non-bonding molecular orbitals does in fact occur in the chair conformation[47], which is the reason for its advantage over the boat conformation of the transition state (XXII).

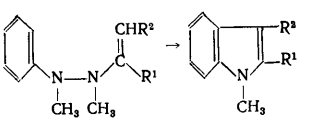


(XVIII) (XXI) (XX) (XXII)

In this approach to the process the nitrogen atoms in the 3- and 4-positions, in the system of atoms in the positions ranging from 1 to 6 which are directly involved in the rearrangement, are formally treated as carbon atoms; hence it is assumed that their n electrons are not involved in the process[43]. The recently described syntheses of 1-acylindoles can probably be regarded as experimental confirmation of this postulate[48-50].

Sigmatropic rearrangements are known to be non-catalysed intramolecular thermal processes. Therefore the question of the validity of the extension of the theory of sigmatropic reactions to the Fischer cyclisation of phenylhydrazones, which are classified as acid-catalysed processes[7-12], may seem to arise at first sight. However, it has recently been suggested in a number of studies that the involvement of acid catalysts in the Fischer reaction is not obligatory[51,52]. Moreover it has been shown that, when the enehydrazine formed is reduced in the synthesis of the arylhydrazone, it is readily converted into an indole derivative on heating both with and without a catalyst[43].

Chiess and Grieder[53] investigated the behaviour of enehydrazines on heating in the absence of a catalyst and established that the enehydrazines (XXIII) give rise in this case to a 25–74% yield of the corresponding indoles (XXIV) in decalin at 110°C. This cyclisation was also achieved in absolute acetonitrile in the presence of 0.5 N dichloroacetic acid:



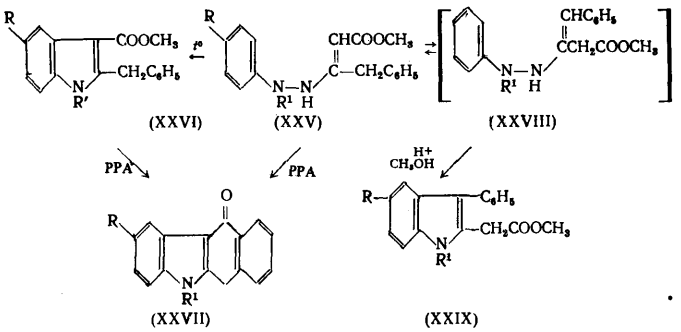
(XXIII) (XXIV)

In most cases the use of an acid catalyst accelerates the process and lowers the reaction temperature.

Kelly et al. investigated the thermal conversion of phenylhydrazones into indoles without using acid catalysts, which proved to be successful[54] (this study is described in detail below).

In a study of the behaviour of methyl γ-phenylacetoacetate in the Fischer indole synthesis, Grinev and coworkers[55,56] established that compound (XXV) is converted in a thermal process into 2-benzylindole derivatives (XXVI). When compound (XXV) was treated with polyphosphoric acid, derivatives of 6,11-dihydro-11-hydroxybenzo[b]carbazole (XXVII) were isolated. The reaction probably proceeded via a stage involving the formation of methyl esters of 2-benzylindole-3-carboxylic acids (XXVI) with subsequent intramolecular cyclisation, since on heating with polyphosphoric acid compound (XXVI) yielded compound (XXVII). When compound (XXV) was treated with sulphuric acid in methanol at room temperature, methyl esters of 3-phenylindole-2-acetic acid (XXIX) were isolated.

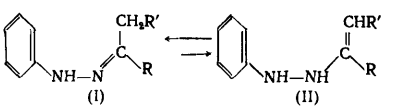
Thus experimental data show that, contrary to the generally accepted view, the Fischer reaction can occur also in the absence of acid catalysts. It is well known that, for compounds containing atoms with different electronegativities in the tautomeric triad (for example, in the keto–enol, lactim–lactam, and thione–thiol tautomerism), the tautomeric equilibrium is usually displaced towards the form in which the proton is linked to the less electronegative atom.



(XXVI) (XXV) (XXVIII)

(XXVII) (XXIX)

For arylhydrazones of the usual carbonyl compounds (I), the shift of the equilibrium towards the hydrazone should be enhanced also in consequence of the electronegative influence of the C_6H_5NH residue on the main tautomeric fragment, since electron-accepting substituents at the nitrogen atom in potentially tautomeric systems are known to shift the tautomeric equilibrium in this particular direction[57]:



(I) (II)

Calculations by the LCAO-MO method in terms of the Hückel approximation of the molecular energies of the tautomeric forms of acetophenone phenylhydrazone confirmed that arylhydrazones exist in the hydrazone and not the enehydrazine form—the latter is less favourable to the extent of approximately 4 kcal mole^{-1} even for acetophenone hydrazone, where it is stabilised by conjugation[58].

This can explain the finding that the existence of the enehydrazine form (II) in solutions of arylhydrazones of aliphatic aldehydes and ketones has not so far been observed by physicochemical methods[10]. The 23 kcal mole^{-1} energy gain for the protonated hydrazine molecule in relation to the enamine is evidence that acid agents displace the equilibrium towards the hydrazone form but at the same time they should increase also the rate of the tautomeric transformation by taking part in proton transfer[43].

However, insufficient attention has been devoted to the mechanism of the tautomeric transformation, particularly bearing in mind that, according to kinetic studies[59-62], this is in fact the rate-determining stage in the Fischer reaction. Pausacker and Schubert[59] made the first attempt to investigate the kinetics of the Fischer reaction. They established that in glacial acetic acid the reaction is of first order. Subsequently this was confirmed by other investigators[60,61], although the cyclisation conditions were different. The reaction was performed in glacial acetic acid[60] and in alcoholic solutions of hydrochloric acid[62], while Grandberg and Przheval'skii[61] studied the kinetics of the conversion of cyclohexanone phenylhydrazone into an indole derivative on treatment with allyl bromide.

Scheltus determined the rate constants for the cyclisation of cyclohexanone phenylhydrazone in an aqueous alcoholic solution of hydrochloric acid[62]. Measurements were

also made of the rate constants for the conversion of the phenylhydrazones of various cyclic ketones into indole derivatives, which were compared with the pK_a values for these compounds[62]. Moreover it has been noted[59-62] that, following the addition of water to the solvent, the rate of reaction increases. Thus Pausacker and Schubert[59] established that, on diluting glacial acetic acid by the addition of 6.3 and 16.0 mole % of water, the rate constant increases from 6.18×10^{-5} to 7.68×10^{-5} and 9.37×10^{-5} respectively.

In a study of the effect of the acidity of the medium on the rate of the Fischer reaction it was established[62] that the values of $\lg k$ are satisfactorily correlated with the acidity functions H_0 (Fig. 1).

