NEW DATA ON THE MECHANISM OF INDOLIZATION (REVIEW)

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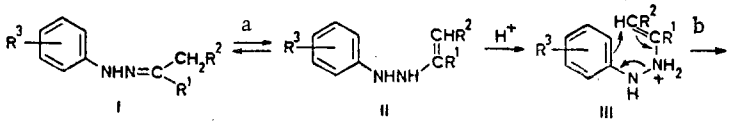
Some new data and concepts relative to the individual steps of the mechanism of the Fischer–Arbuzov synthesis of indoles, including the role of catalysis and complexing, various anomalies during the process, as well as related reactions, are examined.

Almost 100 yr have elapsed since E. Fischer discovered the indolization of arylhydrazones, a process that subsequently came to be known as the Fischer indole synthesis. It is difficult to overestimate the importance of the method for the synthesis of indole derivatives that is based on it. Many reviews [1-4] and sections in monographs (for example, in [5-7]) have been devoted to the Fischer indole synthesis. However, the extremely important aspects of this reaction that pertain to the mechanism have been ascertained only in the last decade. Extensive application of the reaction began only after A. E. Arbuzov established its catalytic nature and improved the method for the synthesis of indoles. The research of Arbuzov constituted the basis for the search for new and more effective catalysts. However, even up to the present time the approach to their selection remains, as a rule, empirical. In the present review we would also like to draw attention to this problem, which is associated with the mechanism of indolization; the latter should evidently be called the Fischer–Arbuzov reaction, if one bears in mind the contribution of Arbuzov to its study. It should also be mentioned that the research of Arbuzov lies at the foundation of yet another trend, which has undergone development only in the last decade — the study of various anomalies in the course of this reaction. Among these anomalies one must point out the phenomenon, discovered by Arbuzov, of nitrile cleavage of the arylhydrazones of some aldehydes and the "anomalous" decomposition of acetone phenylhydrazone, as a result of which, as demonstrated later [8], pyrazole is formed (through a pyrazoline intermediate). A similar trend of the reaction was also observed for acetaldehyde phenylhydrazone [9], which also formed the "anomalous" 1-phenyl-5-methylpyrazoline instead of an indole. The aminonitrile cleavage of arylhydrazones has been examined in a number of reviews and monographs (for example, see [7]) and will not be discussed here. Other anomalies that shed light on the Fischer mechanism were also observed in subsequent years. Their study makes it possible to examine more extensively the diverse catalytic transformations in an entire class of hydrazones. Many papers devoted to the mechanism of the Fischer reaction, the exceptions and anomalies, the catalytic nature of the reaction, and its occurrence under thermal conditions have been published recently. We will deal only with the most important, in our opinion, papers, primarily those that pertain to the development of the creative legacy of A. E. Arbuzov.

New Data on the Individual Steps of the Reaction

The principal steps in the generally accepted scheme of this reaction were proposed by Robinson and Robinson [10] and were subsequently supplemented and refined by other researchers (for example, see [2]):



I II III

A. E. Arbuzov Institute of Organic and Physical Chemistry, Academy of Sciences of the USSR, Kazan 420083. Translated from Khimiya Geterotsiklicheskikh Soedinenii, No. 8, pp. 1011-1027, August, 1978. Original article submitted May 26, 1977.

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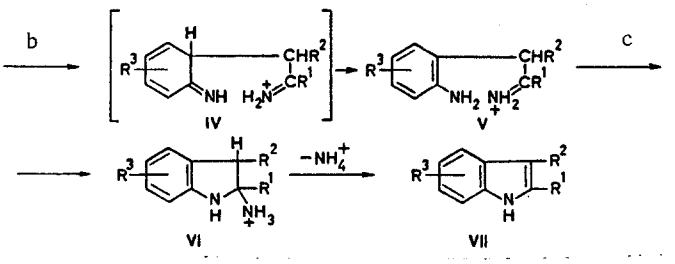
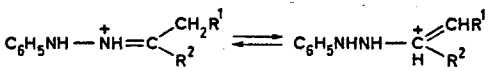
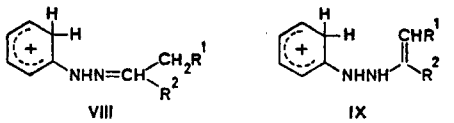


Three steps (a, b, and c) are the most important ones in this scheme. It reflects to a certain extent the role of the catalyst — a protic acid — which many investigators feel consists only of a shift in the hydrazone → enehydrazine equilibrium and that subsequent transformations in the catalysis are not needed. Many studies have been devoted to the protonation of arylhydrazones, and one may consider it to be proved that, although the basicities of the two nitrogen atoms in them are close, the proton adds to the imine nitrogen atom rather than to the amine nitrogen atom [11-13]. Incidentally, protonation of the amine nitrogen atom should have prevented further Fischer rearrangement and promoted nitrile cleavage.



The possibility that the proton may also add to a carbon atom is not excluded; however, the quantum-chemical calculations are not in agreement with this and show that the positive charge in the protonation of the arylhydrazone is not concentrated on the heteroatom but rather is distributed over the various atoms of the molecule, primarily over the hydrogen atoms of the substituents, including the remote hydrogen atoms [13]. It may be assumed that the distribution of the charges in the intermediate protonated complex is close to the distribution in the postulated enehydrazine. The assumption of double protonation of arylhydrazones in strong acids, which was expressed almost simultaneously by several authors [11, 14], has also been discussed.

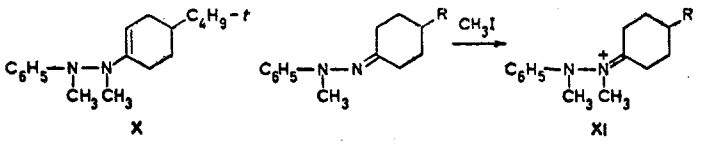
The possibility of protonation of the carbon atoms of the phenyl groups has not been previously taken into account, although form VIII can be regarded as an intermediate in the formation of enehydrazine structure IX.



In general, very little study has been devoted to the role of Lewis acids as catalysts. The formation of intermediate complexes has often been postulated or observed, and in one case an unstable BF_3 complex with an arylhydrazone was even isolated in the form of a heavy oil that was capable of spontaneous explosion [15]. Unstable $ZnCl_2$ and $CuCl_2$ complexes with cyclohexanone azine that are intermediates in the Piloty reaction, which is related to the Fischer synthesis, could be isolated and analyzed thoroughly, but they were converted to the corresponding octahydrocarbazole when they were heated [16].

