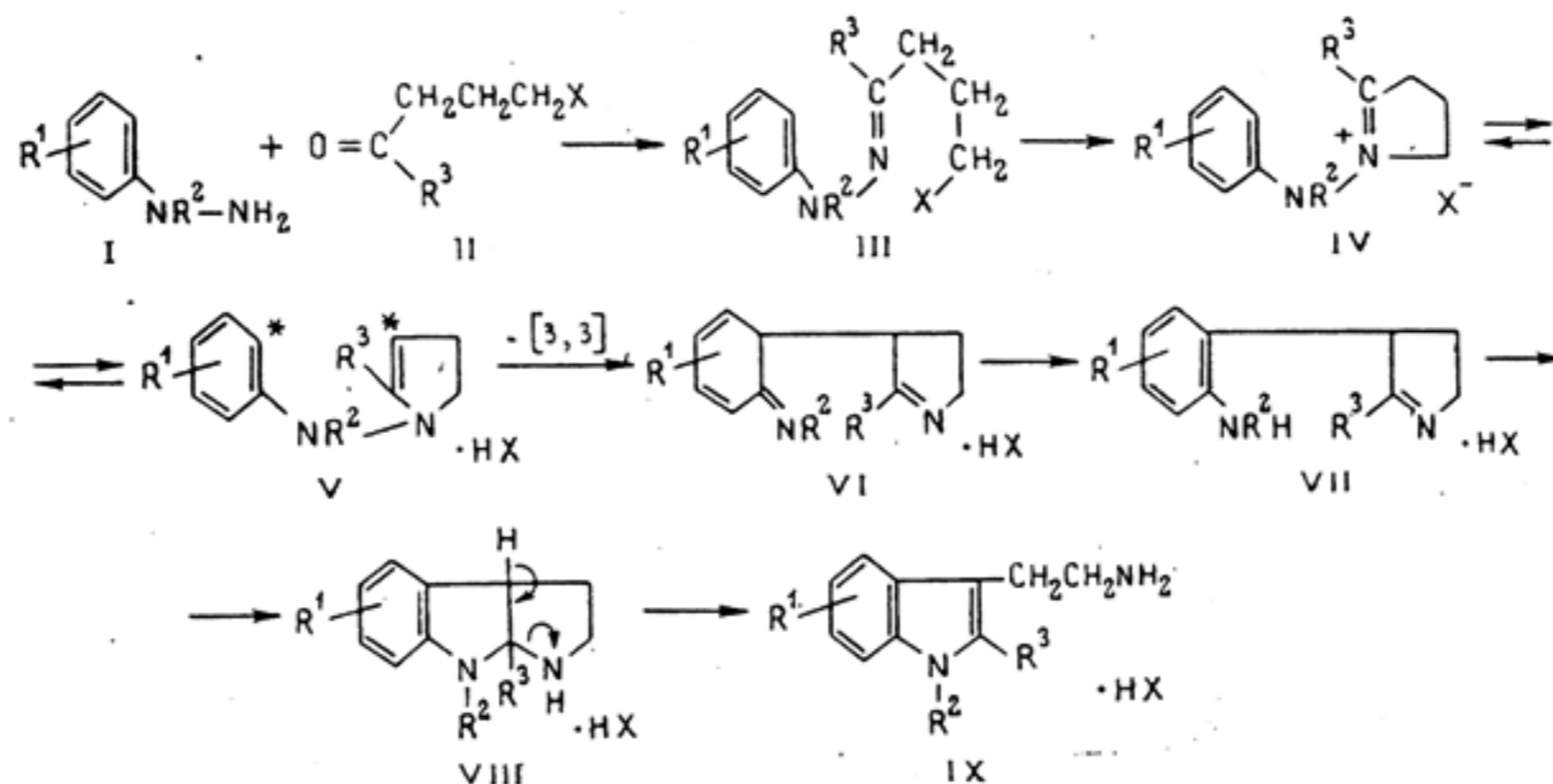


A considerable range of papers on the synthesis of biogenic amines of the indole series and related structures from aryl- and heteroarylhydrazines and  $\gamma$ - or  $\delta$ -halogenocarbonyl compounds are discussed systematically in the article. The reaction mechanism is investigated in detail by the isolation of all the intermediate products, the data from isotopic analysis, and kinetic measurements. The generality of the approach made it possible to assign these reactions to the special case of the well-known Fischer synthesis of indoles and at the same time to solve the problem of the principal stage of this synthesis (formation of the C-C bond), which it is proposed to treat as a sigmatropic [3,3]-rearrangement.

In order to obtain 1-phenyl-1,4,5,6-tetrahydropyridazine we brought  $\gamma$ -chlorobutyraldehyde into reaction with phenylhydrazine (80°C, methanol, 8 h). However, it was possible fairly soon to establish that the compound obtained with a high yield was not tetrahydropyridazine but tryptamine [1, 2]. From 1966 we have investigated this reaction very extensively, and this has led to the development of simple methods for the synthesis of many biogenic amines and other related structures of the indole series. Detailed investigation of the mechanism of the process (see below) has made it possible not only to elucidate the details of this extremely interesting reaction but also to transfer the results to the Fischer synthesis of indoles.