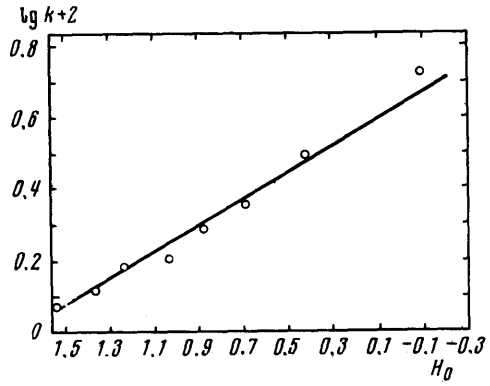


Figure 1. Variation of the logarithm of the rate constant for the reaction of cyclohexanone phenylhydrazone with the acidity function H_0 in 60% methanol as the solvent.

The problem arises of which stage of the conversion of the arylhydrazone into an indole should be regarded as the slowest. If one assumes that this stage is the formation of a new C–C bond as a result of electrophilic attack on the aromatic ring, it is difficult to explain from this standpoint the marked acceleration of the reaction by the p-CH_3O group in relation to the m-CH_3O group (from the standpoint of electrophilic substitution, the opposite effect should have been observed). Moreover, it is well known that electrophilic substitution in the aromatic series is accelerated by the introduction of electron-donating substituents into the ring, but it has been observed that the introduction of the m-CH_3O group leads to a decrease of the rate of reaction compared with the unsubstituted product.

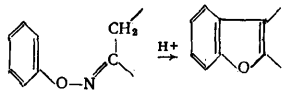
Thus experimental facts suggest that the stage involving the formation of a new C–C bond is hardly rate-limiting in the Fischer reaction and throw doubt on its electrophilic nature.

These kinetic data can be satisfactorily accounted for from another standpoint, namely that the slowest stage is the tautomeric conversion of the hydrazone into the enehydrazine [(I) ⇌ (II)].

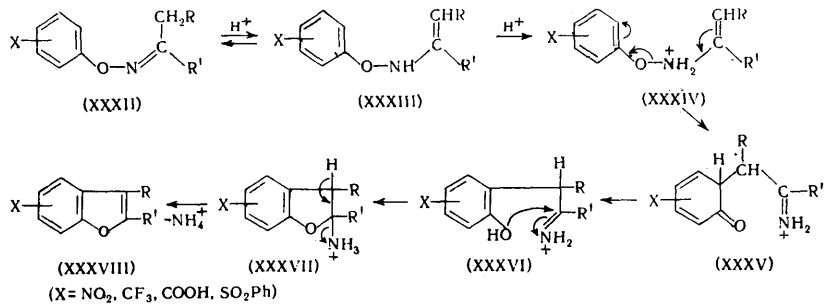
The following facts confirm this view: (1) on cyclisation of the phenylhydrazone of α-deuterated cyclohexanone, a kinetic isotope effect was observed ($K_D/K_H = 1.8$)[62]: (2) in the D_2O–CH_3OH–HCl solution cyclohexanone phenylhydrazone reacts twice as fast as in the H_2O–CH_3OH–HCl system[62]; (3) the rate constants for the phenylhydrazones of cyclic ketones are satisfactorily correlated with the basicities of these compounds[62]; (4) a methyl group introduced into the 2-position of the cyclohexane ring of cyclohexanone phenylhydrazone accelerates the reaction approximately by a factor of eight compared with the unsubstituted hydrazone[60]; an increase of the acidity of the medium leads to an increase of the rate of reaction[62].

In addition it is possible to explain from this standpoint the effect of substituents in the aromatic ring on the rate of reaction. Electron-donating substituents in the p- and o-positions in the aromatic ring of arylhydrazones increase the basicity of the β-N atom (protonation is probably the initial stage of the tautomeric transformation), in contrast to the substituents in the m-position. This is also indicated by the finding[63,64] that the basicity of the three isomeric methoxyphenylhydrazones decreases in the sequence 4 > 2 > 3.

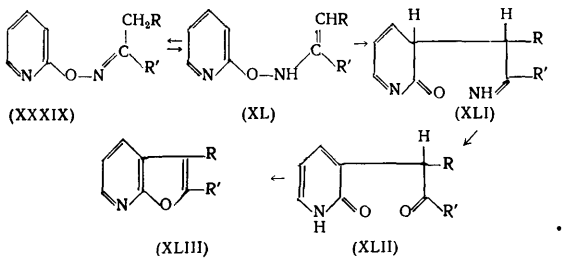
Thus, on the basis of data for the kinetics of the Fischer reaction, one can probably assume that the rate-limiting stage is the tautomeric conversion of the hydrazone into the enehydrazine [(I) ⇌ (II)]. In 1966 Sheradsky reported the acid-catalysed rearrangement of phenyl ethers of oximes (XXX) into benzofuran derivatives (XXXI), which he discovered[65]:



This report was followed by several communications in which it was suggested that the mechanism of this reaction is analogous to that of the Fischer indole synthesis[66-76]:



It is interesting to note that the introduction of two powerful electron-accepting groups, such as two NO_2 groups or a CF_3 and an NO_2 group, into the *o*- and *p*-positions in the aromatic ring does not prevent the closure of the benzofuran ring (39% yield for derivatives with *o*-CF_3 and *p*-NO_2 groups and 20% yield for derivatives with NO_2 groups in *o*- and *p*-positions)[68,72]. The initial attempt to carry out this rearrangement under thermal conditions did not lead to the required result, since on heating the product charred markedly[67]. However, subsequently the thermal rearrangement (XXXIX) → (XLII) was achieved using *O*-(2-pyridyl) oximes of carbonyl compounds[74]:



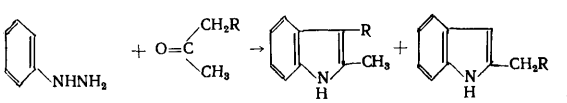
(XXXIX) (XL) (XLI) (XLIII) (XLII)

It has been suggested[43,52] that, in the stage involving the formation of a new C–C bond, this rearrangement should also be regarded as a sigmatropic [3,3] shift and not electrophilic substitution.

2. THE MODE OF CYCLISATION OF ARYLHYDRAZONES OF ASYMMETRIC KETONES

a. The Mode of Conversion of the Arylhydrazones of Alkyl Methyl Ketones into Indoles

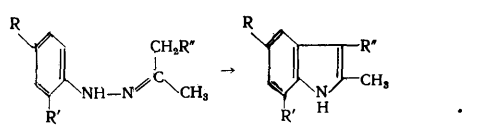
In 1886 Fischer stated that two isomeric indoles, the products of cyclisation involving both alkyl groups, can be formed in the reaction of phenylhydrazine and asymmetric ketones[77]:



(XLIV) (XLV) (XLVI) (XLVII)

However, until recently the entire vast experimental data on the Fischer reaction indicated that only one compound (XLVI) is formed in this process.

Thus Buu-Hoi and Reyer[79] showed that, when a methyl and a methylene group adjoin the carbonyl group, indoles are formed only via the methylene group. Schofield and Theobald[80] demonstrated chromatographically that there is no second substance in the product isolated after the cyclisation of the *o*- and *p*-nitrophenylhydrazones of 2-pentanone (XLVIII, a and b) and *o*- and *p*-nitrophenylhydrazones of phenylacetone (XLVIII, c and d).