Isomerization of Arylhydrazones. The most important intermediate — enehydrazine II — the formation of which is evidently the rate-determining step of the reaction, has not yet been detected. Calculations [17] show that hydrazone form I is more favorable than enehydrazine form II; protonation stabilizes it even more, but at the same time it evidently makes the I ⇄ II equilibrium more mobile [3, 18]. The concept of the intermediate role of enehydrazines is also presently being used successfully to explain the formation of isomeric indoles when acids of different strengths are used. However, the existence of an enehydrazine in the Fischer reaction has not yet been rigorously proved, and the cyclization of enehydrazines, which has been studied in particular by Sucrow and co-workers [19, 20], can be regarded only as analogous to the Fischer reaction. The reversibility of the I ⇄ II step at least seems extremely doubtful to us. It is known that the incorporation of substituents at both nitrogen atoms confers stability on the enehydrazine. Another enehydrazine of this type (X) was recently obtained by methylation of an N-methyl-phenylhydrazone under mild conditions [21].

This compound was converted to an indole under severe conditions in the presence of trifluoroacetic acid. It is interesting that the indolization of cyclohexanone N-methylphenylhydrazones in the presence of CH_3I has been carried out in the cuvette of an IR spectrometer, but no intermediates whatsoever were detected. The first step, which consists of the formation of hydrazone salt XI, probably determined the rate of the entire reaction, and the subsequent transformations proceed very rapidly.



X XI

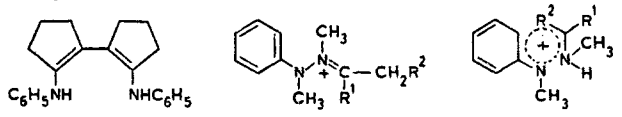
Second Step of the Reaction and the Concept of a [3,3]-Sigmatropic Shift. On the basis of a study of the electronic effects of substituents, which sometimes determine the direction of closing of the indole ring, the second step of the reaction has been previously assumed (for example, see [2]) to be electrophilic attack of the ene fragment on the benzene ring. Arguments that this step is a [3,3]-sigmatropic rearrangement and does not require catalysis have recently been adduced, particularly in papers by Grandberg and co-workers [3, 4]. Similar ideas have also been previously advanced, particularly in the case of thermal indolization [3]. In an earlier review [2] it is noted that this step in the reaction is one of the special cases of rearrangements of 1,6-conjugated systems. This is in agreement with the modern concepts of [3,3]-sigmatropic reactions. However, Grandberg assumes that the sigmatropic rearrangement approach to this step is not trivial, since it eliminates several problems such as, for example, why rearrangement in the para position of the benzene ring is never observed (because a sigmatropic [3,5] shift in the ground state is forbidden according to the supra-supra scheme). However, products of a p-benzidine rearrangement in the indole synthesis were nevertheless recently detected [22]; this had not been hitherto accomplished by anyone and is extremely interesting. In the investigated case para rearrangement is probably preferred (an indole, the ortho rearrangement product, was also formed but only in small amounts) because of steric hindrance. Unfortunately, there has recently been a tendency to underestimate the role of catalysis in proving the sigmatropic character of this step. Thus Grandberg [3] assumes that the role of acid catalysis reduces only to an increase in the rate of the I $\rightleftarrows$ II process. To confirm this [18], he converted an enehydrazine — 2-(N,N'-diacetyl-β-phenylhydrazino)-2-butene — to the corresponding indole under thermal conditions (by heating at 250°C for 3 h). However, this reaction may only demonstrate the severe conditions that are required for a reaction without catalysts. Unfortunately, here, as in most cases in which the so-called "noncatalytic" thermal conditions for indolization are used, the presence of impurities or contaminants with acidic character was not monitored, and this makes it impossible to confidently consider the conditions to be noncatalytic. For example, one can point to an earlier study [23] in which it is shown that treatment of aluminum oxide, which is the catalyst for indolization of acetaldehyde phenylhydrazone, with alkali sharply reduces the reaction rate.

The question as to whether cyclization of enehydrazines is subject to acid catalysis was posed specially in the paper cited above [21]. To resolve this problem, bases were added to the reaction mixture, and it was observed that indolization did not occur when a suspension of K_2CO_3 in DMF was used. In the presence of K_2CO_3 under conditions that could be regarded as thermal the cyclization of the enehydrazine proceeded at a rate that was slower by a factor of 10^6 than when acids were present. The authors also take into account the fact that admixed ammonium salts can catalyze the cyclization process by proton transfer and point out the difficulty involved in the removal of trace amounts of acids in thermal cyclization.

It has been concluded that step b in the synthesis of an indole is a rapid electrocyclic reaction of the N'-protonated enehydrazine. Moderately strong acids lead to this type of protonation, while strong acids protonate the enehydrazine fragment at the carbon atom, in which case an indole is not formed [21]. It has been shown in a small number of cases that electronic effects nevertheless determine the direction of cyclization in those cases in which there is no steric hindrance; however, if the latter is significant, it is precisely this factor that determines the ratio of cyclization products. Although the authors were unable to obtain intermediate diacetylated dienehydrazines similar to the compound synthesized by Suvorov [24] from the three ketazines that they used, XII was isolated in one case.

The authors are inclined to regard it as an intermediate, although it was not converted to a pyrrole. Indoles were obtained in low yields in the cyclization of the products of the reaction of 1,2-dimethyl-1-phenylhydrazine with ketones [21]; this result differs substantially from the results of the Fischer reaction with phenylhydrazones, the yields of indoles in which under mild conditions are close to quantitative.

In agreement with [21], it has been shown [25] that the use of acid increases the rate of indolization of N,N'-dimethyl-N-phenyl-N'-alkenylhydrazines by several orders of magnitude. The authors feel that the observed interrelationship between the structure and reactivity reflects the different tendencies of the starting enehydrazines to undergo protonation at the nitrogen and carbon atoms; the N-protonated isomer undergoes rapid [3,3]-sigmatropic rearrangement, which ultimately leads to an indole. A study of the protonation of enehydrazines [25] by means of NMR spectroscopy and other methods showed that they are protonated only at the nitrogen atom to give cation XIII:



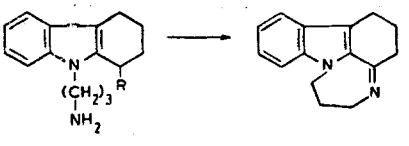
XII XIII XIV

It is possible that this form is capable of existing in equilibrium with the N-protonated particles. In the case of a comparison of the [3,3]-sigmatropic rearrangement of enehydrazines with the Claisen rearrangement of oximes one can note higher reactivities of the latter, which are apparently due to the difference in the energies of the bonds that are cleaved during the rearrangements. It is assumed that the positive charge in the six-membered transition state (XIV) is not localized on one nitrogen atom but rather is distributed over several centers.

