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Recent data on the mechanism of the rearrangement of arylhydrazones to indoles (the Fischer reaction) are examined. The effect of electronic factors and the acidity of the medium on the rate of the process is discussed. The regioselectivity of the indolization reaction and its quantum-chemical interpretation are analyzed.

### Introduction

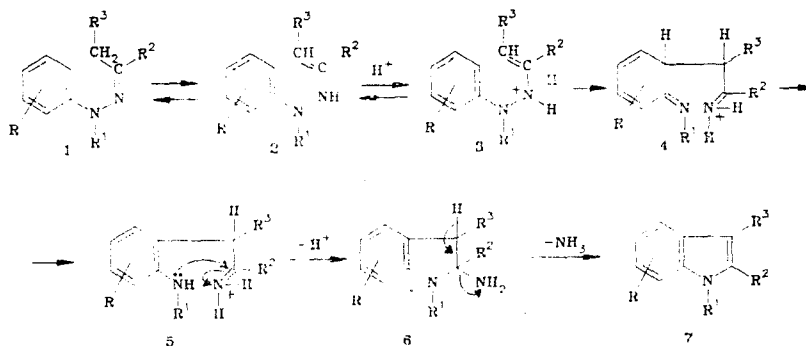
The rearrangement of arylhydrazones (the Fischer reaction [1]) still remains the most important method for the construction of an indole ring [2], which is the practical structural fragment of diverse biologically active compounds [3-6].

A number of reviews [7-12] and sections in monographs [2, p. 60; 13-16] have been devoted to various aspects of the mechanism of this reaction. However, many essential details of the Fischer reaction have been clarified only recently. Progress in approaching the principal step from the point of view of the theory of concerted processes, in the study of the regioselectivity and kinetics, and in the quantum-chemical interpretation of the process has primarily been charted. Precisely these problems are discussed in the present review.

Problems involving "anomalous" Fischer reactions [11, 17-19] are not examined in our review.

### 1. General Scheme of the Reaction and Its Substantiation

The modern generally accepted scheme of the Fischer reaction (according to [2]) was first proposed by Robinson and Robinson [20, 21]. The research of Brunner [22], Allen and Wilson [23], Carlin and Fischer [24], Arbuzov and Kitaev [25], Suvorov [26], Fusco and Sanniccolo [19], Ishii [18], and Kost [27] has made a substantial contribution to the development of this scheme. Several studies by the authors of the present review [9-11] have also been devoted to this problem.



Most of the intermediately formed reaction products of the 2-6 type - enehydrazine 2 [28-30] (see also section 2.2), dieronimine 4 [31], imine 5 [32-34], and amine 6 [35], which were subsequently converted to the corresponding indoles - have been isolated and their structures have been established. On the basis of this one might assume that the scheme of the indolization process has been elucidated in its general features.

Steps  $1 \rightleftharpoons 2$ ,  $3 \rightarrow 4$  and  $5 \rightarrow 6$  are of greatest significance. Process  $1 \rightleftharpoons 2$  is worthy of attention, since precisely hydrazones 1 are virtually always the starting compounds in

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the Fischer synthesis [2] and precursors of enehydrazines 2. Compounds 2 are intermediates that determine the direction of the rearrangement in a number of cases [36-44] (see section 2.2 for greater detail). The elucidation of the mechanism of the key step - the formation of the C-C bond (3 → 4) - is an important problem, to which sections 2.1 and 3 are devoted. As regards the step in which the pyrrole ring is formed (5 → 6), it has been described in rather great detail [2].

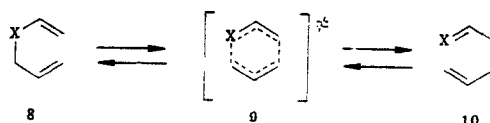
2.1. Scheme of the Cope 3,4-Diaza Rearrangement. The hypothesis of the electrophilic character of the step involving the formation of the C-C bond [7, 8] that was asserted in the 1960s (other mechanisms and analogies of the Fischer reaction were also proposed [45-47] was subsequently subjected to criticism [9, 10].

It has been noted that the indolization of arylhydrazones does not always require the use of acidic catalysts; it can be accomplished thermally [16, 27, 38, 39, 42, 43, 48-50], in the presence of bases [44, 51], as well as under the influence of other catalysts such as rhodium complexes [52] and  $\text{PCl}_3$  [53-56], and in the presence of salts ( $\text{Hg}^{2+}$  and  $\text{Pd}^{2+}$ ) [57]. As regards the effect of substituents on the rate of rearrangement, comparable kinetic data (particularly for the thermal process) are not available in the literature, and the data based on the yields of the corresponding indoles have proved to be extremely contradictory [9, 10].

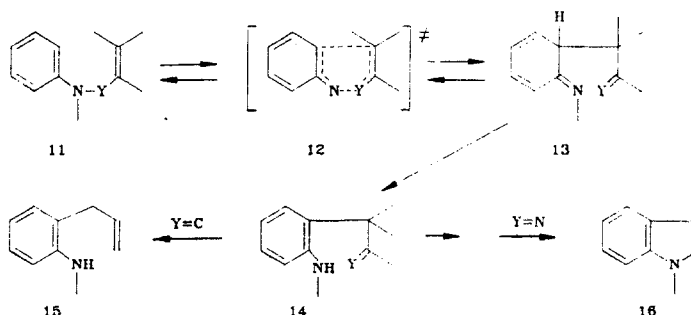
The experimental data according to which the formation of the C-C bond occurs at the carbon atom of the aromatic ring that is occupied by a substituent [9-12, 17-19] are also not in agreement with the general tenets of electrophilic substitution. Furthermore, the concept of electrophilic substitution raises doubts, since  $\sigma$  complexes could not be detected in the indolization process, whereas a number of intermediates were isolated (see above). Finally, it should be noted that the mechanism of the Fischer reaction carried out in heterogeneous [58-60] and gas [61] phases is similar to the mechanism of the reaction in solutions.