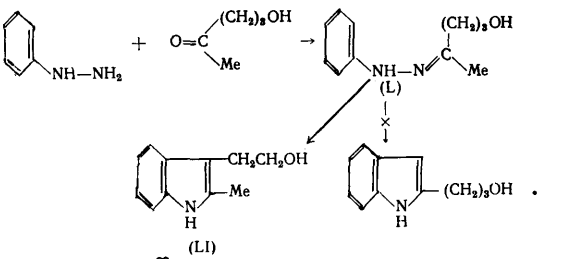


(XLVIII) XLIX

(a) R=NO_2 R′=H R″=Et
(b) R=H R′=NO_2 R″=Et
(c) R=NO_2 R′=H R″=Ph
(d) R=H R′=NO_2 R″=Ph

Later a very small amount of a dark tarry product, the structure of which was not established, was isolated in the chromatographic separation on alumina of the cyclisation products of the phenylhydrazone of phenylacetone (XLVIII, R = R′ = H, R″ = Ph). However, it was suggested that this consisted of traces of 2-benzylindole.

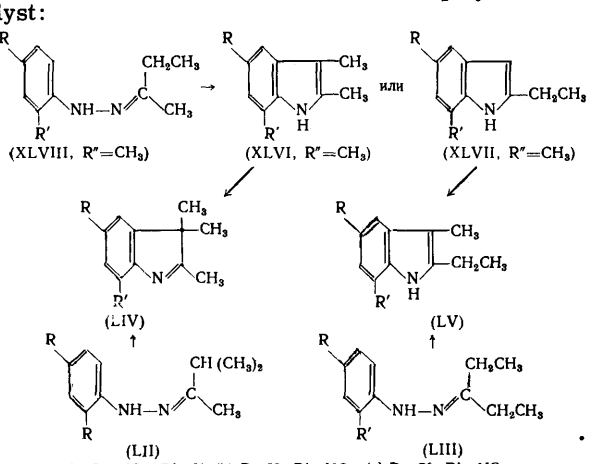
Grandberg et al.[82] established that the reaction of phenylhydrazine (XLIV) and 1-hydroxypentan-4-one yields the hydrazone (L); they cyclised it under the conditions of the Fischer reaction using zinc chloride and copper(I) chloride as catalysts. In both cases 3-(β-hydroxyethyl)-2-methylindole (LI) was isolated in a pure form and 2-(γ-hydroxypropyl)indole, the possible second product, was not detected:



(L) (LI)

Deorha and Joshi[83] confirmed that the methylene group is exclusively involved in the Fischer conversion of the phenylhydrazones of asymmetric ketones into indoles. The structures of the compounds isolated were established by methylation. Thus the methylation product of the indole obtained from the arylhydrazone of 2-butanone (XLVIII) is either compound (LIV) or (LV), since the indole has either the structure (XLVI) or (XLVII). It was established that compound (LIV) is identical with the compound obtained in the cyclisation of the arylhydrazone of 3-methylbutan-2-one (LII) and compound (LV) is identical with the product of the cyclisation of the arylhydrazone of 3-pentanone (LIII). Thus the indole obtained from compound (XLVIII) is 2,3-dimethylindole formed as a result of the cyclisation involving the methylene group [compound (XLVI)].

The formation of two isomers was noted only in a study by Korczynski et al.[78]; having discovered that *p*-diazonitrobenzene reacts with 2-monosubstituted indoles but not with 2,3-disubstituted derivatives, the authors established that the phenylhydrazone of ethyl methyl ketone yields a mixture of products as a result of the Fischer reaction, containing 20% of ethylindole and 80% of 2,3-dimethylindole, when an excess of zinc chloride is employed as the catalyst:



(XLVIII, R″=CH_3) (XLVI, R″=CH_3) (XLVII, R″=CH_3)
(LIV) (LV)
(LII) (LIII)

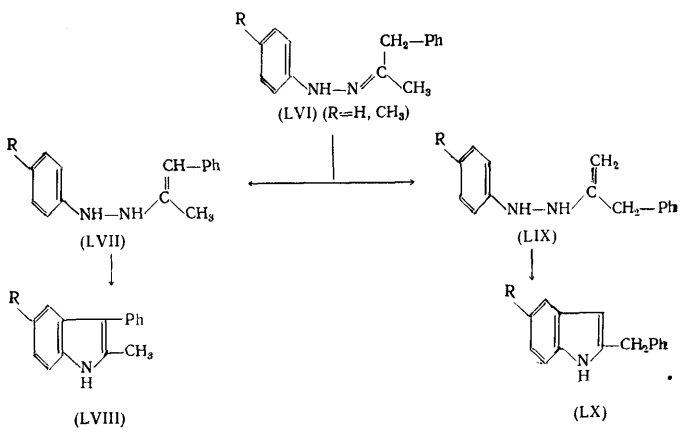
(a) R=NO_2, R′=H; (b) R=H, R′=NO_2; (c) R=Cl, R′=NO_2; (d) R=NO_2, R′=Cl; (e) R=I, R′=NO_2; (f) R=NO_2, R′=I

Thus numerous examples of the synthesis of 3-substituted 2-methylindoles by the Fischer reaction using various catalysts, which have been described in the literature[7-12], suggest that the arylhydrazones of asymmetric ketones yield exclusively 3-substituted 2-methylindoles as a result of the Fischer reaction.

Against the background of the numerous investigations published in 1965, the study by Buu-Hoi et al.[84] appeared to be an exception to this rule. When polyphosphoric acid (PPA) was used as the catalyst in the cyclisation of the arylhydrazone of phenylacetone (LVI), it was found that the product of the cyclisation involving the methyl group (LX) is formed together with the usual product (LVIII) in proportions of 1 : 5.

Earlier they showed that the Fischer reaction of this compound under the influence of gaseous hydrogen chloride in glacial acetic acid leads to cyclisation involving the methylene group, yielding indoles which do not contain any traces of 2-substituted isomers[85].

It was suggested that the action of the catalyst in the Fischer reaction involves the tautomeric conversion of the phenylhydrazone (LVI) into two intermediate enehydrazines (LVII) and (LIX), (LVII) being formed when zinc chloride, boron trifluoride, and hydrogen chloride in acetic acid are employed as catalysts and compound (LIX) is formed in the presence of polyphosphoric acid[84].



Yamamoto's data[49] confirm these results: for example, it was shown that, when R = Ph, the ratio of the two isomeric indoles (XLVII)/(XLVI) increases with increase of the concentration of phosphorus pentoxide in the orthophosphoric acid employed as the catalyst.

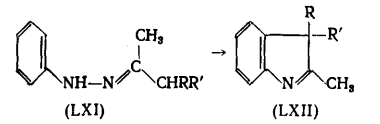
The selective action of the catalysts was investigated in greater detail by Palmer and McIntyre[86]. It was established by ^{1}H NMR that the reaction yields a mixture of isomeric indoles in which the (XLVI) : (XLVII) ratio depends on the catalyst employed. The following catalysts were investigated: boron trifluoride-ether in acetic acid, sulphuric acid at different concentrations in 1 : 1 aqueous ethanol, 90% orthophosphoric acid, and various polyphosphoric acids.