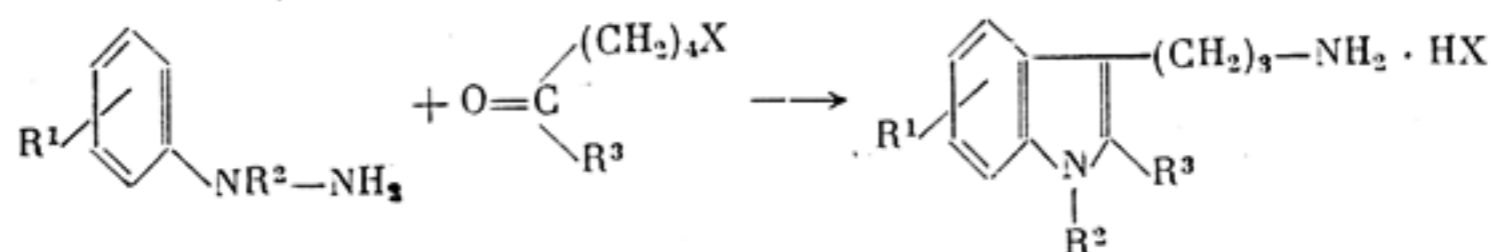
Even in one of the first papers [3] we proposed a scheme for the process (given below) which closely explains nearly all the experimental facts. It was subsequently confirmed in detail during investigation of the mechanism [4, 5] and proved extremely promising for the development of researches in this region. According to this scheme, the arylhydrazine (I) with the  $\gamma$ -halogenocarbonyl compound (II) forms the hydrazone (III), which undergoes cyclization to the N-anilinopyrrolone (IV). The latter is in equilibrium with the enamine (V). By the mechanism of a sigmatropic [3,3]-shift with cleavage of the N-N bond and the formation of a new C-C bond the enamine (V) is converted into the unstable structure (VI), stabilized to the ortho-substituted aniline (VII), which forms derivatives of eserine (VIII) through addition of the NHR group at the active C=N bond. The eserine (VIII) is then stabilized by  $\beta$ -elimination with the ejection of a proton and closure of the pyrrolidine ring into the aromatic structure of the tryptamine salt (IX).



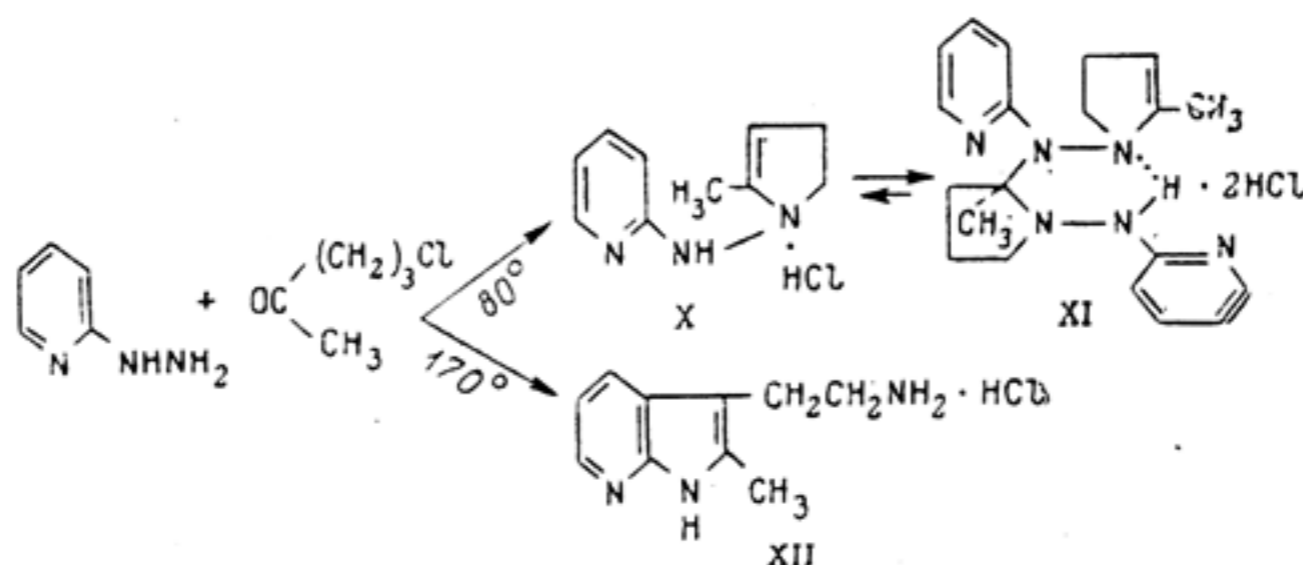
K. A. Timiryazev Moscow Agricultural Academy. Translated from Zhurnal Organicheskoi Khimii, Vol. 19, No. 11, pp. 2439-2452, November, 1983. Original article submitted December 17, 1982.

**Tryptamines.** Variation of the substituents in the arylhydrazine ring or at the  $\alpha$ -nitrogen atom and the use of  $\gamma$ -chloro(bromo, iodo)carbonyl compounds and also esterification of the  $\gamma$ -hydroxycarbonyl compounds with toluenesulfonic acids did not give rise to any complications in the realization of the reaction. The yields varied but did not fall below 50% and in most cases were greater than 70% [3, 6-13].