A study of the facts enumerated above has enabled a number of authors [8-11, 62] to reconsider the existing concept and to interpret the mechanism of the formation of the C-C bond from the point of view of the principle of retention of the orbital symmetry [63]. This theory was developed most consistently in [9-11, 64-67] and has presently been accepted by most chemists [16, 18, 19, 38, 39, 50, 60, 68-71].

In accordance with the formal nomenclature [72, 73], [3,3]-sigmatropic rearrangements of the 8 → 10 type, which proceed through transition state 9, are called Cope hetero rearrangements (oxa, aza, and thia, in conformity with the nature of heteroatom X).



When one of the double bonds in rearrangement fragment 8 is part of aromatic system 11, process 11 → 14 is called a Cope aromatic hetero rearrangement.



The Fischer reaction can consequently be considered to be a Cope aromatic 3,4-diaza rearrangement [74]. A peculiarity of this system is the ability of intermediate 14 to undergo cyclization to indole 16 (in contrast to the Claisen rearrangement and the Claisen amino rearrangement, where  $\text{Y} = \text{C}$ ).

To facilitate the exposition of the subsequent material let us enumerate the principal criteria for distinguishing concerted processes ([3,3] shift) from stepwise processes ( $\text{S}_{\text{E}}$ ).

The following are characteristic for the former: Relatively small changes in the rate when substituents with different electronic natures are introduced or when the solvent is replaced, large negative values of the entropies of activation, inversion of the allyl groups, first-order reactions, and retention of the optical activity in the products when it is present in the starting molecule. The mechanisms of a number of sigmatropic rearrangements were established on the basis of these criteria (for example, see [75, 76]), and an interpretation of the mechanism of the indolization reaction was also realized.

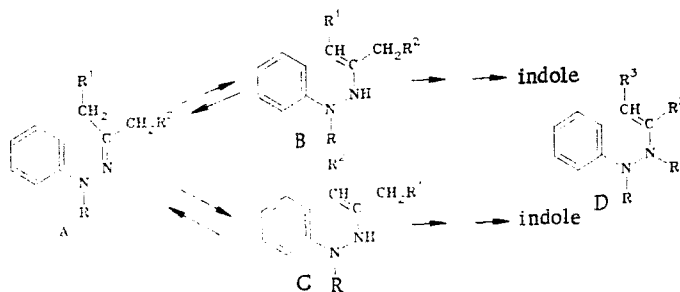
In particular, the conclusion that cleavage of the N-N bond and the formation of the C-C bond in the Fischer reaction occur via a concerted mechanism was made in [64-66] on the basis of the small effect of substituents on the ratio of the isomer N-aryltetrahydrocarbolate which is formed by the unsymmetrically substituted cyclohexanone N,N-diarylhydrazones. In addition, in a study of the Stollé intramolecular cyclization of m-substituted chloroacetyl-diarylamines it was established [67] that high selectivity of attack by the carbonium ion on the phenyl rings with more donor substituents occurs. These results, as well as the data of Schiess [38, 39] on the transformation of enehydrazines of the 2 type, evidently were the first confirmation of the concept of a [3,3] shift in the 3 → 4 step. The modern state of the problem of the mechanism of this step is discussed in detail in section 3.

## 2.2. Hydrazone-Enehydrazone Tautomerism and Regioselectivity of the Fischer Reaction.

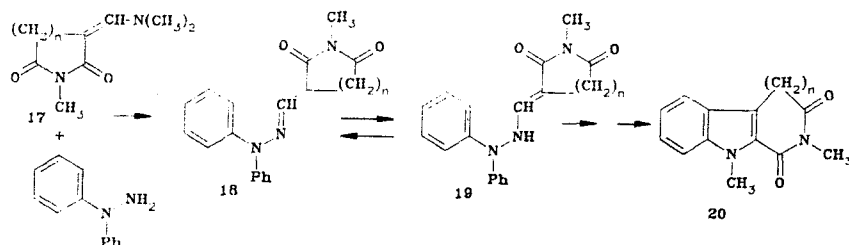
A number of studies dealing with the effect of electronic and steric factors and the acidity of the medium on the direction of the indolization reaction have been published in recent years [50, 55, 56, 68-70, 77, 78]; most of the authors proceed from the concept of the existence of a hydrazone-enehydrazone tautomeric pair ( $A \rightleftharpoons B$ ), and the regioselectivity of the process is explained by the development of different enehydrazines (B and C,  $R^1 \neq R^2$ ), which then undergo cyclization to the corresponding indoles.

In addition to this, rearrangements of enehydrazines with a fixed structure (D) to indoles are well known (for example, see [38, 39, 42, 43]).

In contrast to D, an enehydrazone form of the B type could not be detected, which raised definite doubts regarding the reversibility of the 1 ⇌ 2 step [11]. These failures are evidently associated with the fact that, as demonstrated by calculations [79], hydrazone form A is more favorable than the enehydrazone form, and protonation stabilizes it even more, simultaneously increasing the mobility of the  $A \rightleftharpoons B$  (of C) equilibrium [9, 41].