On the basis of the facts obtained, it has been concluded [25] that the function of the acid in the Fischer indole synthesis consists not only in acceleration of the shift of the hydrazone → enehydrazine equilibrium but also in catalysis of the [3,3]-sigmatropic rearrangement of the latter to a dienoneimine.

Of great interest in the elucidation of this step (b) in the indolization reaction are studies by Kost and co-workers [26, 27], in which opening of the pyrazolidine ring at the N–N bond under the influence of acidic reagents and the formation of indoles from 1-aryl- and 1-aryl-2-acylpyrazolidines were described for the first time. The formation of enehydrazines in the condensation of 1-arylpyrazolidines with cyclohexanone was accomplished under very mild conditions without the addition of catalysts, while indolization occurred under the influence of acids.

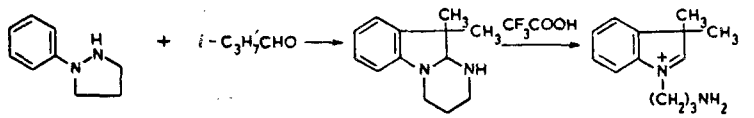
Similar products of condensation of 1-phenylpyrazolidines with ketones were subsequently used [28] in an effort to prevent splitting out of a second nitrogen atom during cyclization to indoles. The formation of intermediate XV, which was subsequently (when R = =O) converted to an indole derivative, was observed in this case:



XV

In contrast to [26, 27], Eberle and co-workers [28] feel that the [3,3]-sigmatropic reaction of the product of condensation of 1-phenylpyrazolidine with cyclohexanone does not require the presence of an acid, although CH_3COOH was used in the case of the cyclopentanone derivative.

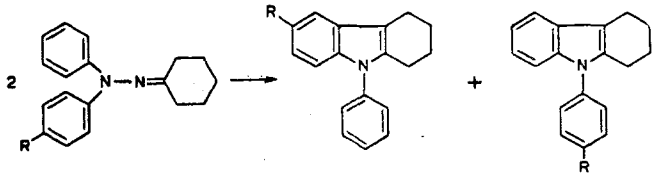
Similar intermediates that are stable in acidic media owing to the presence of substituents were also obtained from 1-phenylpyrazolidine and α-disubstituted aldehydes [29]. Indole derivative XVI was isolated in 86% yield when the starting reagents were refluxed in toluene without a catalyst with removal of the water by azeotropic distillation [29]. It can be converted to a hydrochloride but is protonated in the presence of CF_3COOH to give cation XVII:



XVI XVII

Thus it has been proved that the acid plays a substantial role in the step involving splitting out of the amino group. It must be noted that, in contrast to [26, 27], an intermediate enehydrazine was not isolated; instead, a mixture of the hydrazine and ketone was used, although in this case the probability of catalysis of the process by any impurities or components of the mixture is increased.

Grandberg and co-workers [30, 31] assume that they obtained direct proof of the occurrence of the Fischer reaction within the scheme of a [3,3]-sigmatropic rearrangement when they used competitive ring closing by p-substituted cyclohexanone diphenylhydrazones. They regard step b from the positions of the principle of retention of orbital symmetry, i.e., as a concerted process in which the six-membered transition state has the form of two upper occupied MO of the type ascribed to allyl radicals, and assume that in this case the effect of a substituent in the phenyl ring of the hydrazone should be low, and the possible isomers XIX and XX are therefore formed in close ratios:



XVIII XIX XX

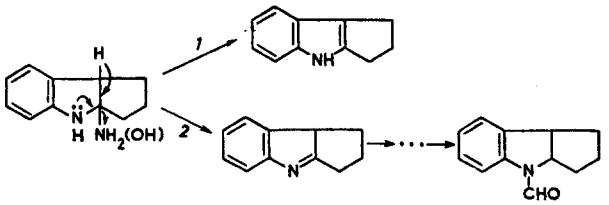
When R = OCH_3, XIX:XX is 4:1 or 3:1, as compared with 1:2 when R = Cl. The ratio depended somewhat on the strength of the acid. The authors feel that this ratio is close to 1:1, although the electronic nature of the substituent still evidently has a substantial effect on the direction of cyclization. Similar results were obtained by another group of investigators [32, 33] in the case of a somewhat larger number of test compounds, although they did not, as in [30, 31], draw categorical conclusions regarding the direct proof of a [3,3]-sigmatropic rearrangement; they pointed out that the substituents exert their electronic effect on the direction of ring closing. A similar conclusion was drawn [33] in the case of cyclization of 1-methyl-3-piperidone arylhydrazones, which form tetrahydrocarbinols with the participation of the ring methylene group that is farthest from the electron-acceptor groups. The Woodward–Hoffman principles have also been applied to the Fischer reaction in studies by other researchers in which they also studied the effect of substituents on the direction of indolization of 2-alkylcyclopentanone phenylhydrazones [34]. In the case of the use of the method of competitive cyclization of N'-substituted ethyl pyruvate diphenylhydrazones it was observed [35] that the cyclization proceeds mainly with the participation of that aromatic ring in which the electron density is higher, although under "sigmatropic" conditions, which is probably how the authors refer to thermal conditions, the effect of the substituent is smaller. Without denying the significance of a [3,3]-sigmatropic mechanism in the Fischer reaction even under acidic conditions, this group of investigators point out the electrophilic character of the process, which is confirmed by the fact that cyclization takes place in the ring that has a donor substituent. They also noted the important role of a catalyst in indolization. Thus $ZnCl_2$ proved to be more active than an alcohol solution of HCl.

In fact, catalysis by acids cannot serve as an argument either for or against a sigmatropic reaction mechanism.

As an example from a somewhat different area one can point out a study [36] in which thermal [3,3]- and [1,5]-sigmatropic rearrangements of pyrazolenines and isopyrazoles to pyrazoles were described, and it was pointed out that mild Lewis acids can catalyze them.

All of these facts indicate that the concept of a [3,3]-sigmatropic shift in the Fischer reaction nevertheless is too general in character and does not exhaust all of the complexity of the cyclic process in step b. It is very interesting that the order of the Fischer reaction in acid was found to have a fractional value (1.28) [37], i.e., some intermediate steps also have an effect in addition to protonation.