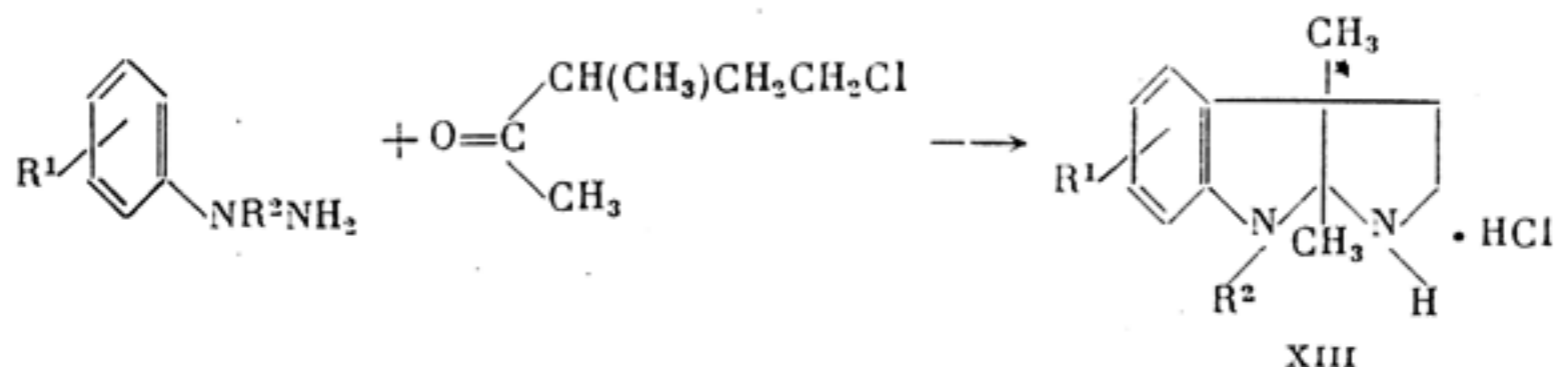
**Homotryptamines.** The use of  $\delta$ -halogeno carbon compounds was also successful. In all cases 3-( $\gamma$ -aminopropyl)indoles (homotryptamines) were formed smoothly [9, 12-14].



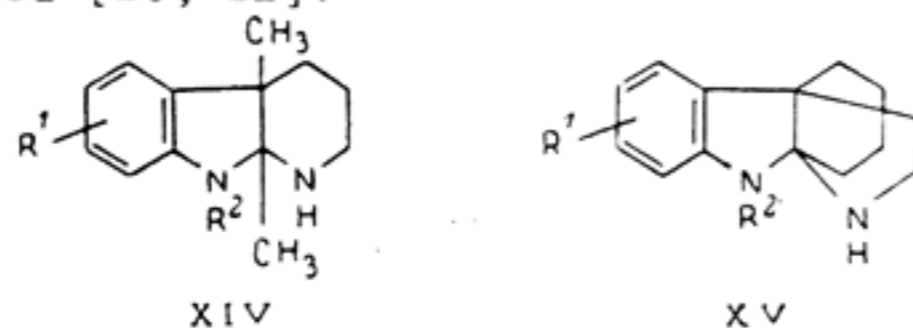
**Azatryptamines.** The use of 2-pyridylhydrazine in this reaction under normal conditions ( $80^{\circ}\text{C}$ ) led to the formation of the pyridylaminopyrrole (X) [similar to the intermediate structure (V) in the general scheme], which existed in the form of the stable dimer (XI). Only increase in the temperature to  $170^{\circ}\text{C}$  led to the azatryptamine (XII) [15, 16].



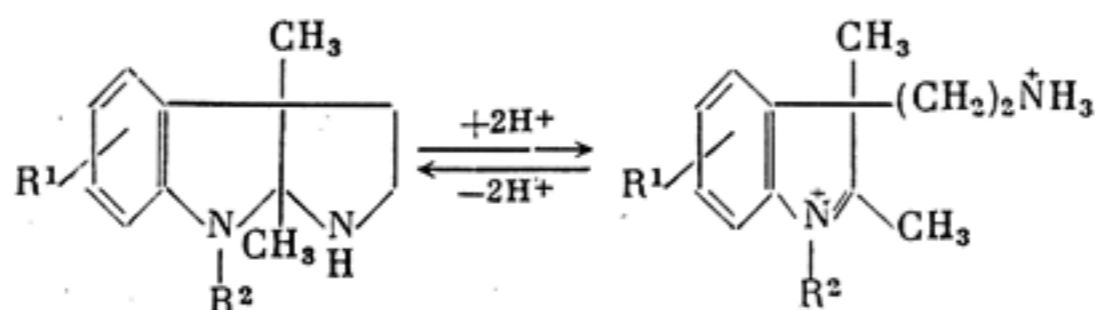
**Eserine Structures.** The use of  $\alpha$ -alkyl-substituted  $\gamma$ -halogeno ketones stopped the process at the production of the eserine structures (XIII) [of type (VIII) in the general scheme], since in this case the system could not be stabilized with the formation of the indole [17-20].