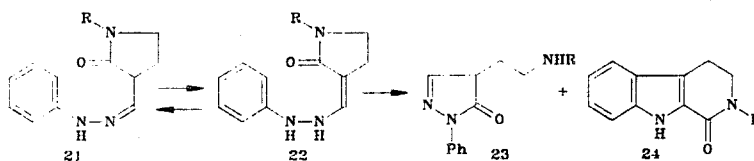
In the study of a new reaction for obtaining β-carbolines [80, 81] it was found that it was possible to stop the reaction of N-methyl-α-dimethylaminomethylenesuccinimide (17, n=1) with diphenylhydrazine (isopropyl alcohol, HCl) at the step involving the hydrazone and to isolate enehydrazone 19 in crystalline form [82].



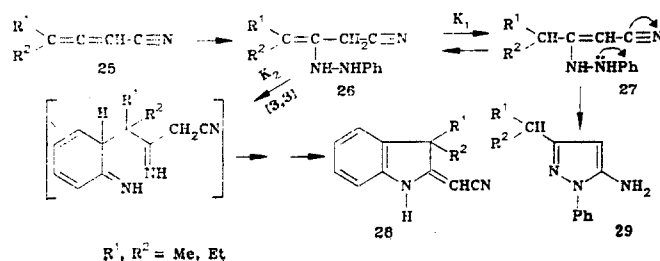
In solution enehydrazone 19 exists in an equilibrium mixture with hydrazone 18 (the ratio of 19 to 18 is 2:1 according to PMR data). Under more severe conditions (refluxing

in glacial acetic acid saturated with dry HCl) enehydrazine 19 is converted smoothly to  $\beta$ -carboline 20 [83]. Thus these data unequivocally prove the rightfulness of regarding enehydrazines as intermediates in the Fischer reaction.

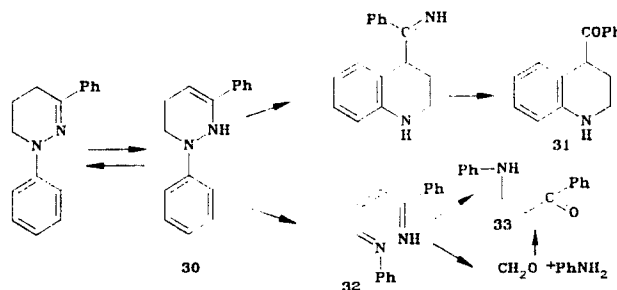
In a number of cases the structural peculiarities of the enehydrazine that develops may direct the reaction along a pathway other than the "Fischer" pathway. For example, 16% pyrazolone 23 and 84% carboline 24 are formed from enehydrazine 22 (R = C<sub>6</sub>H<sub>5</sub>) [81]. The presence of a bulky substituent (R = n-C<sub>4</sub>H<sub>9</sub>) leads only to carboline 24, while the absence of such a substituent (R = H) leads to pyrazolone.



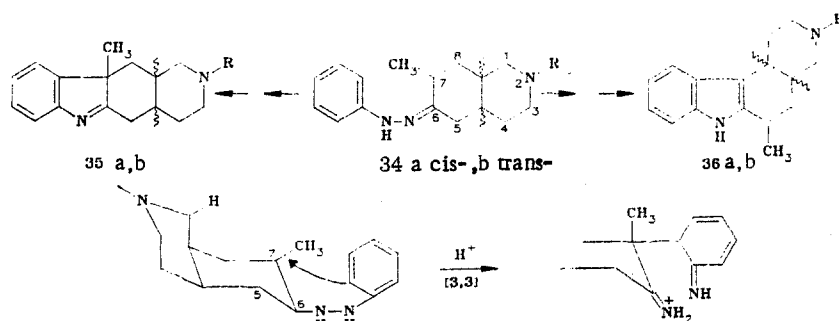
Landor and co-workers [68] explain the formation of a mixture of indole 28 and pyrazole 29 from allenic nitriles by the possibility of the existence of two enehydrazines 26 and 27. The relative rates of prototropic isomerization  $26 \rightleftharpoons 27$  ( $k_1$ ) and sigmatropic shift ( $k_2$ ) determine the ratio of the reaction products.



An interesting example of the appreciable effect of steric factors on the Fischer reaction was described in [70]. Under the influence of polyphosphoric acid (PPA) enehydrazine 30 undergoes rearrangement to 4-benzoyltetrahydroquinoline (35% and simultaneously undergoes cleavage of the retro-Diels-Alder type (30  $\rightarrow$  32), which ultimately leads to 2-anilinopropiophenone 33.