Final Steps of the Transformation. Much less attention has been recently directed to the previously investigated (in greater detail) [2] subsequent steps of the Fischer reaction. Of the studies in this direction one can adduce, for example, a study [38] in which it is shown that 1-acetyl-2-(o-toluidinyl)indoline splits out toluidine to give 1-acetylindole under very mild conditions (when it is passed through a column filled with Al_2O_3 or silica gel). The results obtained in this case confirm the conclusion [39] that the amide nitrogen atom can add to the imine group without prior conversion to an imine, as reported in [24]. Formylindoline XXI was unexpectedly isolated in the indolization of cyclopentanone phenylhydrazone [35] in anhydrous HCOOH; this is also of interest in the light of modern concepts regarding the mechanism of indolization and is in agreement with pathway 2 in the scheme:



XXI

Catalysis in the Indolization Reaction

From the preceding sections one can draw a conclusion regarding the role of protic acids in the Fischer reaction. However, special attention should be directed to the problems associated with catalysis by Lewis acids, the specific character of which has not yet been adequately studied. With respect to the role of catalysts, one must nevertheless emphasize that: 1) thermal indolization frequently leads to indoles in low yields, and sometimes they are not obtained at all, so that in practice catalytic conditions are, as a rule, used; 2) the mechanism of thermal indolization, to which very little study has been devoted, differs substantially from the mechanism of the catalytic reaction. One must also bear in mind the possibility of the effect of acid impurities and, probably, other factors. Thus, for example, 2-phenylcyclopent-2-en-1-one N-methylphenylhydrazone did not undergo thermal cyclization [40]. In this connection, the question arises: cannot a sufficiently acidic proton of the NH group of the hydrazone sometimes act as the indolization catalyst (autocatalysis)? Although cross products were never obtained in the thermal indolization of two hydrazones [40], a radical mechanism cannot be excluded from consideration, since the radicals may exist briefly in a solvent cage. In fact, it is difficult to imagine that the mechanism of this reaction would be unchanged in the light of the pronounced variety of conditions under which it is realized (here we have in mind the enormous range of temperature, the different natures of the catalysts, and other factors). It is also possible that catalysis can also eliminate the limitations with respect to symmetry in some cases. Of course, a study of Lewis acids as catalysts and, particularly, a comparison of them are difficult, especially since catalysis by Lewis acids may be associated with the presence of impurities [41]. Although instances in which the Fischer reaction proceeds in the presence of alkaline agents have also been described, they nevertheless should not be considered to be catalysts in this reaction. The reaction more likely proceeds "despite them." Bases usually promote cleavage of the N–N bond. Thus, for example, under the influence of alkali-metal alkoxides, cyclohexanone 4-pyridylhydrazone gives, in addition to the normal indolization product, products of cleavage of the N–N bond in high yields [42]. However, 1,2,3,4-tetrahydrocarbazole was obtained in high yield when cyclohexanone phenylhydrazone was heated in the presence of sodium ethoxide [43]. In studies by Yakhontov and Marshalkin it was noted that the indolization of pyridylhydrazones nevertheless proceeds under more severe conditions and gives the products in lower yields than in the case of arylhydrazones and, in contrast to the latter, does not take place in the presence of catalytic amounts of Lewis acids [43]. Zinc chloride was found to be the best catalyst for the indolization of pyridylhydrazones, although precisely thermal conditions have been proposed for hydrazones of this type, which are sensitive to acids [44].

It has previously been noted that a number of pyridylhydrazones could not be "indolized" under thermal conditions, much to the surprise of Kelly and Parrick [45]. They also noted that the reaction proceeds at lower temperatures in the presence of $ZnCl_2$ than under thermal conditions.

Thus a study of the transition state in the form of a complex of the hydrazones with the catalyst, which makes it possible to ascertain the existence of transformation in the first step of the Fischer reaction, holds great promise. The assumption of a diprotonated form of the arylhydrazones in strongly acidic media makes it possible to dispense with the concept of tautomerization of the hydrazone to an enehydrazine. From the point of view of application, elucidation of the structure of the transition complex would make it possible to purposefully select the catalysts and control the course of the reaction.

A difference in the transition states in the coordination of Lewis acids and a proton and its effect on the ratio of the isomeric indoles because of different degrees of steric hindrance have been indicated in, for example, [46]. The problem of the status of research dealing with the steric factors was set forth in a review by Grandberg and Sorokin [4].

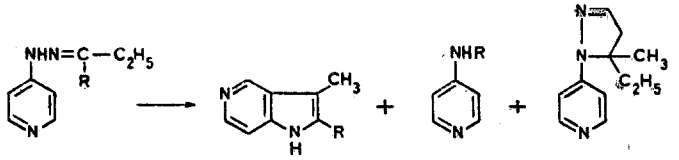
The following fact can be presented to illustrate the effect of the nature of various Lewis acids on the trend of the reaction: acetone phenylhydrazone reacts with $ZnCl_2$ to give primarily indole, whereas it gives pyrazole with Cu_2Cl_2 and $CdCl_2$; the yield of indole is low with protic acids (because of resinification), and no indole at all is formed with BF_3. The indolization of acetaldehyde phenylhydrazone, which was not accomplished for a long time with any of the previously known catalysts or under thermal conditions, serves as another remarkable example of the effect of the nature of the catalyst. This reaction had been considered to be one of the solidly established exceptions, until it was realized on modified aluminum oxide [23, 47, 48]; it was recently accomplished [49] with a classical Fischer catalyst ($ZnCl_2$) with rapid removal of the products from the reaction mixture with a stream of an inert gas. In [49] it was assumed that the failures of the predecessors are associated with the difficulty involved in the isolation of the indole from the reaction mixture because of its resinification. However, this is probably not the only reason. It was shown in [9] that acetaldehyde phenylhydrazone is capable of an "anomalous" transformation to give pyrazoline and aniline. At least twice the amount of aniline as that which might have been expected only for the side reaction of aminonitrile cleavage was also detected in [49]. The possibility that pyrazoline is also formed in the thermal reaction of acetaldehyde phenylhydrazone is not excluded [40]. Thus a nonbasic product (C_6H_6N, n_D^{21} 1.5998), the structure of which was not accurately established, is possibly 1-phenyl-5-methylpyrazoline containing a small amount of indole (from ν_{NH} in the IR spectrum and a positive test for indole), since we obtained 1-phenyl-5-methylpyrazoline (C_5H_6N, n_D^{18} 1.6039) as a result of a similar reaction with Cu_2Cl_2.

Anomalies in the Fischer Reaction

The anomalies that were uncovered during a study of the indolization reaction can be arbitrarily divided into two groups.