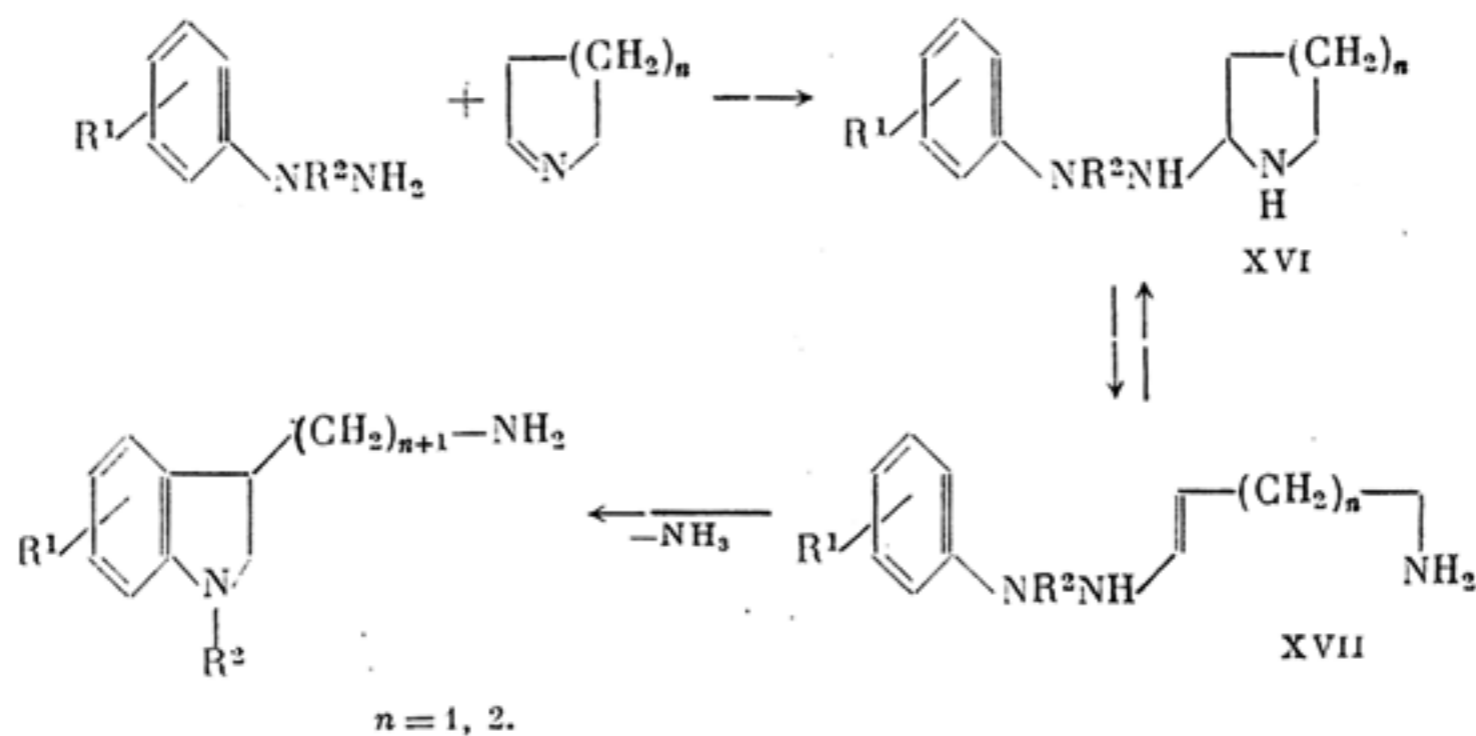
**Homeseroline Structures (XIV).** Homoeseroline structures (XIV) [21] and derivatives of echiboline (XV) were also obtained readily and with good yields when the corresponding halogenocarbonyl compounds were used [20, 21].



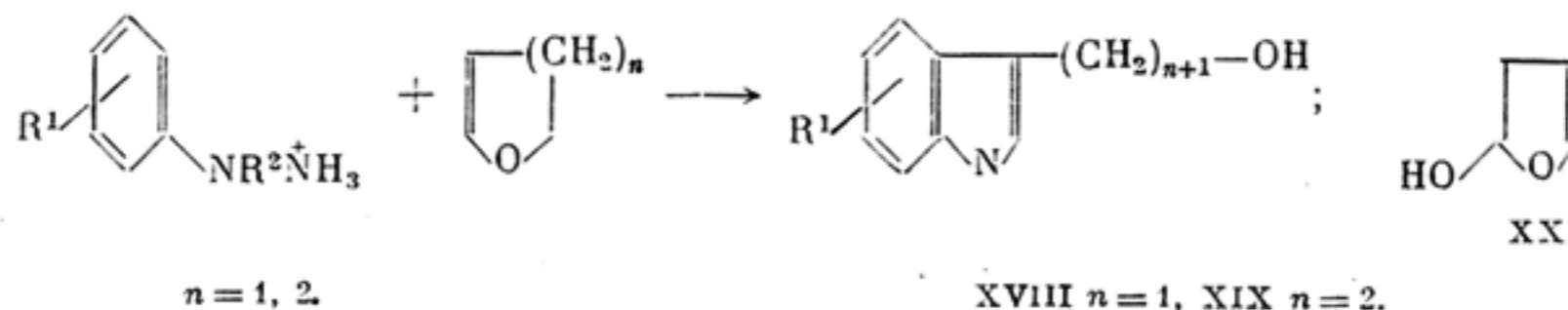
Ring-chain tautomerism was observed for the obtained eserines in an acidic medium. The regions for the existence of the tautomers varied extremely significantly in relation to the structure, and this made it possible to use them and the corresponding oxygen analogs (physo-venines) as indicators of acidity in the medium [21-23].



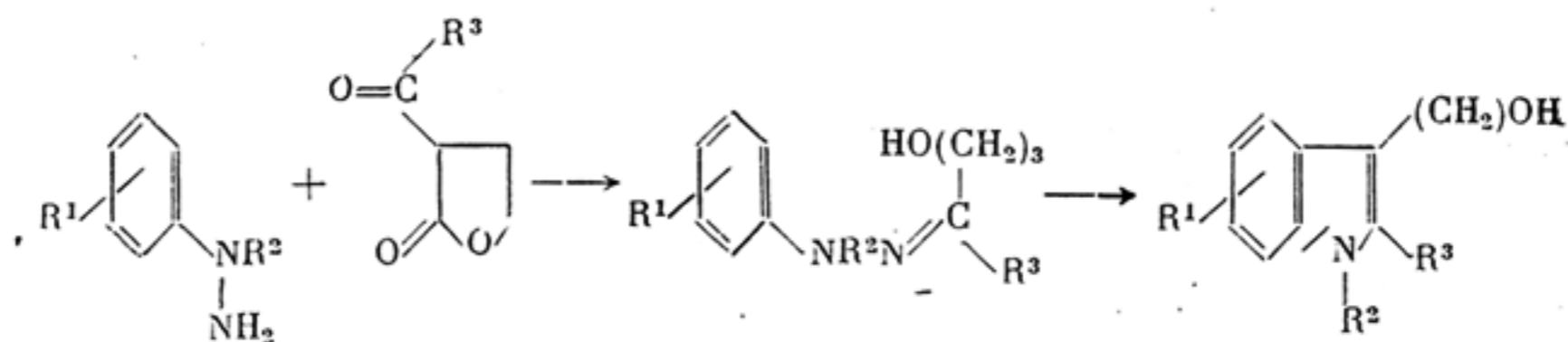
Tryptamines and Homotryptamines from Cyclic Enamines. Using our ideas about the mechanism of the process and its analogy with the Fischer synthesis of indoles, we decided to use cyclic enamines in a similar reaction. In fact, after the addition of arylhydrazine to the active double bond of the cyclic enamine the obtained aminal (XVI) rearranged to the arylhydrazone of the aminoaldehyde (XVII), which gave tryptamine with  $n = 1$  or homotryptamine with  $n = 2$  by a normal Fischer mechanism. In a number of cases the merely satisfactory yields were compensated by the availability of the initial compounds [24-29].