When boron trifluoride-ether in acetic acid was employed as the cyclising agent, only one product (XLVI, R = CH_3, C_6H_5, or p-$NO_2C_6H_4$), formed as a result of the cyclisation involving the methylene group, was isolated. The use of other catalysts led to the formation of a mixture of indoles, the ratio of the isomers depending on the concentration of phosphorus pentoxide in orthophosphoric acid. In all the reactions the fraction of the 2-substituted indole (XLVII, R = CH_3, C_6H_5, or p-$NO_2C_6H_4$), the product of the cyclisation involving the methyl group, increases from 0 when 90% H_3PO_4 or 40% H_2SO_4 is employed to a level which makes it the main component in 70% sulphuric acid or 83% solution of phosphorus pentoxide in 90% orthophosphoric acid.

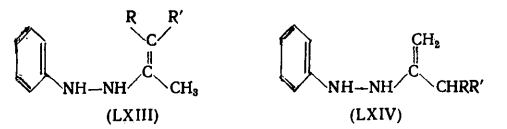
It was shown[86] that the formation of two isomeric indoles is not a consequence of an intramolecular rearrangement, which might have been postulated by analogy with the familiar migrations of substituents in indole systems[87], since the indoles isolated remain unchanged on heating under conditions where mixtures of two isomeric compounds are formed.

b. The Mode of Conversion of Arylhydrazones of 3-Substituted Alkyl Methyl Ketones into Indoles

For arylhydrazones of ketones with an α-branched alkyl chain, there is a rule[88] according to which these compounds cyclise exclusively via the third carbon atom, yielding 2-methylindolenines:

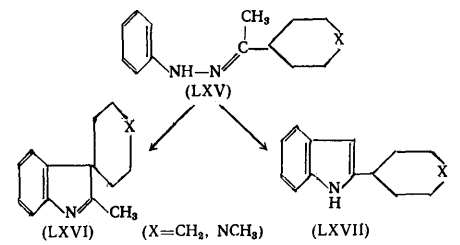


This mode of cyclisation was explained by the fact that the enehydrazine (LXIII), which has the greatest number of substituents at the double bond, is more stable than compound (LXIV).



Numerous examples of this type of cyclisation have been compiled[7-12].

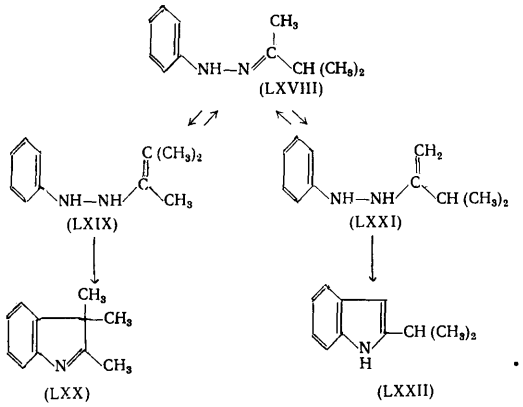
However, it is striking that the cyclisation of the phenylhydrazone of cyclohexyl methyl ketone (LXV, X = CH_2) resulted in an 18% yield of 2-cyclohexylindole (LXVII)[89], an excess of zinc chloride being used as the catalyst. Spiro-3*H*-indole (LXVI), expected as the product of the main reaction pathway, was not isolated, although it had been shown previously that the reaction does in fact follow this pathway[90]:



Later Lyle and Skarlos reinvestigated this reaction[91]. They converted into indoles the phenylhydrazones of cyclohexyl methyl and methyl 1-methyl-4-piperidyl ketones (LXV, X = CH_2 or NCH_3) and established that the Fischer indole synthesis catalysed by polyphosphoric acid yields mainly the products of the cyclisation via the methyl group (LXVII), while the use of an excess of zinc chloride or acetic acid as the catalyst makes it possible to obtain the corresponding spiro-3*H*-indoles (LXVI) alone.

The authors suggested[91] that the mode of cyclisation leading to two products is associated with the stability of the transition states for two different cyclisation pathways. (The cyclisation mechanism is discussed in greater detail below.)

In a study of the cyclisation of the phenylhydrazone of isopropyl methyl ketone (LXVIII), Illy and Funderburk concluded that the pathway followed in the indole formation reaction depends on the acidity of the medium[92]:



Zinc chloride, acetic acid, the hydrogen sulphate ion, and aqueous phosphoric acid always give rise to 2,3,3-trimethyl-3*H*-indole (LXX), the product of the cyclisation involving the more branched chain of the ketone. Polyphosphoric acid and concentrated sulphuric and hydrochloric acids give rise to a mixture of products, the yield of 2-isopropylindole, the product of the cyclisation involving the methyl group, increasing with the acidity of the medium (Fig. 2).

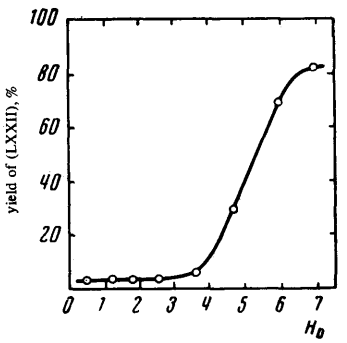
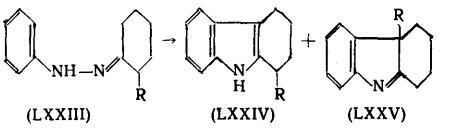


Figure 2. Variation of the yield of 2-isopropylindol (LXXII) with the acidity function H_0 in the cyclisation of compound (LXVIII) for the molar ratio catalyst : hydrazone = 5 : 1.

Palmer and McIntyre[86] also investigated the cyclisation of the phenylhydrazone of isopropyl methyl ketone (LXVIII) as a function of the concentration of the acids employed as catalysts. Their results agree satisfactorily with those of Illy and Funderburk[92]. At relatively low catalyst concentrations the cyclisation involves the more branched chain of the ketone, but, on increasing the concentration, the cyclisation involves the less branched chain[86].

c. The Mode of Conversion of the Phenylhydrazones of 2-Substituted Cyclohexanones into Indoles

The cyclisation of the phenylhydrazones of 2-substituted cyclohexanones (LXXIII) leads to two products: 1,2,3,4-tetrahydrocarbazole (LXXIV) and 1,2,3,4-tetrahydro-4a*H*-carbazole(LXXV)[9,10,12]:



(LXXIII) (LXXIV) (LXXV)

Table 1.

R in phenylhydrazone (LXXIII)	(LXXIV) : (LXXV)		
	catalyst		thermal cyclisation
	20% H_2SO_4	CH_3COOH	
CH_3	45:21	6:61	49:51
C_2H_5	44:28	13:76	—
n-C_3H_7	—	—	72:28
i-C_3H_7	44:18	16:70	—
cyclo-C_6H_{11}	29:17	9:79	94: 4
C_6H_5	54:19	27:69	87:13

Hughes and Lions[90] and subsequently Pausacker and Schubert[93,94], established that the ratio of the isomers formed depends on the catalyst employed and the substituent R (Table 1).