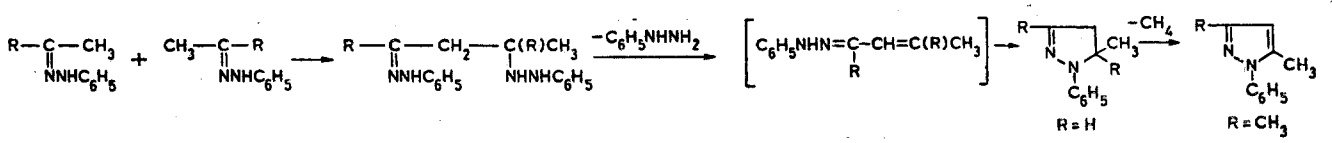
Anomalies of the First Type. Reactions that compete with "normal" indolization and lead to the formation of nitriles, amines, pyrazolines, pyrazoles, and other nitrogen compounds of nonindole character are a consequence of these anomalies. Their occurrence is due to the dual reactivity of arylhydrazones and depends on the reaction conditions.

As we have already stated above, these anomalies were first observed by A. E. Arbuzov and include, in particular, aminonitrile cleavage, which has become an independent branch of the chemistry of hydrazones (for example, see [7]) and will not be examined here. A less-studied pathway associated with the formation of nitrogen heterocycles with nonindole character (pyrazoles and pyrazolines) has also been described in a monograph [7]. Among the recent studies within this area one can point out a study of the cyclization of propionaldehyde and methyl ethyl ketone 4-pyridylhydrazones, which form 3-methyl- and 2,3-dimethyl-5-azaindoles, 4-aminopyridine, 4-ethylaminopyridine, and 1-(4-pyridyl)-3,5-diethyl-5-methylpyrazoline [50]; the direction of the process and the ratio of the indicated compounds depend substantially on the nature of the catalysts. Only the corresponding azaindoles were previously obtained under thermal conditions "in the absence of catalysts" (the authors' quotation marks). The relative activities of the catalysts, which were previously studied [51] in the case of the reaction of cyclohexanone 4-pyridylhydrazone, were basically also retained for these compounds. The highest yields of "normal" indoles (XXII) were observed with $ZnCl_2$; on passing to p-toluenesulfonic acid, polyphosphoric and sulfosalicylic acids, and Cu_2Cl_2 the yields of side products increased regularly. The principal products when C_2H_5ONa was used was 4-ethylaminopyridine, i.e., this alkaline agent did not catalyze indolization.



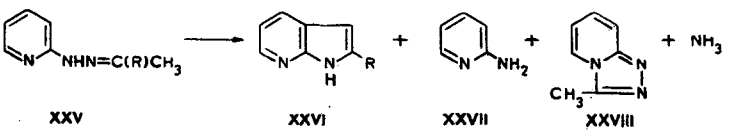
XXII, XXIII R = H, CH_3, C_2H_5

The formation of anomalous pyrazolines (XXIV) in the pyridylhydrazone series was previously observed by these authors [51], although we were the first [8, 9] to prove the formation of pyrazolines and their aromatization products — pyrazoles — in the Fischer reaction as a competitive pathway in the arylhydrazone series. The following mechanism of the "anomalous" reaction, some steps of which could be experimentally confirmed [9], has been proposed:



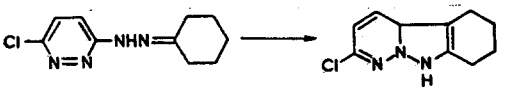
The "anomalous" acetone 2,6-dichloro-4-pyridylhydrazone, 1-(2,6-dichloro-4-pyridyl)-5-methylpyrazoline, and 2,6-dichloro-4-aminopyridine were also obtained from acetaldehyde (2,6-dichloro-4-pyridyl)hydrazone in the presence of $ZnCl_2$ [44]. The authors explain the formation of the acetone derivative by alkylation with methyl radicals formed at high temperatures.

The use of yet another relatively new catalyst (Al_2O_3) in the reaction of acetone and acetaldehyde 2-pyridylhydrazones (XXV), which do not form indoles in the presence of acids, also leads to certain anomalies [52]. In addition to 7-azaindoles XXVI, 2-aminopyridine (XXVII) and the product of cyclization at the pyridine nitrogen atom — 3-methyl-5-triazolo-[4,3-a]pyridine (XXVIII) — were obtained in this case:

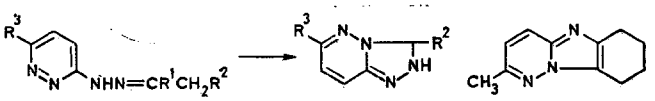


XXV, XXVI R = H, CH_3

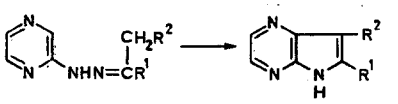
The mechanism of this reaction was not discussed. Similar anomalies were also found to be characteristic for other N-hetarylhydrazones, for example, for cyclohexanone 5-chloro-2-pyridazinylhydrazone [53], which undergoes cyclization at the azine nitrogen atom under very severe conditions ($ZnCl_2$, 250-260°C) to give a pyridazino[2,3-b]indazole system:



In the case of the thermal reaction of 6-methyl-3-pyridazinylhydrazones of the XXIX type [54], one observes splitting out of the elements of a hydrocarbon (probably R'H) instead of ammonia evolution, and 3-substituted 6-methyl-5-triazolo[4,3-b]pyridazines (XXX) were obtained instead of the expected pyrrolo[2,3-c]pyridazines (XXXI):

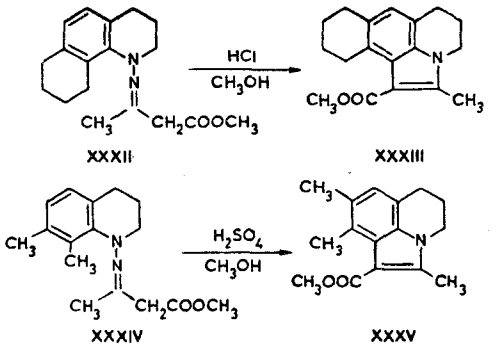


6,7,8,9-Tetrahydro-2-methylpyridazino[2,3-a]benzimidazole (XXXI) was also obtained in the case of cyclization of hydrazone XXIX [$RR^1R^2 = (CH_2)_4$, $R^3 = CH_3$]; however, the mechanism of these transformations also was not discussed. Substituted 5H-pyrrolo[2,3-b]pyrazines were formed from pyrazinylhydrazones under similar conditions [55]:

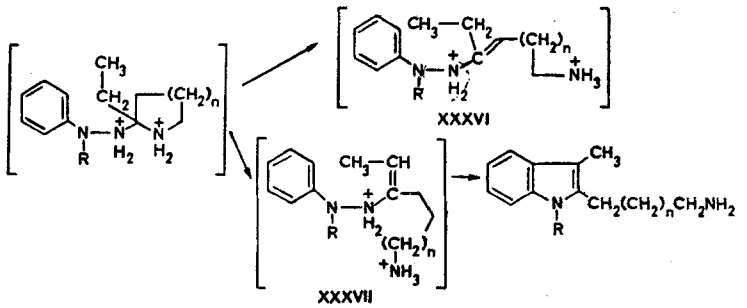


The presence of yet another nitrogen atom in these cyclic systems hinders cyclization even more as compared with pyridine derivatives.