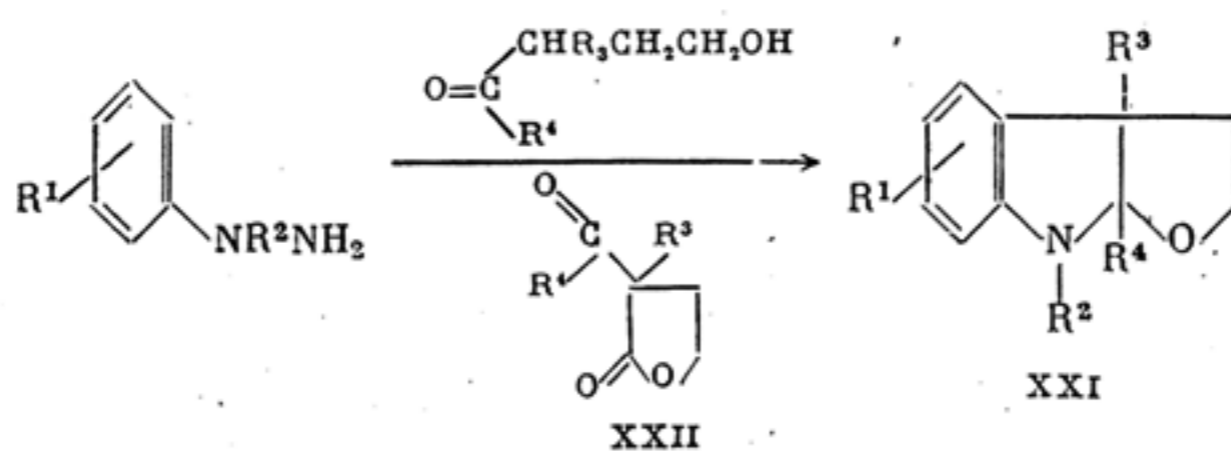
Tryptophols and Homotryptophols. The reaction with cyclic vinyl ethers, leading to the tryptophols (XVIII) with  $n = 1$  (30, 31) or homotryptophols (XIX) with  $n = 2$  [30-35] took place in exactly the same way but with higher yields.



The reaction also took place similarly with cyclic semiacetals of the (XX) type [34]. A modification of the method with the readily obtainable  $\alpha$ -acylbutyrolactones, which gave the tryptophols directly in the reaction on account of hydrolysis and decarboxylation, proved extremely convenient.



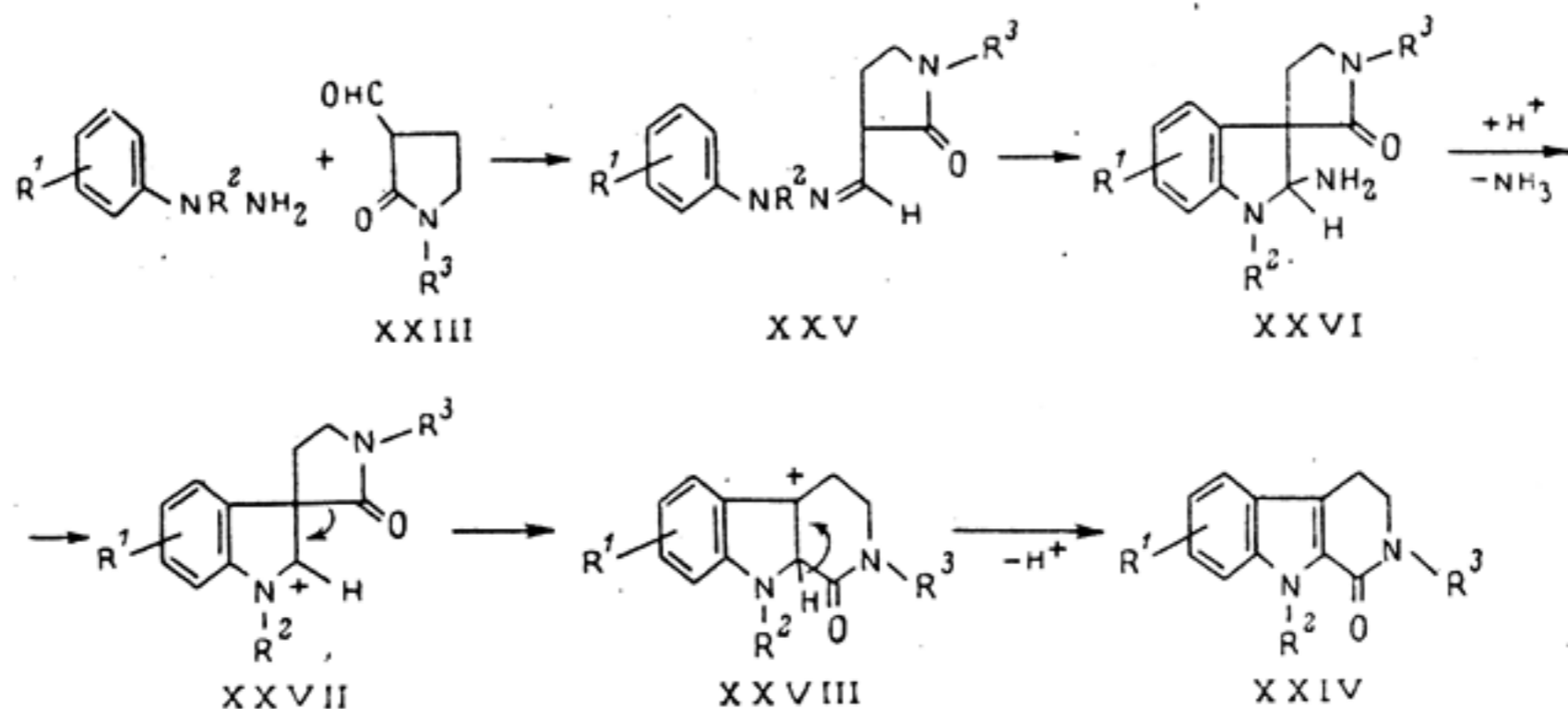
Physovenine Structures. Using our ideas about the mechanism of the Fischer synthesis of indoles and some of its modifications [37-40], we developed an important scheme in the applied sense for the production of physovenine structures (XXI) from  $\alpha$ -alkyl-substituted acetopropyl alcohols [42-47]. It was also possible to use the available  $\alpha$ -alkyl- $\alpha$ -acylbutyrolactones (XXII) in this reaction in a single-stage process [41, 48]. Their salts, like the salts of the eserines, were characterized by ring-chain tautomerism, which was considered in detail in [22, 23].