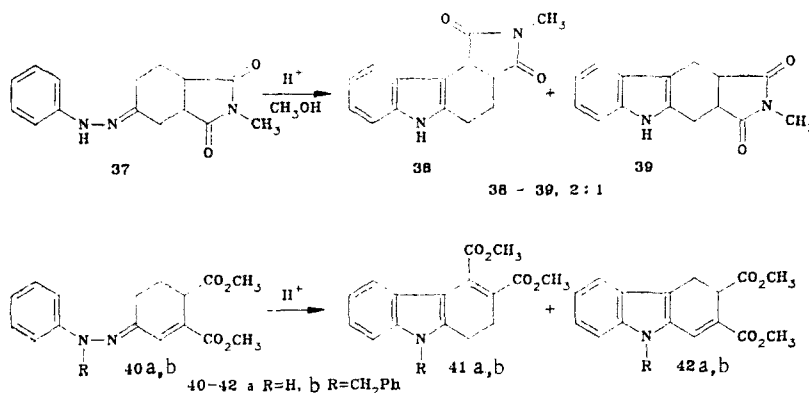
Fretter and co-workers [77] have demonstrated the importance of the stereochemical peculiarities of the structure of enehydrazines on the occurrence of the indolization reaction in the case of the rearrangement of arylhydrazones of hexahydro-7-methyl-6-isoquinolones (34a, b).



Depending on the acidity of the medium, either indolenine 35a or indole 36a is formed from cis-fused heterocycle 34a, while trans isomer 34b gives only indolenine 35b. The conformations and relative configurations of the intermediates and reaction products were established on the basis of an analysis of the vicinal spin-spin coupling constants (SSCC) obtained by two-dimensional PMR spectroscopy and the dihedral angles. These data made it possible to explain the regioselectivity of the process.

The formation of an indole and/or an indolenine occurs through two possible enehydrazines in which the double bond is located in the 5 and 6 positions, respectively. It was shown that the 5,6-enehydrazine develops preferably in cis- and not trans-isoquinolines, while the trans-fused enehydrazine contains the double bond in the 6 position, which leads to indolenine 35b. It was found that indolenine 35a has only one definite configuration relative to the C(7) atom. The key step in the process that determines this configuration is shown in the scheme. A priori the CH<sub>3</sub> group attached to the carbon atom in sp<sup>2</sup> hybridization can be attacked on both sides of the plane; however, steric repulsion of the cis-fused piperidine ring forces attack only from below, which leads to indolenine 35a with a cis orientation of the CH<sub>3</sub> group. The indicated steric interaction is absent in the formation of indolenine 35b, and the latter therefore exists in the form of two isomers with cis- and trans-CH<sub>3</sub> groups in the 7 position.

The regioselectivity of the formation of dihydro- and tetrahydrocarbazoles in the Fischer reaction was studied by Reed and co-workers [69].



Regardless of a change in the sulfuric acid concentration (7...60%), the ratio of carbazoles 38 and 39 remained virtually constant at 2:1.

At the same time, indoles 41a, b and 42a, b were formed in equal amounts in the rearrangement of hydrazones 40a, b.

The development of two isomers in each of the reactions under discussion is readily explainable from the point of view of the existence of a tautomeric pair of enehydrazines that are converted to the corresponding indoles via the scheme of a [3,3]-sigmatropic shift [69].

However, the reasons for the absence of regioselectivity in the reaction 40 → 41 + 42 and its presence in the indolization of hydrazones 37 (37 → 38 + 39) have remained unexplained. One must evidently determine whether the equilibrium between the isomeric enehydrazines is subject to kinetic or thermodynamic control and also study the reaction under thermal conditions.

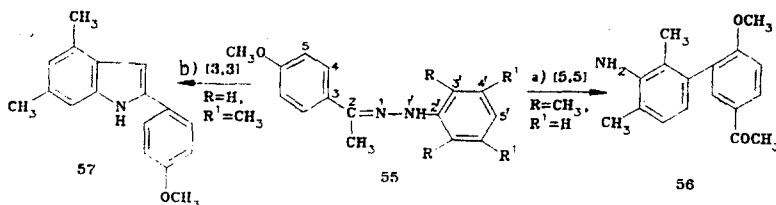
The discussion of the effect of various factors on the direction of cyclization of phenylhydrazones of 2-alkylcyclohexanones is important in a theoretical respect [50]. The principal results of this investigation will be set forth in sections 3.1, 3.2, and 3.4.

The regioselectivity of the Fischer reaction, which is associated with the formation of 4- and 6-substituted isomers from m-substituted arylhydrazones [78], is examined in sections 3.2 and 3.3.

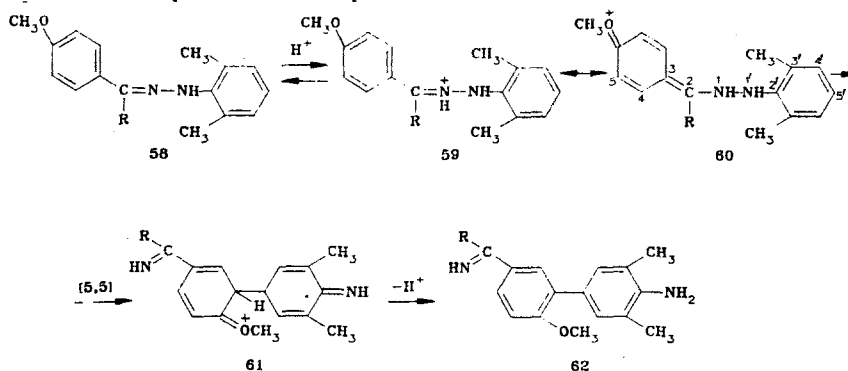
2.3. [3,3]-Sigmatropic Rearrangement and Other [i,j] Shifts for the Aromatic 3,4-Diazahexadiene System. A series of papers by Fusco and Sannicola [19, 70, 71, 83-89] devoted

to new aspects of the indole synthesis, viz., to the study of the rearrangements of arylhydrazones that have steric hindrance to realization of Fischer indolization, has been published in recent years. For example, the conversion of methyl p-methoxyphenyl ketone phenylhydrazones 55 in PPA at 100°C to biphenyl derivative 56 competes with Fischer indolization 55 → 57 [84].