Anomalies of the Second Type. The second type of anomaly in the Fischer reaction is associated with the production of indoles with unexpected structures. Their formation is not explained by the classical scheme of this reaction but can be understood after the scheme is modified somewhat. It is due mainly to migration or splitting out of substituents in the phenyl ring of the starting arylhydrazine. The study of anomalies of this type is hindered by the fact that, as known for quite some time, migration is frequently observed in the resulting indoles. Of the latter studies, which deal with a similar migration of substituents, one should particularly note papers [56, 57] in which [1,3] migration and even the very rare [1,4] migration of a methyl group during indolization are described. The mechanism of this reaction is not a [1,3]- or [1,4]-sigmatropic shift but rather consists of two successive [1,2] shifts of the methyl group, i.e., it is similar to the mechanism proposed for cyclohexanone mesitylhydrazone [58]. It has been reported [59, 60] that hydrazone XXXII gives indole XXXIII in the Fischer reaction and that indole XXXV is similarly formed from hydrazone XXXIV as a result of a double 1,2 shift of the methyl group in the intermediate dienoneimine.



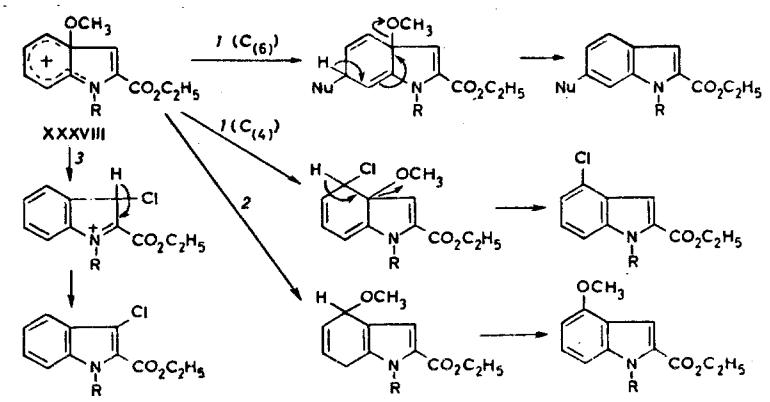
The mechanism of this rearrangement has also been discussed by other authors [62], who present evidence that the apparent [1,4] migration of the methyl group actually proceeds through a number of [1,2] shifts. It has been observed [63] that migration of the alkyl substituents occurs in addition to the previously observed dealkylation and ring expansion in the case of N-, 2-, and 3-methylindoles and N- and 3-benzylindoles under severe conditions. It was found that 2- and 3-substituted indoles exist in equilibrium at high temperatures. Benzylindoles are more reactive than methyl-substituted indoles; this is in agreement with the radical character of the transition states that is proposed by the authors. Rearrangement of 3-alkyl- and 3-arylindoles to the 2 isomers proceeds particularly readily but not under thermal conditions; the interesting point here is that the rearrangement does take place under the conditions of the Fischer reaction in the presence of acids [64]. The investigated radicals are arranged in the order $CH_3 < C(CH_3)_3 < CH_2C_6H_5 < C_6H_5$ with respect to the ease of migration; this order coincides with the order of stabilities of the corresponding intermediate cations. Since cross products were not formed, the mechanism of this transformation, in contrast to thermal rearrangement, should be considered to be an intramolecular mechanism. Nevertheless, the thermal rearrangement of benzaldehyde, acetophenone, propiophenone, and benzophenone phenylhydrazones most likely proceeds via a "four-center" rather than a radical mechanism [65]. The rearrangement of 2-acylindoles to the 3 isomers has also been described [66]. When 2-substituted indoles were isolated instead of the expected 3-phosindoles in the Fischer reaction with acylhydrazines and phosphorylated acetals in the presence of $ZnCl_2$, this was explained [67] by intramolecular rearrangement of the initially formed "normal" products, since the 2 isomers were obtained when the 3 isomers were heated with $ZnCl_2$. The "anomalous" 3-methyl-2-indolylalkylamines rather than the 2-ethylindolylalkylamines were formed in the reaction of 2-ethyl-Δ^1-pyrroline and 2-ethyl-Δ^1-piperideine with arylhydrazine hydrochlorides [68]. This fact was explained by isomerization of the intermediate hydrazone with the participation of the ethyl group to enehydrazine XXXVII rather than to XXXVI (only one compound was obtained):



XXXVI

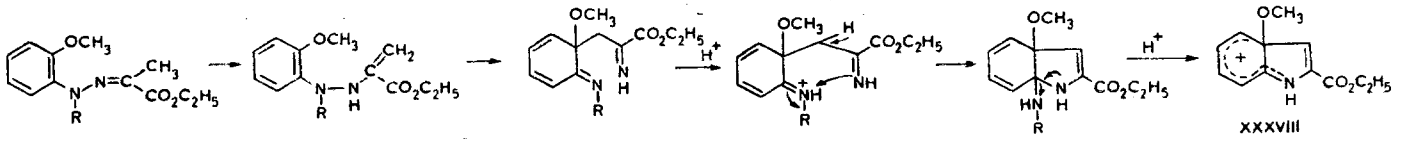
XXXVII

The greatest progress in the study of this second group of anomalies in the Fischer reaction was recently made by Japanese researchers. In the case of indolization of methoxyphenylhydrazones they detected substances that they classified [69] as products corresponding to the so-called ortho-$C_{(5)}$ anomalous rearrangement (5-substituted indoles) and ortho-$C_{(6)}$ anomalous rearrangement (6-substituted indoles). For example, one expected and seven "anomalous" indoles were obtained from ethyl pyruvate 2-methoxyphenylhydrazone in the presence of protic acids [70]. In order to explain the latter, it was necessary to somewhat modify the classical scheme of the indolization reaction. A special role in the new scheme was assigned to the intermediate key cation (XXXVIII), which is capable of various changes: first, addition to the nucleophilic agent present in the reaction mixture (Cl^-, C_2H_5OH, indoles, etc.) to the C_6 or C_4 atom; second, 1,2 migration of the CH_3O group with subsequent intramolecular stabilization; third, replacement of the CH_3O group in the 3 position by a nucleophile:



XXXVIII

In an investigation of the various factors that determine the direction of these reactions it was concluded that it does not depend, for example, on the nature of the solvent and that the most important factors are the reagent used and the electron density in the benzene ring [71]. The authors assume that o-substituted phenylhydrazones with a high electron density in the benzene ring are capable of undergoing cyclization to 5-substituted rather than 6-substituted indoles. Both protic acids and Lewis acids were used at catalysts for the anomalous cyclization, but the results differ somewhat for these types of acids. The nucleophilicity of the nucleophiles present in the reaction mixture also affects the direction of the reaction [71].