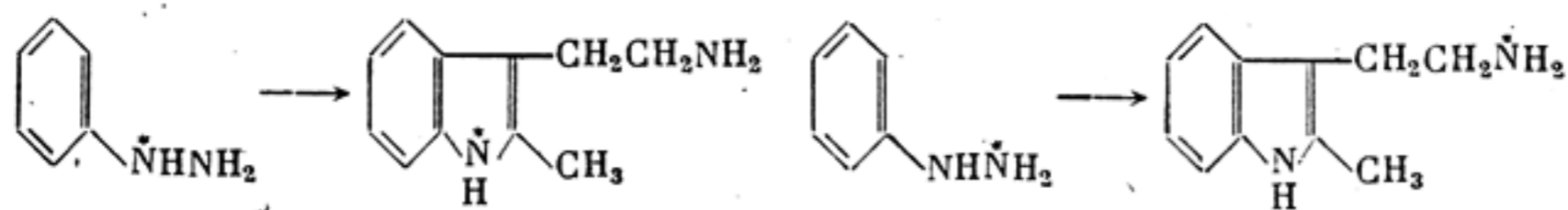
$\alpha$ -Acyllactams in the Fischer Reaction. We tried to obtain tryptamines from 3-formyl-2-pyrrolidone (XXIII) by analogy with the synthesis of tryptophols described above. However, 1-oxo-1,2,3,4-tetrahydrocarbolins (XXIV) were obtained with high yields as the only products



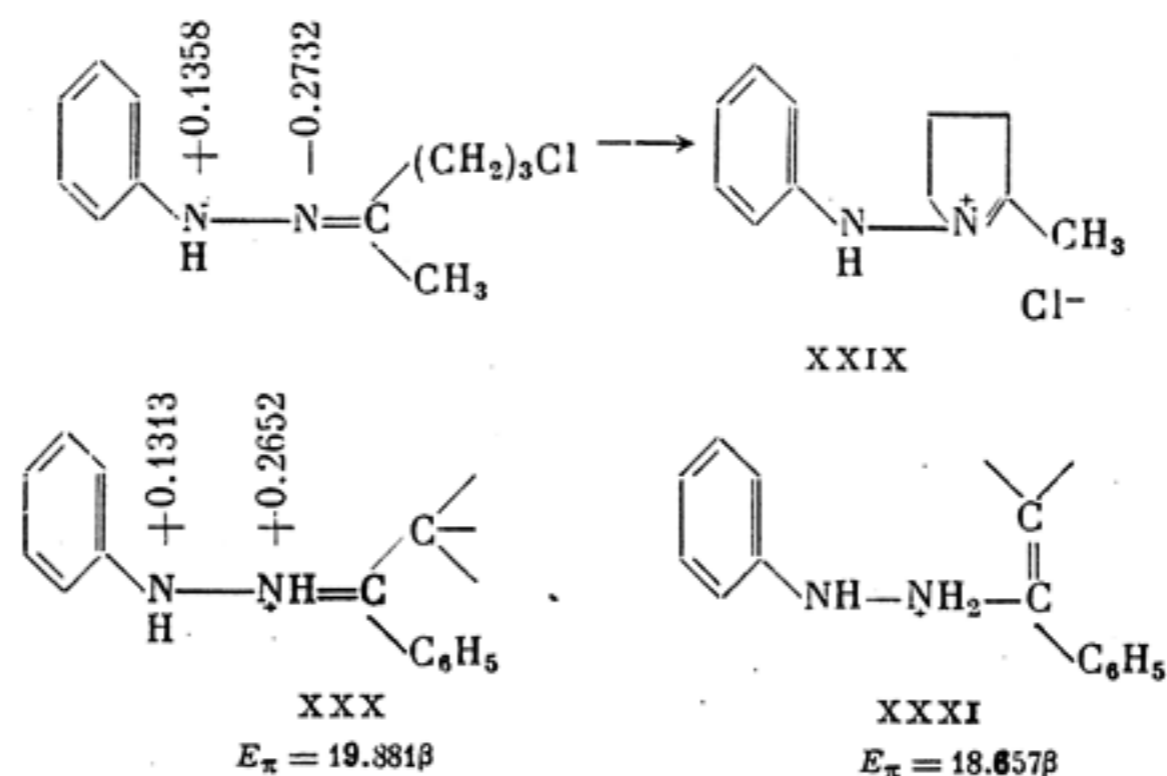
[49, 50], and they are evidently formed in the following way. At the first stage the formylpyrrolidone (XXIII) with the arylhydrazine gives the hydrazone (XXV), which undergoes cyclization by the Fischer mechanism to the spiroindoline (XXVI). After protonation of the amino group the latter loses a molecule of ammonia to form the cation (XXVII), which rearranges to the cation (XXVIII), and the latter is stabilized in turn to the carbolin (XXIV).