The authors found that indolization (pathway b) via a [3,3]-sigmatropic rearrangement mechanism proceeds primarily only in the case of 55 (R=H, R<sup>1</sup>=CH<sub>3</sub>). However, if both ortho positions of the benzene ring that participates in the rearrangement are blocked by substituents 55 (R=CH<sub>3</sub>, R<sup>1</sup>=H), the primary process is the formation of a biphenyl derivative via a [5,5]-sigmatropic rearrangement mechanism (this sort of rearrangement was first described in [90]).

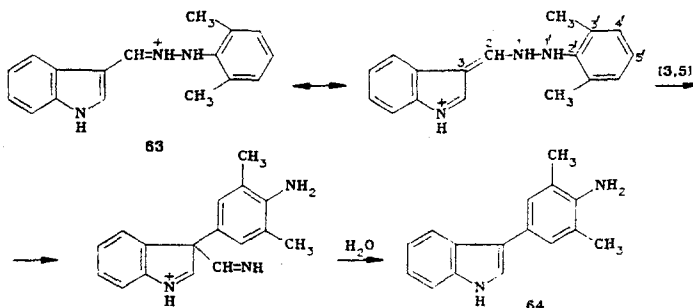


According to the data in [84-87], a [5,5]-sigmatropic shift (60 → 61) occurs when there are ortho substituents (CH<sub>3</sub>) in the benzene ring of the hydrazine component (58) and electron-donor groups (OCH<sub>3</sub>) in the para position of the benzene ring (58) of the carbonyl component and leads to the formation of biphenyl derivatives 62.



58—62 R=H, Ph; 4-OMePh, 2-MePh, 4-ClPh, 4-BrPh

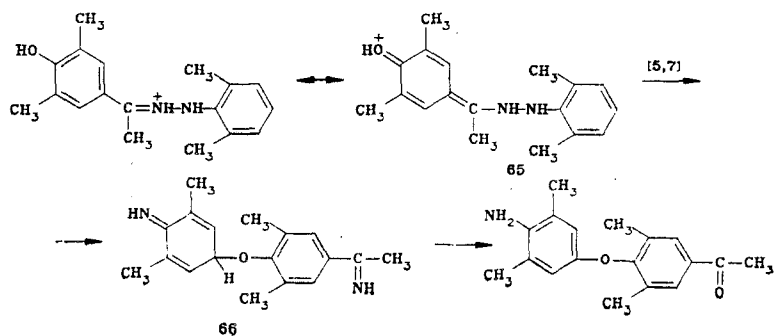
Similar rearrangements are observed in series of arylhydrazones obtained on the basis of carbonyl derivatives of thiophene [70, 88, 89] and indole [70,88].



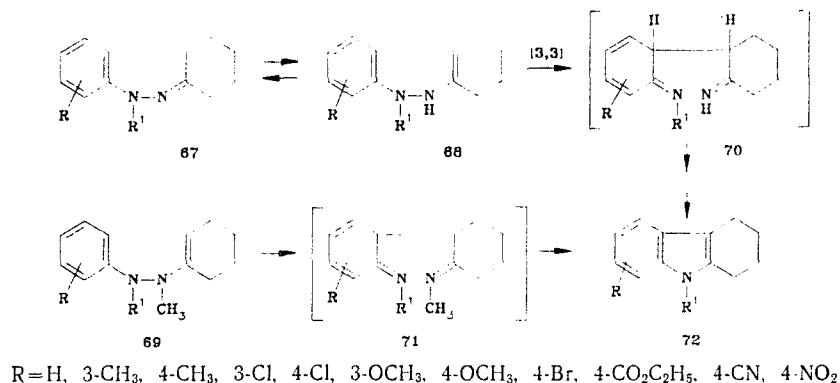
In an acidic medium 2-methyl-3-indolylcarboxaldehyde 2,6-dimethylphenylhydrazone 63 is converted to 64 via a [3,5]-sigmatropic rearrangement scheme [18]. (See scheme on top of following page.)

Yet another new type of rearrangement, viz., a [5, 7] shift (65 → 66) was observed in a series of 4-hydroxyacetophenone and benzophenone derivatives of arylhydrazones [18].

Thus the probability of the occurrence of competing processes via [3,5], [5,5], and [5,7]-sigmatropic shift mechanisms increases sharply when steric hindrance to realization of indolization via a [3,3]-shift mechanism is present.



**3. Kinetics of the Fischer Reaction and Mechanism of the Formation of a Carbon-Carbon Bond.** As pointed out in section 2.1, kinetic data are necessary for the use of the criteria for distinguishing concerted processes from stepwise processes. The rate of indolization in acidic media of various arylhydrazones of cyclic ketones substituted in the benzene ring and carbonyl component was studied in [91-95], and it was determined that the process is a first-order reaction. These data were discussed in part in a review [10] and were analyzed in detail in [96]. They were recently supplemented substantially by the results of an investigation of the kinetics of the indolization of cyclohexanone arylhydrazones 67 of the A ( $R^1 = H$ ) and B ( $R^1 = CH_3$ ) series and of enehydrazines 69 by a spectrophotometric method under thermal conditions and in the presence of acids [97-101].