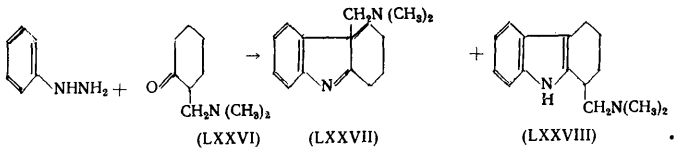
Table 2.

Catalyst	Solvent	Yield of (LXXIV), %	Yield of (LXXV), %
CH_3COOH	CH_3COOH	6	61
CH_3COOH	H_2O	—	56—40*
CCF_3COOH	H_2O	—	53
HCL(gas)	C_6H_6	4	65
HCL(gas)	C_2H_5OH	19	44
HCl(conc.)	H_2O	40	38
H_2SO_4(conc.)	C_2H_5OH	33	36
H_2SO_4(conc.)	H_2O	45	21

*The yields varied with the concentration of acetic acid in water.

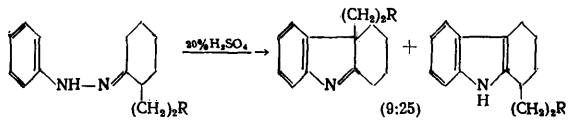
Pausacker showed[94] for 2-methylcyclohexanone phenylhydrazone that the ratio of the products formed is influenced by the nature of the acid catalyst and the solvent employed (Table 2). However, in a later study[95] on the behaviour of compounds (LXXIII) (R = CH_3, C_2H_5, C_3H_7, C_4H_9, C_6H_{11}, and C_8H_{17}) products other than (LXXV) were not detected. Concentrated hydrochloric acid in glacial acetic acid was used as the catalyst. The absence of the second isomer (LXXIV) when the reaction was carried out under these conditions appears strange, since subsequent studies on these lines demonstrated the formation of two products.

Thus Grandberg et al.[96] established that the reaction of phenylhydrazine and the ketone (LXXVI) yields two products (LXXVII) and (LXXVIII):



(LXXVI) (LXXVII) (LXXVIII)

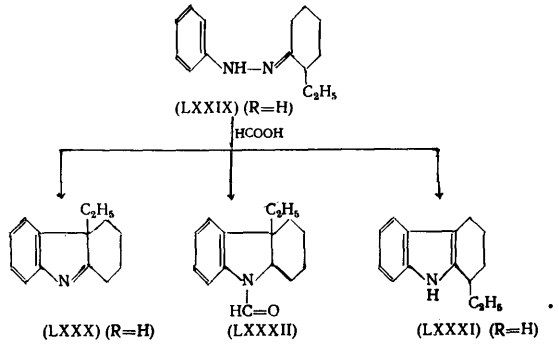
Two products are formed also on cyclisation of the phenylhydrazone of 2-(2-cyanoethyl)cyclohexanone (LXXIX)[97]:



(LXXIX) (LXXX) (9:25) (LXXXI) (R=CN)

A tetrahydrocarbazole was obtained together with compound (LXXXI) on heating compound (LXXIX) with a catalytic amount of zinc chloride at 170–190°C. The appearance of the tetrahydrocarbazole among the reaction products was explained by the elimination of the cyanoethyl group from compound (LXXXI). However, one cannot rule out the possibility that the cyanoethyl group can be eliminated not only from compound (LXXXI) but also from compound (LXXX) and reaction intermediates. On the basis of these findings, the authors concluded[96,97] that, when there is competition between the methylene and methyl groups, the Fischer reaction proceeds via both pathways.

However, when 98–100% formic acid is used as the catalyst, the cyclisation of (LXXIX) leads mainly to 4a-ethyl-1,2,3,4-tetrahydro-4a*H*-carbazole (LXXX), although it was isolated in only a low yield, since it reacts with formic acid under the process conditions, yielding 4a-ethyl-9-formyl-1,2,4,4a,9a-hexahydrocarbazole (LXXXII). The ultraviolet spectra of the product also indicate the formation of a small amount of 1-ethyl-1,2,3,4-tetrahydrocarbazole (LXXXI)[98]:

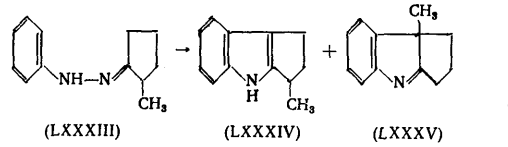


(LXXIX) (R=H)

(LXXX) (R=H) (LXXXII) (LXXXI) (R=H)

Kelly et al.[54] carried out the thermal conversion of compound (LXXIII) into an indole. They found that here too a mixture of indoles (LXXIV) and (LXXV) is formed. The ratio of the isomers is given in Table 1, where it is compared with the results of other studies[93,94].

In addition the phenylhydrazone of 2-methylcyclopentanone (LXXXIII) was converted into indoles by the thermal reaction[54], since the previous attempt to carry out this reaction with the aid of acid catalysis failed[95]. The authors report that in this case two products are also formed, but do not quote their proportions:

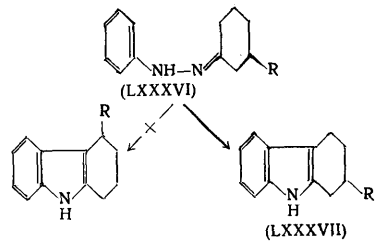


(LXXXIII) (LXXXIV) (LXXXV)

According to the results of Berlin et al.,[99] when equimolar amounts of phenylhydrazine and 2-cyclohexylcyclohexanone are refluxed in glacial acetic acid, 1-cyclohexyl-1,2,3,4-tetrahydrocarbazole (LXXIV, R = C_6H_{11}) is formed in 28.5% yield.

d. The Mode of Conversion of Phenylhydrazones of 3-Substituted Cyclanones

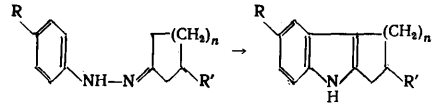
It has been reported[100] that 3-methylcyclohexanone phenylhydrazone (LXXXVI, R = CH_3) gives rise to one product, the structure of which was not established. Later, it was shown[101] that it is a tetrahydrocarbazole (LXXXVII, R = CH_3), since its dehydrogenation yields 2-methylcarbazole. An admixture of 4-methylcarbazole was not detected.



(LXXXVI) (LXXXVII)

In one of the earlier studies it was stated[102] that the cyclisation of the phenylhydrazones of 3-oxocyclohexanecarboxylic acid (LXXXVI, R = COOH) yields one isomer of unknown structure. Later Allen[103] took up the study of this problem and established that the product is 1,2,3,4-tetrahydrocarbazole-2-carboxylic acid (LXXXVII, R = COOH).

A similar study was made recently on the phenylhydrazones of cyclopentanone and cycloheptanone[104]. The structures of the compounds formed under the conditions of the Fischer reaction were established on the basis of their ^1H NMR spectra using Eu(DPM)$_3$. In both cases the formation of only one isomer was demonstrated.