**Reaction Mechanism.** According to the reaction scheme given at the beginning of the review, the  $\beta$ -nitrogen atom of the arylhydrazine takes part in the formation of the amino group in the aminoethyl part of the tryptamine molecule. In order to confirm this suggestion the phenylhydrazine- $\alpha$ - $^{15}\text{N}$  was converted into 2-methyltryptamine by heating under normal conditions with  $\gamma$ -chloropropyl methyl ketone. If the scheme is correct, the 2-methyltryptamine should contain the  $^{15}\text{N}$  isotope at position 1, while the 2-methyltryptamine obtained from phenylhydrazine- $\beta$ - $^{15}\text{N}$  should contain the  $^{15}\text{N}$  isotope in the amino group of the indole side chain. In fact, mass-spectral analysis of the tryptamines showed the presence of the label at the appropriate positions in the molecule and this confirmed the scheme [51].

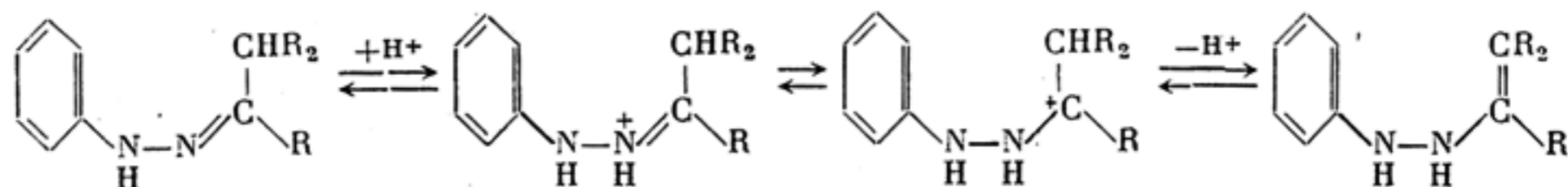


During examination of the scheme the question naturally arises of the preferred direction of cyclization, i.e., quaternization of the  $\alpha$ - or  $\beta$ -nitrogen atoms in the hydrazone molecule. This question was solved partly by MO LCAO calculations on certain systems in the Hückel approximation [24]. Comparison of the  $\pi$ -electron densities at the  $\alpha$ - and  $\beta$ -nitrogen atoms of the hydrazones showed clearly that the  $\beta$ -nitrogen atom is always more basic, although the basicity of the hydrazones is lower than the basicity of hydrazines on the average by two orders of magnitude [53]. The formation of 1-anilinopyrroline (XXIX) and not the tetrahydropyridazine system during quaternization is quite regular [54].



In spite of the fact that the "hydrazone" form is energetically more favorable for the obtained anilinopyrroline salt ( $V \rightleftharpoons IV$ ) [see  $E_\pi$  for (XXX) and (XXXI) and [52]], the tautomeric and, evidently, unprotonated enehydrazine form (V), in which atoms 1 and 6 (indicated by an asterisk in the scheme) are close enough for the formation of the C-C bond, naturally enter into the reaction [52]. The following fact should be specially mentioned. According

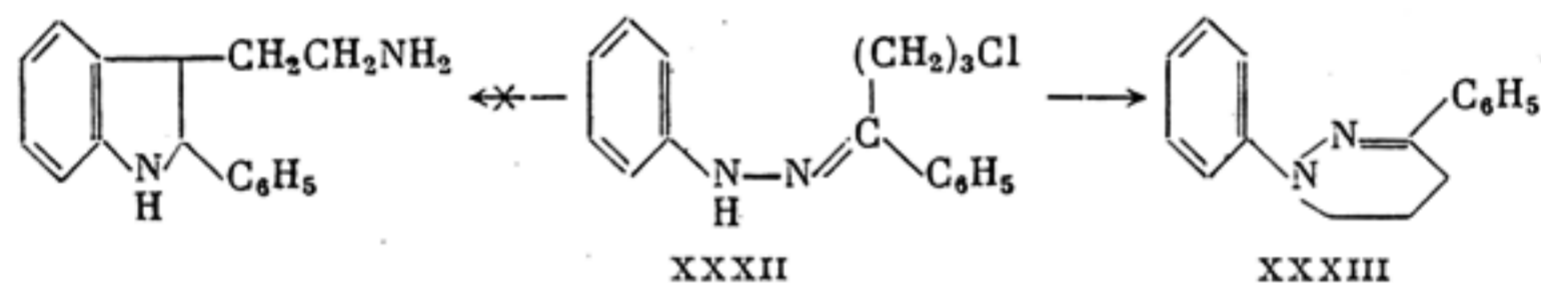
to the general scheme for the Fischer synthesis of indoles, the stage which determines the rate of the process is the formation of the enamine form as a result of prototropic catalysis [55]. (For the role of enamines in the Fischer reaction, see also [56].)