A combination of all of the kinetic data, the conclusions of quantum-chemical calculations, and the results of other studies that clarify to a significant degree a number of details of the mechanism of the formation of a C-C bond are presented below.

**3.1. Effect of Solvents on the Rate of Fischer Indolization.** A quantitative evaluation of the effect of solvents on the rates of the thermal and acid-catalyzed Fischer reaction was first made in [97, 98]. It was shown that the rate of rearrangement of hydrazones 67 and enehydrazines 69 depends little on the ionizing capacity of the solvent (ethylene glycol, decane, diamyl ether). Thus the rate constants ( $k \cdot 10^5 \text{ sec}^{-1}$ ) of the thermal rearrangement of enehydrazone 69 ( $R = H, R^1 = CH_3$ ) at 70°C in the indicated solvents are, respectively, 2.9, 2.1, and 2.5 [97]. These results are in complete agreement with the data of Schiess [38, 39], who showed that the presence or absence of a solvent does not have a substantial effect on the yields of indoles in the thermolysis of enehydrazines of the 69 type.

In [50] it was observed that in the acid-catalyzed ( $H_2SO_4$ ) cyclization of 2'-methylcyclohexanone phenylhydrazone the size of the alkyl radical in the alcohols used as the solvents (MeOH, EtOH, iso-PrOH, tert-BuOH) has little effect on the ratio of the yields of the isomeric reaction products (indole/indolenine), which ranges from 1.4 (MeOH) to 3.1 (tert-BuOH).

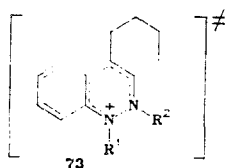
Consequently, the data presented indicate low polarity of the transition state of the key step 68 → 70 (or 69 → 71); this constitutes evidence in favor of a concerted mechanism.

**3.2. Effect of Electronic Factors on the Rate of Indolization.** The qualitative picture of the effect of substituents on the ease of the occurrence of the Fischer reaction was based

chiefly on a comparison of the yields of indoles and was reflected to some extent in virtually all reviews and monographs devoted to this reaction (the problem was illuminated most fully in a book [2]). This problem was examined from a quantitative point of view for the first time in [91] and was subsequently developed in [92-95]. The authors of these investigations studied the indolization of arylhydrazones of the 67 type (the reaction was actually carried out by mixing of the corresponding arylhydrazine and ketone) in the presence of acids and it was established that, as a rule, electron-donor substituents in the benzene ring accelerate the process, whereas electron-acceptor substituents retard it. A similar conclusion was drawn by Schiess and co-workers [38, 39], who studied the effect of substituents in the carbonyl part of enehydrazines of the 69 type on their ability to undergo rearrangement  $69 \rightarrow 72$ . Moreover, some facts have not been satisfactorily explained [10, 96] and have been resolved only in recent studies.

An analysis of the effect of electronic factors on the rates of the thermal and acid-catalyzed Fischer reaction of arylhydrazones 67 showed [97-99] that in the first case the maximum ratio of the rate constants of reactions with donor and acceptor groups 67 ( $R = 4\text{-CH}_3$ ) ( $R = 4\text{-CN}$ ) does not exceed 80...100, as compared with 20...30 in acid catalysis. The rates of rearrangements of m- and p-substituted hydrazones were close, although a somewhat higher rate was always observed for the para isomers. The introduction of a methyl group relative to the nitrogen atom increases the rate of indolization of both hydrazones 67 and enehydrazones 69 [97-99]. The difference in the rates of reactions with substituents with different natures was explained and confirmed by the existence of a quantitative dependence of the rate constants for rearrangement of hydrazones of the A series on the ionization constants of the corresponding monosubstituted anilines [100] (this relationship was first noted in [94]).

The data obtained were interpreted in favor of concerted character of the formation of the C-C bond. It is assumed that the reaction proceeds through cyclic transition state 73.



Important information was obtained by means of calculations of a number of model structures of the scheme of the Fischer reaction. The calculations were made on the basis of a bonded variant of perturbation theory in the MO LCAO SCF method [99]. Quantum-chemical interpretation of the effect of substituents in the indolization reaction of m-substituted arylhydrazones makes it possible to explain and predict its regioselectivity. Thus the calculations show that the ratio of isomeric 6- and 4-substituted indoles (7- and 5-substituted tetrahydrocarbazoles 70, respectively) is greater than unity if R is a donor and less than unity if R is an acceptor. These conclusions are in good agreement with numerous experimental data [2, 48, 101-103] (however, it was recently observed [78] that the rearrangement of m-substituted phenyl benzyl ketone arylhydrazones under the influence of  $\text{PCl}_3$ , regardless of the nature of the substituent, always leads to a mixture of compounds with preponderance of the 6-substituted isomer).

**3.3. Effect of the Acidity of the Medium on the Rate of Indolization.** The problem named in the title of this section has been under discussion since Fischer discovered this reaction, inasmuch as for preparative purposes in most cases it is carried out in an acidic medium [2]. The first attempt to obtain the quantitative principles of the effect of the acidity of the medium on the reaction rate in the formation of indoles was made in [44]; however, a satisfactory correlation could not be obtained. The reason for acceleration of the indolization reaction on passing from thermal conditions to the acid-catalyzed process has been seen chiefly in catalysis of the tautomeric conversion of the hydrazone to an enehydrazine ( $1 \rightarrow 2$ ,  $67 \rightarrow 68$ ) [2, 7, 8, 10, 12]. (Let us note that primarily catalysis by protic acids is discussed in this section; the question of catalysis by Lewis acids is examined in a previous review [12].)