XXXVIII

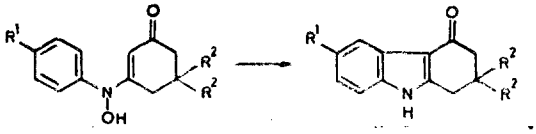
It has also been noted [72] that the formation of a complex with $ZnCl_2$ accelerates replacement of the methoxy group in the 5 position of the key cation (XXXVIII) and that this complex is readily converted to 5-chloroindole via the well-known scheme [58]. However, data that would make it possible to ascertain which mechanism of migration of the substituent attached to $C_{(5)}$ of the indole ring via a suprafacial [1,3] shift is operative — a concerted or ionic mechanism — have not yet been obtained. The above pathway for the formation of intermediate carbonium ion XXXVIII is assumed in [70].

As a result of the reaction of ethyl pyruvate 2-methoxyphenylhydrazone with p-toluenesulfonic acid, which was selected because of its low nucleophilicity (to prevent reaction

with the XXXVIII cation), Ishii and co-workers [71] obtained either an indole with an active methylene group at $C_{(6)}$ or a new 3,6-diindolyl compound in the presence of the enolized compounds. In addition to the dimer that was evidently previously obtained by Gennon, they isolated yet another dimer, thereby expanding the scope of the ortho-$C_{(6)}$ anomalous Fischer reaction [71]. The formation of a 4-aminoindole derivative in the anomalous reaction is explained [69] by means of an intermediate dienoneimine, which apparently could not be isolated, since it was lost in the process of separation of the products. Incidentally, the authors note in their paper that there have been many attempts (some successful) to obtain chemical proof for the existence of an intermediate dienoneimine in the Robinson scheme, but no one has yet succeeded in the preparation of an intermediate enehydrazine.

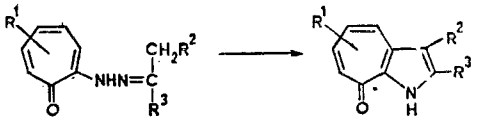
Investigations of Related Reactions

Several reactions related to Fischer indolization have recently been observed, and advances have been made in the investigation of similar previously discovered reactions. The research in this area is also interesting in that it makes it possible to shed light on some problems in the mechanism of the indolization of arylhydrazones in the opinion of, for example, Okamoto and Shudo [73], who studied the cyclization of adducts of arylhydroxylamines and 1,3-diones to indole derivatives under the influence of acids:

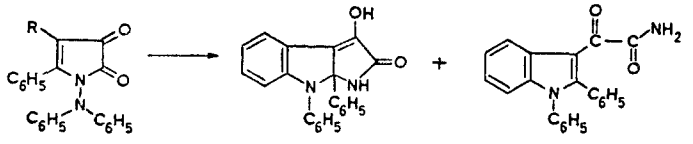


A similar transformation was accomplished with N-(p-tolyl)hydroxylamine and ethyl acetate, as a result of which 2,5-dimethyl-3-ethoxycarbonylindole, N-(p-tolyl)-2,4-dimethyl-3,5-diethoxycarbonylpyrrole, and p-azoxytoluene were obtained [74]. Other investigated N-arylhydroxylamines behaved similarly, but the yields of reaction products were low.

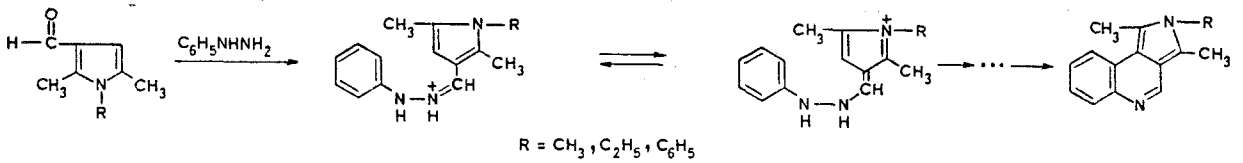
It has been found that tropone analogs of phenylhydrazones [75] are also capable of a reaction of the Fischer indolization type under the influence of dilute sulfuric or polyphosphoric acid; in this case the corresponding derivative for acetaldehyde hydrazone was also obtained, although in low yield:



The mechanism of the synthesis of tryptamines [3, 37] — a reaction that is related to the indole synthesis — has also been subjected to a detailed investigation and it has been shown that the β atom of the hydrazine migrates to the side chain, while the α-nitrogen atom is incorporated in the indole ring. This process can occur in neutral media and does not require acid catalysis, although the proposed reaction scheme includes intermediate steps involving the formation of an enehydrazine and 1,6 addition. The cyclization of 1-diphenylamino-2,3-dihydropyrrole-2,3-diones to pyrrolo[2,3-b]indoles and 3-indolylglyoxylamides, which also displayed features similar to those of the Fischer reaction, has also been accomplished recently [76]:



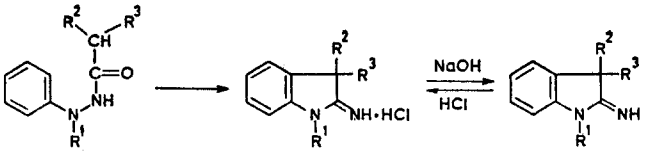
It is assumed [77] that the formation of 2H-pyrrolo[3,4-c]quinolines from phenylhydrazones of substituted 3-formylpyrroles (the intermediate hydrazones were not isolated because of their instability) is a [3,7]-sigmatropic process that takes place through the protonated form of the arylhydrazones and an intermediate that forms a pyrroloquinoline system after splitting out ammonia:



R = CH_3, C_2H_5, C_6H_5

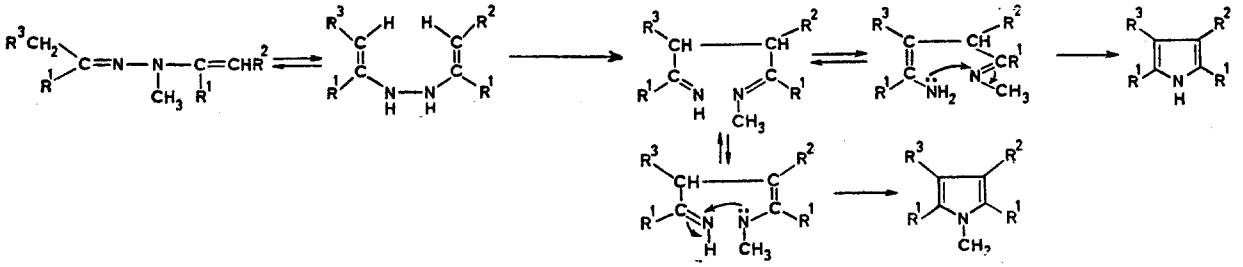
Although the individual steps of the reaction have not been studied, it may be assumed that its mechanism should display features similar to those of the mechanism of the formation of indoles from arylhydrazones.