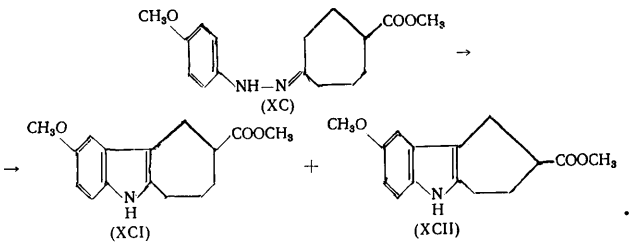


(LXXXVIII) (LXXXIX)

n=1, R=H, OCH_3 R′=COOH, $COOCH_3$

n=3, R=H, OCH_3 R′=CN, COOH, $COOCH_3$

As expected, the cyclisation of the phenylhydrazone of a 4-substituted cycloheptanone yields a mixture of two isomeric compounds (XCI) and (XCII):



(XC) → (XCI) + (XCII)

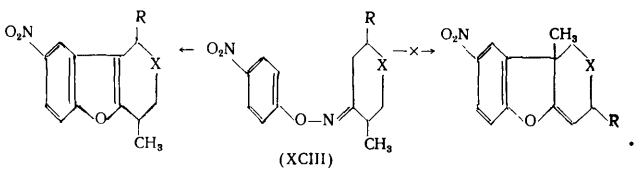
Calculations by the LCAO-MO method in terms of the Hückel approximation for model compounds showed that the equatorial 4-methylcyclohexene is more stable than the pseudoequatorial 3-methylhexene to the extent of 0.8 kcal mole^{-1}.[104] The authors used this fact in an attempt to explain the high selectivity of the Fischer reaction for the phenylhydrazones of 3-substituted cyclanones, although such a small difference can hardly exert a large influence under fairly severe reaction conditions. It is much more likely that steric factors operate in the transition state in the formation of the carbon–carbon bond.

3. THE MODE OF REARRANGEMENT OF *O*-PHENYL ETHERS OF THE OXIMES AND ASYMMETRIC KETONES

Mainly the aryl ethers of the oximes of symmetrical carbonyl compounds or compounds capable of rearranging in one specific position were investigated in rearrangements of the type (XXX) → (XXXI). However, the rearrangement of the oximes of asymmetric ketones was studied in several investigations.

Mooradian noted initially that a mixture of two benzofurans may be formed in the rearrangement of the *p*-nitrophenyl ether of the oxime of 2-butanone, as shown by the ^{1}H NMR spectrum of the unpurified reaction product[68]. However, the product of the rearrangement involving the methyl group could not be isolated.

On cyclisation of aryl ethers of the oximes of 2-methylcyclohexanone (XCIIIa)[69] and 1,2,5-trimethylpiperidin-4-one (XCIIIb)[76] in dilute acid solutions, compounds were formed as a result of a rearrangement involving exclusively the methylene group [compound (XCIVb)] and not the methine group [compound (XCV)]:

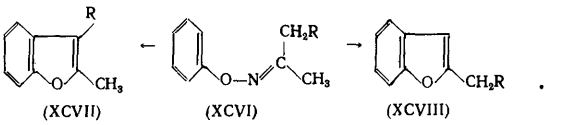


(XCIV) ← (XCIII) → (XCV)

(a) X=CH_2, R=H
(b) X=NCH_3, R=CH_3

The authors noted that, under analogous steric conditions, the closure of the indole ring in the Fischer reaction of the arylhydrazones of the same ketones involves exclusively the α-methine group. However, no explanation of this phenomenon has been put forward[69,76].

The mode of rearrangement of compounds of this kind was investigated in greater detail in other studies[52,105]. It was established that the cyclisation of compound (XCVI) (for R = alkyl) involves both the α-methylene and the α-methyl groups with formation of a mixture of isomeric benzofurans. The reaction was carried out in a dilute alcoholic solution of hydrochloric acid. However, when the substituent was a powerful electron-accepting group, only one compound (XCVII) was formed. The ratio of the isomers formed was determined by ^{1}H NMR and by gas-liquid chromatography (Table 3).



(XCVII) ← (XCVI) → (XCVIII)

It has also been shown[52] that the ratio of the products [(XCVIII) : (XCVII), R = CH_3] is determined by the reaction conditions (Table 4).

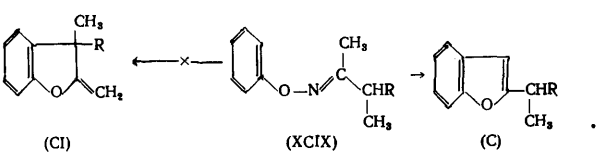
Table 3.

R in compound (XCVI)	Isomer ratio (XCVIII): (XCVII)	R in compound (XCVI)	Isomer ratio (XCVIII): (XCVII)	R in compound (XCVI)	Isomer ratio (XCVIII): (XCVII)
CH_3	55:45	C_6H_5	40:60	$COCH_3$	0:100
C_2H_5	65:35	$CH_2C_6H_5$	60:40	$COOC_2H_5$	0:100
n-C_3H_7	70:30	C_2H_4OH	70:30	CN	0:100
i-C_3H_7	85:15				

Table 4.

Reaction conditions (t = 100°C)		Isomer ratio (XCVIII): (XCVII)
acid catalyst [acid : (XCVI) = 1 : 1]	solvent	
HCl	methanol	78:22
—	2-propanol	55:45
—	t-butyl alcohol	37:63
—	nitromethane	33:67
—	DMSO	30:70
—	DMF	25:75
—	dioxane	12:88
—	THF	8:92
—	benzene	22:78
H_2SO_4	methanol	82:18
—	2-propanol	75:15
—	dioxane	58:42
$CH_3C_6H_4SO_3H$	2-propanol	65:35
$HClO_4$		81:19

^{1}H NMR and gas-liquid chromatography[52] have shown that the products of the rearrangement of the *O*-phenyl ethers of the oximes of branched alkyl methyl ketones are benzofurans (C). This is evidence that the closure of the benzofuran ring involves only the α-methyl group:



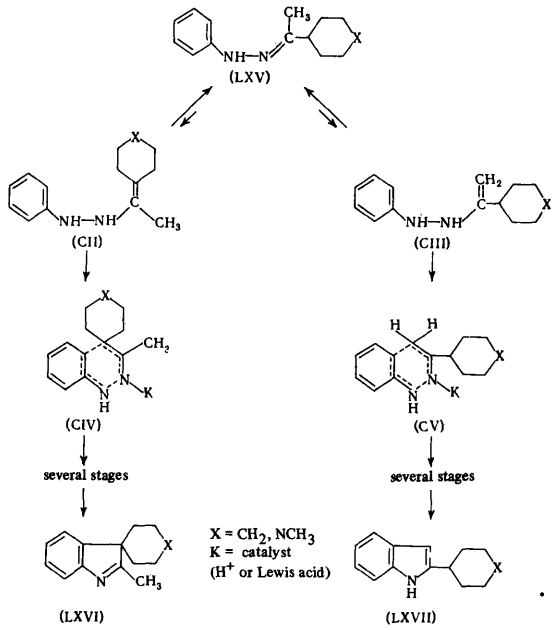
(CI) ← (XCIX) → (C)

4. FACTORS DETERMINING THE MODE OF CYCLISATION

The first attempt to explain the formation of two isomeric products in the Fischer reaction was made by Lyle and Skarlos[91]. In their discussion of the reaction mechanism they suggested that the mode of cyclisation of phenylhydrazones of asymmetric ketones should be related to the

energy of the transition state for two different cyclisation pathways.