The effect of an acid on the rearrangement of enehydrazines of the 69 type was first investigated in [38, 39], and it was concluded that its marked acceleration (by a factor of

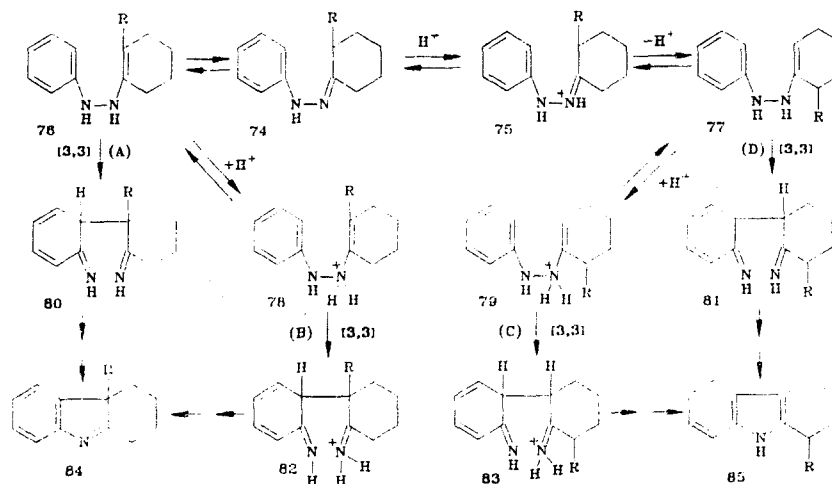


of  $10^3 \dots 10^6$  as compared with the thermal process) is associated with the realization of a charge-induced pericyclic reaction [104] in the step  $69 \rightarrow 71$ . The indicated conclusion was confirmed in [97] and was extended in [97-100] to the rearrangement of arylhydrazones 67, since it was established that the basic principles of the effect of acids on the enehydrazine are also retained for the hydrazones. The more marked acceleration of the reaction (on passing from a neutral medium to an acidic medium) in the case of enehydrazines as compared with hydrazones is associated with the absence of isomerization  $67 \rightleftharpoons 68$  in the first steps and with the difference in the basicities of these two systems [97]. The increase in the rate of the Fischer reaction with an increase in the acid concentration and intensification of its acidic properties is explained by differences in the stabilities and concentrations of the intermediately formed hydrazoneium and enehydrazinium salts [97]. Yet another important conclusion was drawn on the basis of kinetic data on the acid-catalyzed rearrangement of cyclohexanone arylhydrazones: The effect of substituents in the benzene ring and attached to the nitrogen atoms is similar on the whole to the effect of these groups in the thermal reaction; this indicates a common mechanism for the processes. It is assumed that the acid-catalyzed Fischer reaction proceeds through six-membered transition state 73 with a delocalized charge [97]. It is known that the energies of the bonding molecular orbitals of 1- or 2-azaallylic systems that have a positive charge are lower than the energies of the MO of the corresponding uncharged system [16]. Since precisely the combination of two azaallylic radicals is the transition state of the Cope aza rearrangement (the Fischer reaction - a special case of this reaction), which is accelerated in the presence of acid [16], the analogous acceleration of the indolization reaction becomes understandable.

In the opinion of Miller and Schinske [50] the acid in the indolization process affects not only regulation of the rate of tautomeric conversion of the hydrazone to the enehydrazine but also catalysis of the [3,3]-sigmatropic rearrangement of the enehydrazine to the dienone-imine ( $67 \rightarrow 68$ ). This assumption was based on the results of a study of the effect of the acid concentration on the ratio of the products of indolization of cyclohexanone 2'-methylphenylhydrazone:

H <sub>2</sub> SO <sub>4</sub> , %	Hammett Acidity Function	84/85 Ratio
10	0.43	1.8
20	1.10	0.8
40	2.54	0.4
60	4.51	0.5
80	7.52	0.7

The increase in the yield of indolenine 84 vis-a-vis greater acidity of the medium is explained by the fact that in this case not only tautomeric transformation  $76 \rightleftharpoons 74 \rightleftharpoons 77$ , but also the subsequent rearrangement of enehydrazines 76 and 77 to dienoneimines 82 and 83 begin to be catalyzed, i.e., in addition to reaction pathways A ( $76 \rightarrow 80$ ) and D ( $77 \rightarrow 81$ ), pathways B ( $78 \rightarrow 82$ ) and C ( $79 \rightarrow 83$ ) develop.



a R=CH<sub>3</sub>; b R=C<sub>6</sub>H<sub>5</sub>; c R=*i*-C<sub>3</sub>H<sub>7</sub>; d R=*i*-C<sub>4</sub>H<sub>9</sub>

In summarizing the results of investigations set forth in this section one may arrive at the conclusion that the concerted character of the step involving the formation of a carbon-carbon bond in the indolization reaction is retained on passing from the thermal process to the acid-catalyzed process.

3.4. Activation Parameters of the Fischer Reaction and Hammett Correlations. Good correlation of the rate constants of the thermal and acid-catalyzed indolization of arylhydrazones 67 with the substituent parameters was observed on the basis of kinetic data [97-100], and it was concluded that the rate-determining step of the process is rearrangement of the enehydrazine to a dienoneimine. The enthalpies of activation of the Fischer reaction of hydrazones 67 (series A and B) lie in the range 13...31 kcal/mole, while the entropies of activation in all cases have rather large negative values (-8...-30 eu) [97-100].