Examples of other reactions of this type can also be found in papers by Kost and co-workers; of these, one should point out the synthesis of 2-aminoindoles under the influence of $POCl_3$ and similar agents on β-acylhydrazones [27, 78-80]. It is interesting that tetrahydroquinoline and cyclohexadienoneimine derivatives were obtained in the, as it were, analogous cyclization of N-acyl derivatives of 2,6-disubstituted arylhydrazides in the presence of PCl_5. The mechanism, which may explain the formation of these reaction products, is similar to the mechanism proposed by Kost for the formation of aminoindoles, at least in its initial steps. The synthesis of 3,3-disubstituted 2-iminoindoles from 1-phenyl-2-acylhydrazines and 1-phenyl-2-acylpyrazolidines, which are cyclic analogs of arylhydrazines, has also been accomplished [80]:

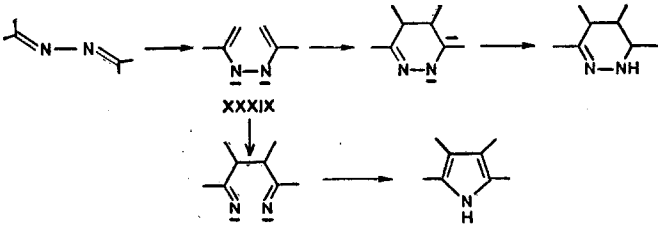


The cyclization of 1-arylthiosemicarbazides under the influence of polyphosphoric acid (the so-called Hugershoff reaction) is analogous to the Fischer reaction [82].

Several rearrangements that display features similar to those of one of the modifications of the Fischer synthesis — the Piloty reaction — have recently been described. Thus Baumes and co-workers [83] are continuing their study of the cyclization of the products of condensation of N-methylhydrazones with enolized ketones, a reaction that is similar to the Piloty reaction. For reactions catalyzed by $TiCl_4$ or molecular sieves they have proposed a mechanism that resembles the corresponding scheme for the transformation of azines [84]:



The rearrangement of the ketazine dianion, which opens up a new pathway for the synthesis of pyrroles and tetrahydropyridazines, was described in [85]. It can be depicted schematically as



In the opinion of Yoshida and co-workers [85], intermediate dianion XXXIX is most likely formed by a [3,3]-sigmatropic rearrangement. The direction of the reaction depends on the nature of the substituents in the starting azine. However, this new reaction differs appreciably from the Piloty synthesis, which proceeds in acidic media, since it takes place in the presence of an alkaline agent — lithium diisopropylamide in tetrahydrofuran.

Grandberg and co-workers [3, 4] have attempted to extend the concepts of sigmatropic rearrangement to a number of reactions related to the Fischer indole synthesis: for example, the preparation of pyrroles from oxime ethers, the Brunner synthesis, the Piloty reaction, the Kost rearrangement of β-acylhydrazines to α-aminoindoles, the synthesis of tryptamines from γ-halo carbonyl compounds, etc. In fact, the common character of the mechanism of these reactions is sufficiently distinctly traced in the schemes presented above, but each specific case nevertheless requires experimental evidence. Thus it has been assumed that

the p-benzidine rearrangement also belongs to this series of reactions, although it was recently shown [86] that in some cases it may proceed through intermediate cation radicals.

In conclusion, it should once again be emphasized that studies of transformations related to the Fischer reaction and of various anomalies and new forms of catalysts, in addition to their purely theoretical interest due to the complexity of the mechanism of this reaction, are also necessary from a practical point of view, since a rational and purposeful approach to the synthesis of numerous derivatives not only of the indole series but also of other valuable heterocycles is possible only on the basis of such research.

We sincerely thank Professor A. N. Kost for his interest and valuable advice in the writing of this review.

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POLAROGRAPHIC STUDY OF FLAVONOIDS.

FLAVONE, FLAVONOL, AND 3-CHLOROFLAVONE

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The polarographic behavior of flavone and its 3-hydroxy and 3-chloro derivatives on a dropping mercury electrode was studied. It is shown that the investigated compounds in solution are represented by two polarographically active forms in equilibrium, one of which is reduced primarily in acidic media, the other of which is reduced primarily in neutral and alkaline media.

A number of papers on the use of polarography for flavonoid compounds have been published [1-7]. However, most of them [1, 2, 4, 6] are devoted to the application of the polarographic method for quantitative analytical purposes, and the mechanism of electrochemical reduction is not discussed in them. There is no commonly shared opinion with respect to the mechanism of the reduction of flavonoids in the literature [3, 7]. The authors investigated polyhydroxylated natural flavonoids (for example, quercitin and morin). In this case, because of the complexity of the structure, it was difficult to establish an interrelationship between the electrochemical behavior and the electronic structures of the flavonoids.

In this connection we began a study of the polarographic reduction of flavonoids in the case of a systematic series of mono-, di-, and polysubstituted derivatives with various electrophilic and nucleophilic substituents.

The polarographic properties of flavone and two of its derivatives with substituents in the pyrone fragment (3-hydroxy- and 3-chloroflavones) are examined in the present paper.

Flavone

It is apparent from Fig. 1 that the reduction of flavone in acidic media (up to pH 7.5) takes place in one step. The $E_{1/2}$ value of the corresponding polarographic wave is shifted to the more negative region as the pH of the medium increases (Fig. 2). The diffusion character of the wave for the reduction of flavone in acidic media provides evidence for the possibility of the application of the Ilkovic equation for the determination of the number of electrons consumed per molecule of depolarizer. This theoretical calculation and the millicoulometric determination of the number of electrons make it possible to conclude that the reduction of flavone in acidic media is a one-electron process. However, the shift of the half-wave potential to the negative region as the pH of the medium increases indicates participation of protons in the electrochemical process.

In alkaline media (pH > 7.5) the first reduction wave of flavone decreases rapidly, but a second less negative wave appears and increases. The overall height of both waves at pH 10 considerably exceeds the current of a one-electron process (Fig. 1). This decrease in the first wave, which resembles a dissociation curve, may correspond to the presence in weakly alkaline media of two forms of flavone molecules. In this case the reduction

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