For phenylhydrazones of cyclohexyl methyl ketones (LXV), there is a possibility of the formation of two enehydrazines (CII) and (CIII), which should subsequently cyclise via the transition states (CIV) and (CV) respectively. For the formation of a new C–C bond, the benzene ring must approach the π electrons of the double bond. Conformational analysis of the molecules of the enehydrazines (CII) and (CIII) showed that such approach is prevented by the 2- and 6-axial hydrogen atoms on approach from one side and the 3- and 5-axial hydrogen atoms on approach from the other side (cyclisation involving the methine group) [Fig. 3, compounds (CII, a and b)].



In cyclisation involving the methyl group, the steric interaction between the cyclohexane ring and the catalyst is enhanced [Fig. 3, compound (CIII)].

Therefore in the presence of "small" catalysts "K", such as a proton derived from polyphosphoric acid, cyclisation should proceed via the energetically more favourable transition state (CV) in which there is no interaction between the benzene ring and the axial hydrogen atoms of the cyclohexane ring. In the presence of "large" catalysts "K" such as zinc chloride or an acyl group (the authors apparently find it more convenient to assume that acetic acid behaves not as a protic acid but as an acylating agent[91]), the energy of the transition state (CV) increases in consequence of the interaction between the bulky catalyst and the cyclohexane ring. In this case the reaction proceeds via the transition state (CIV), since the enehydrazine (CII) is energetically more favourable.

Ultimately, when the cyclisation proceeds via the transition state (CIV), the products are 3*H*-indoles (LXVI), while cyclisation via the transition state (CV) gives rise to 2-substituted indoles (LXVII).

Lyle and Skarlos suggest that the ratio of the isomers (LXXIV) and (LXXV) formed from the phenylhydrazones of 2-substituted cyclohexanones (LXXIII) should be correlated with the steric $A^{(1,2)}$ strain (Johnson and Malhotra[106])

in the corresponding pairs of intermediate enehydrazines (CVI) and (CVII)[91]:

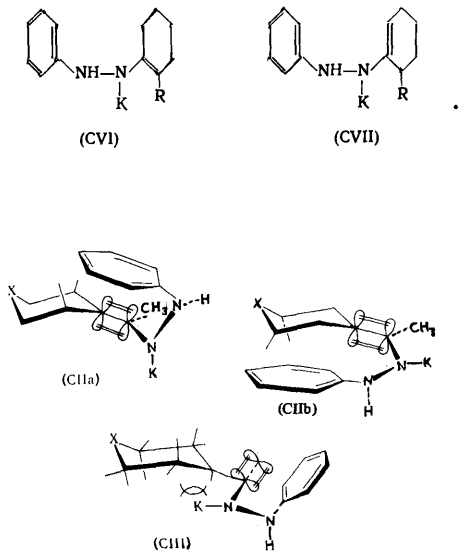


Figure 3. Conformation of the molecules of the enehydrazines (CII, a and b) and (CIII) (Dreiding models).

The authors believe that the transition state in the cyclisation of the enehydrazine (CVII) is preferable when a protic acid is employed as a catalyst or in a thermal rearrangement. Lewis acids or acetic acid should lead to an unfavourable steric interaction between K and the substituent R in the tautomer (CVII) and should favour the formation of the transition state from the enehydrazine (CVI) (Fig. 4).

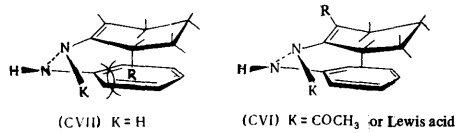
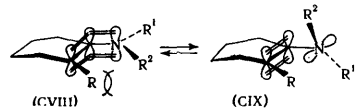
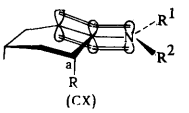


Figure 4. Conformations of the molecules of the enehydrazines (CVI) and (CVII) (Dreiding models).

These considerations are based on the following factors. The enamines obtained from 2-substituted ketones are known to exist as a mixture of isomers[107,108]. The isomer ratio is determined by different steric and electronic factors, which influence the conjugation of the n-electron pair of the nitrogen and the C=C double bond. Complete conjugation requires the coplanarity of the substituent at the nitrogen atom and the olefinic groups:

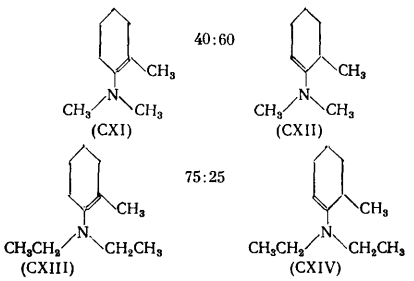


Steric interaction between the groups and the nitrogen atom (R^1 or R^2) on the one hand and the substituent R in the cyclohexane ring of (CVIII) on the other hinders the coplanarity of the substituents and a high degree of overlapping. Therefore the groups are displaced from coplanarity with a consequent weakening of their steric interaction and a simultaneous decrease of the degree of conjugation of the n-electron pair of the nitrogen with the C=C double bond of compound (CIX). The isomer (CX) with an axial R group is free from such steric interaction and therefore it can remain coplanar with a high degree of overlapping[109]:



(CX)

However, with increase of the size of the substituent R^1 or R^2 (in phenylhydrazones of ketones one of the substituents is the "large" NHC_6H_5 group), the relative degree of conjugation may prove to be low in any of the three structures quoted [(CVIII), (CIX), and (CX)]. Even the isomer (CX) does not have an energetically favourable structure in consequence of the increase of the steric interactions between the substituents at the nitrogen atom (R^1 or R^2) and the substituent R in the cyclohexane ring, regardless of whether R is an axial, equatorial, or vicinal substituent. It has been shown[108] that the isomer ratio (CXI) : (CXII) differs markedly from (CXIII) : (CXIV). The authors suggested that, with increase of the intensity of the steric interactions, the isomer (CXIV) with an axial methyl group is not energetically more favourable[108]. In order to weaken these interactions, the groups are displaced from coplanarity and the factors determining the stability of the normal (not conjugated) double bond operate independently—the more substituted double bond is preferred.



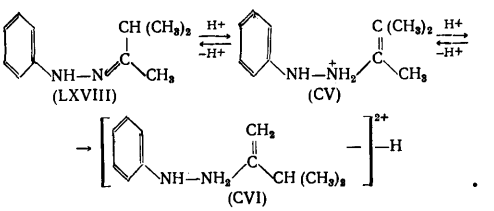
(CXI) (CXII) (CXIII) (CXIV)

Consequently, as suggested by Lyle and Skarlos, when an attempt is made to predict the mode of conversion of the phenylhydrazones of asymmetric ketones into indoles, account must be taken of the fact that the two possible intermediate enehydrazines are sterically hindered to different extents and the stabilisation due to the polyalkyl substitution of the C=C bond in the enehydrazine tautomer[91]. Robinson adheres to this view in his latest review[10].