#### 4. Reactions Related to the Fischer Synthesis

It has been proposed [9] that the key steps in the synthesis of tryptamine structures [105, 106], the Brunner synthesis of oxindoles [107], the Kost synthesis of  $\alpha$ -aminoindoles [27], the Bucherer synthesis of benzocarbazoles [108], the Piloty synthesis of pyrroles [109, 110], and other reactions related to the Fischer synthesis (and formally belonging to reactions of the Cope aromatic 3,4-diaza rearrangement type) be considered from the point of view of the principle of retention of orbital symmetry.

This approach is worthy of attention, since the elucidation of the details of the mechanism of one of the reactions makes it possible, taking into account the common character of the mechanism, to extend it also to other systems.

Evidence for a concerted mechanism in the Brunner [111], Kost [112, 113], and Piloty [114, 115] syntheses, and also for rearrangements of systems of the 11 type when Y = O [116-120] and Y = S [121, 122], has recently been obtained.

Thus the concept of a [3,3]-sigmatropic shift in the step involving cleavage of the N-heteroatom bond and the formation of the C-C bond evidently can be successfully used for interpretation of the mechanisms of reactions related to the Fischer synthesis.

#### Conclusion

At present the mechanism of the Fischer reaction is generally rather clear, although individual details of it will undoubtedly be refined even more in subsequent research. In addition to this, a realization of the fact that this reaction belongs to the family of rearrangements that are typical for 3,4-diazahexadiene systems makes it possible to expand its synthetic possibilities. The material examined in this review also shows that some advances in the study of the mechanism of the indolization reaction can be successfully used in the investigation of related systems.

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## SPIRO EPOXY KETONES.

### 2.\* THERMAL TRANSFORMATIONS OF 2-BENZYLIDENEINDAN-1,3-DIONE $\alpha$ -OXIDE

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2-Phenyl-3,3,4,4-diphthaloyloxetane is formed when solutions of 2-benzylideneindan-1,3-dione  $\alpha$ -oxide in benzene or carbon tetrachloride are heated, while 5-oxo-3-phenyl-2,2-phthaloyl-2,3-dihydroindeno[2,3-b][1,4]dioxine is formed when solutions in dioxane are heated.

2-Benzylideneindan-1,3-dione  $\alpha$ -oxide (I) undergoes thermal 1,3-dipolar cycloaddition reactions with most electron-deficient olefins [1]. Continuing our study of the reactivity of  $\alpha$ -oxide I we have observed interesting transformations when solutions of it in benzene,  $\text{CCl}_4$ , and dioxane are refluxed.

In benzene and carbon tetrachloride the principal reaction product is 2-phenyl-3,3,4,4-diphthaloyloxetane (IV), the structure of which was established on the basis of spectral data. The mass spectrum contains a molecular-ion peak with  $m/z$  394, as well as intense peaks of ions formed in the fragmentation of  $M^+$ : diphthaloylethylene ( $m/e$  288) and benzaldehyde ( $m/z$  106). Alternative fragmentation of the molecular ion gives triketoindan and the 2-benzylideneindan-1,3-dione ion with  $m/z$  234. The ion with  $m/z$  250, which corresponds to a fragment of  $\alpha$ -oxide I, is also extremely intense. The characteristic doublet of the absorption frequencies of the carbonyl groups of an indandionyl fragment ( $1730$  and  $1765\text{ cm}^{-1}$ ) is observed in the IR spectrum of IV. In addition to multiplets of aromatic protons, the PMR spectrum contains a singlet at  $\delta$  4.55 ppm. This shift of the signal of the 2-H proton to strong field as compared with the signal of the methylidyne proton of  $\alpha$ -oxide I ( $4.72$  ppm) is probably explained by the anisotropic effect of the carbonyl group of the substituent in the 3-position of the oxetane. An analysis of molecular models shows that the 2-H proton falls into the cone of positive anisotropy.

A mixture of 5-oxo-3-phenyl-2,2-phthaloyl-2,3-dihydroindeno[2,3-b][1,4] dioxine (VI) and oxetane IV in a ratio of 7:1 is formed when  $\alpha$ -oxide I is refluxed in dioxane. The structure of VI was established by spectral and chemical methods. The molecular mass determined by mass spectrometry is 394, and the given substances are isomers. The presence of a cyclic ether C-O-C grouping in indenodioxine VI is confirmed by the presence of an  $[M - 16]^+$  fragment ion with  $m/z$  378 [2]. In addition, the mass spectrum contains intense peaks of ions with  $m/z$  105 and 106 ( $\text{PhC}\equiv\text{O}^+$  and  $\text{PhCHO}^+$ , respectively), 250 (ion after the elimination of a phthaloyl fragment), and 306 and 278 (fragmentation of the phthaloyl fragments of the molecular ion). Absorption frequencies of the carbonyl groups of the indandionyl part ( $1730$  and  $1750\text{ cm}^{-1}$ ), of a keto group conjugated with a C=C bond ( $1690\text{ cm}^{-1}$ ), and of an aromatic ring and a C=C bond ( $1610\text{ cm}^{-1}$ ) are observed in the IR spectrum of VI. A singlet and a methylidyne proton at 6.1 ppm and a multiplet of aromatic protons are present in the PMR spectrum.

\*See [1] for Communication 1.

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