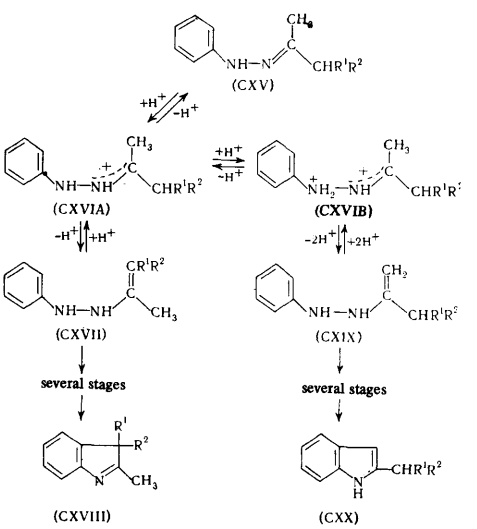
However, this concept is inconsistent with Pausacker's experimental data[94] and those of Canadian workers[54] (Table 1). The steric interactions between the substituents and the catalyst K in structure (CVII) should be greater the greater the bulk of the substituent R and hence the formation of the transition state from the other enehydrazine (CVI) should be favoured. On the other hand, experimental data show that the opposite situation obtains, i.e. that the isomer (LXXIV), formed from the sterically hindered isomer (CVII), predominates in the mixture of indole products isolated (particularly in a thermal rearrangement). Thus the explanation proposed for the formation of two isomers in the cyclisation of the phenylhydrazones of asymmetric ketones[91], based on the correlation between the steric strain of the $A^{(1,2)}$ type in the intermediate enehydrazines (CVI) and (CVII) and the ratio of the isomeric indoles (LXXIV) and (LXXV), does not take into account all the factors which determine this ratio.

Moreover, it is difficult to explain by the steric influence alone the formation of two products from the phenylhydrazones of ethyl methyl and isopropyl ethyl ketones in which there is no strain of the $A^{(1,2)}$ type. Nor is there any answer to the question concerning the influence of the concentration of the catalyst on the isomer ratio.

The approach to the consideration of the possible formation of two isomers in the Fischer reaction from other standpoints proved to be more promising. In an endeavour to account for the influence of the acidity of the medium on the proportions of the products of the Fischer reaction of the phenylhydrazone of isopropyl methyl ketone (LXVIII), Illy and Funderburk[92] suggested that an increase of the acidity of the medium (Fig. 2) entails double protonation of the molecule of the hydrazone (LXVIII), which causes the process to proceed via a different mechanism, leading to the formation of compound (CVI):


(LXVIII) (CV) (CVI)

This hypothesis was confirmed by the formation of 2-isopropylindole (LXXII) only when more than two moles of hydrochloric or sulphuric acid are involved in the reaction. Weak acids do not result in double protonation, because the acidity H_0 does not increase to the required value with increase of the concentration of the acid. Palmer and McIntyre also suggest that at a low concentration of the acid catalyst monoprotonation takes place, while on increase of the acidity of the medium to $H_0 \simeq -4.40$ the hydrazone molecule may be doubly protonated[86].

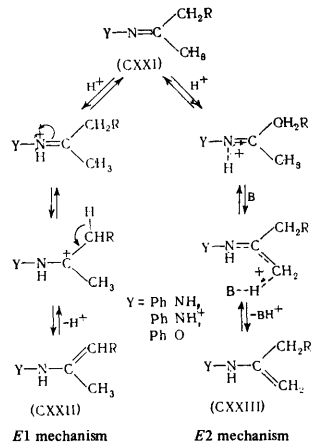

(CXV) (CXVIA) (CXVIB) (CXVII) (CXIX) (CXVIII) (CXX)

The authors believe that in solutions of weak acids the formation of the enehydrazines (CXVII) or (CXIX) from the cation (CXVI) is the slow stage in the sequence (CXV) → (CXVI, A) → (CXVII) or (CXIX). This is analogous to an

$E1$ elimination reaction where the product in which the C=C double bond is substituted by alkyl groups to the maximum extent should predominate. In very acidic solutions, there is an additional inductive withdrawal of electrons from the alkyl groups in the diprotonated molecule of compound (CXVIB), which increases the probability of the attack of the C–H bond by the anion. This is analogous to an $E2$ elimination reaction.

In a study of the rearrangement of the O-phenyl ethers of ketone oximes (XCVI) to benzofurans (XCVII) and (XCVIII), the authors concluded that the reaction constitutes a satisfactory model of the Fischer synthesis of indoles in highly acidic media[52,105]. Comparison of the pK_a values for the phenylhydrazones of the same ketones shows that the basicity of O-phenyloximes is smaller by factor of approximately 10^3 than the basicity of the corresponding phenylhydrazones.

The formation of two isomeric benzofurans (XCVII) and (XCVIII) is evidently associated with two possible modes of "migration" of the double bond in the tautomeric transformation caused by different mechanisms, analogous to the mechanisms of $E1$ and $E2$ elimination. It is clearly seen when one examines the fragment responsible for the pathway followed in the β-elimination reaction.



The double bond $N{=}\overset{|}{C}{-}\overset{|}{C}{-}H$, which dissociates on protonation, plays the role of the group X split off on β-elimination from $X{-}\overset{|}{C}{-}\overset{|}{C}{-}H$. The lower the basicity of the nitrogen atom the more difficult it is to protonate it, which in turn makes it more difficult to dissociate the N=C bond. This is analogous to the hindrance of the dissociation of the substituent X, which always leads to the $E2$ mechanisms becoming predominant.

In the usual Fischer reaction carried out in a weakly acid medium (Y = PhNH), the enehydrazine is formed via the $E1$ mechanism. After protonation of the β-N atom, there is a rapid shift of π-electrons with formation of a carbonium ion stabilised by the ejection of a proton with transformation into the thermodynamically favourable structure in which there is a maximum degree of branching at the double bond (cyclisation involving the CH_2 group).

As a result of the formation of the diprotonated structure ($\overset{+}{Y}$ = $Ph\overset{+}{N}H_2$), in an acid medium the fragment $Ph\overset{+}{N}H_2\overset{+}{N}H{=}$ becomes such a weak acceptor ($-I$ effect) that the hydrogen atoms in the α-alkyl groups become much more acidic. The α-hydrogen atoms are then split off from the most "acidic" CH_3 group via a synchronous mechanism under the influence of the nucleophilic agents present in the reaction medium.

If Y is a fairly strong acceptor (Y = PhO) with a high $-I$ effect, its electron-accepting activity favours the tautomeric transformation via the $E2$ mechanism even in a weakly acid medium. Naturally the kinetically more favourable isomer is then formed under the influence of solvent molecules (cyclisation involving the CH_3 group). Thus the mode of conversion of the phenylhydrazones of asymmetric ketones into indoles and the mode of cyclisation of the O-phenyl ethers of the oximes of the ketones are determined by the ratio of the probable intermediate enehydrazines and vinylhydroxylamines formed on tautomeric transformation of the initial compounds under acid conditions. The ratio depends on the probability of the tautomeric transformation via one of the possible β-elimination mechanisms.

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