However, not every protonation event must lead to the enamine form, and due to the "energetic unfavorability" of the enamine form the length of its existence may be so short that the next stage (the sigmatropic [3,3]-shift) is not able to be realized (see below). For the analogous fragment of 1-anilinopyrroline in the scheme for the synthesis of tryptamines the position differs greatly. The unprotonated form (V) cannot exist in the hydrazone form and only exists in the enamine form. This greatly increases the possibilities for the occurrence of the next stage, i.e., the sigmatropic [3,3]-shift.

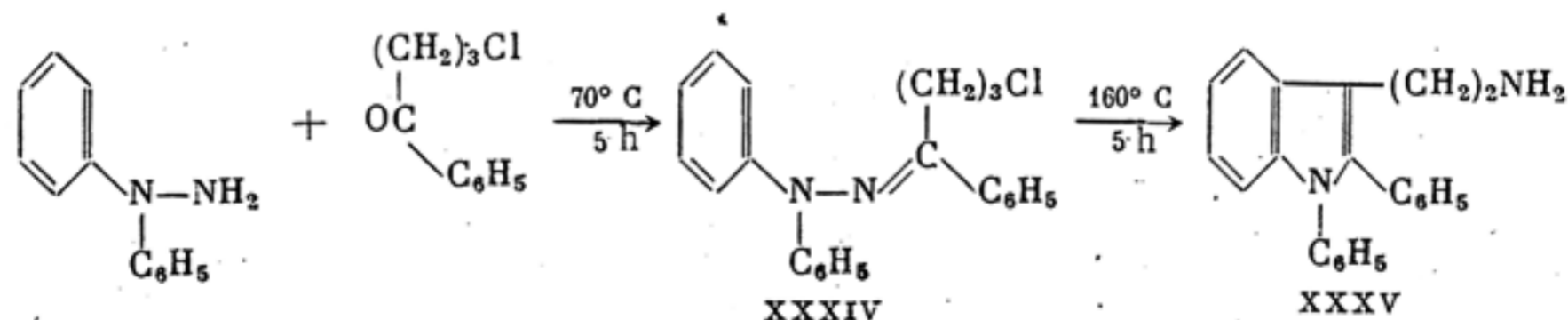
During a more detailed study of the reaction results were obtained which show that conformational factors have a significant effect on the process. For instance, the reaction of phenylhydrazine with  $\gamma$ -chloropropyl phenyl ketone, which takes place through the formation of the hydrazone (XXXII), gives the tetrahydropyridazine (XXXIII) instead of the expected tryptamine. Moreover, cyclization took place at the  $\alpha$ -nitrogen atom even in the reaction with  $\alpha$ -benzylphenylhydrazine with the formation of the same pyridazine (XXXIII) on account of the elimination of benzyl chloride from the unstable quaternary salt. The differences in the  $\pi$ -electron densities of the nitrogen atoms in the molecules of the hydrazones with the methyl and phenyl groups are not so significant as to give rise to reorientation during intramolecular cyclization. The reason for the change in the course of the reaction was explained successfully by conformational analysis of the molecules of the hydrazones [52].

Let us consider the syn and anti forms of the  $\gamma$ -chloropropyl methyl ketone arylhydrazone (Fig. 1). In them atoms 1-5 are in the same plane; in the anti form (a) the steric prerequisites exist for the formation of a bond between the atoms 2 and 7 (Dreiding models). In addition, the distance between atoms 2 and 7 in the anti form is close to the length of the C-N bond (2 Å).



In the case of the hydrazone (XXXII) by virtue of  $\pi, \pi$  conjugation the phenyl ring at the carbon atom tends to lie in the plane of the fragment 1,2,3 (Fig. 1), as a result of which the existence of the anti form becomes sterically impossible, and in practice the hydrazone can exist in the syn form. The mutual arrangement of the nitrogen atoms and the C-Cl fragment in it is such that only the  $\alpha$ -atom and not the  $\beta$ -atom can undergo electrophilic attack, although the latter is more basic.

The accuracy of these arguments was confirmed by the isolation of phenyl  $\gamma$ -chloropropyl ketone diphenylhydrazone (XXXIV) under the normal reaction conditions [52]. Pyridazine was not formed in this case on account of the greatly reduced basicity of the  $\alpha$ -nitrogen atom, while tryptamine was not formed on account of the fact that the hydrazone exists in the syn form. Only under significantly more rigorous conditions (160°C, 5 h) did isomerization of the syn form to the anti form occur, and the corresponding tryptamine (XXXV) was formed.



Thus, calculation of the  $\pi$ -electron density in the molecules of the hydrazones, their conformational analysis, and specific variation of the basicity of the  $\alpha$ - and  $\beta$ -nitrogen atoms of the hydrazones have made it possible to explain one of the principal stages which



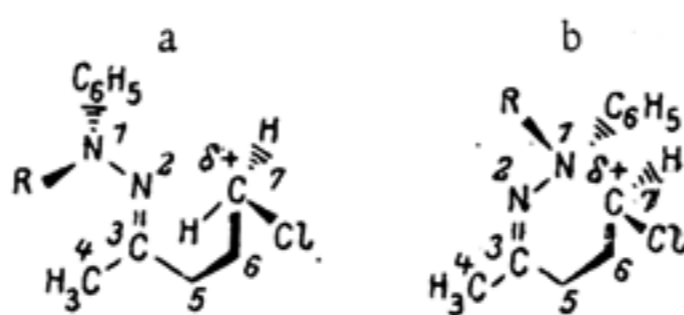


Fig. 1.  $\gamma$ -Chloropropyl methyl ketone arylhydrazone: a) Anti form; b) syn form.

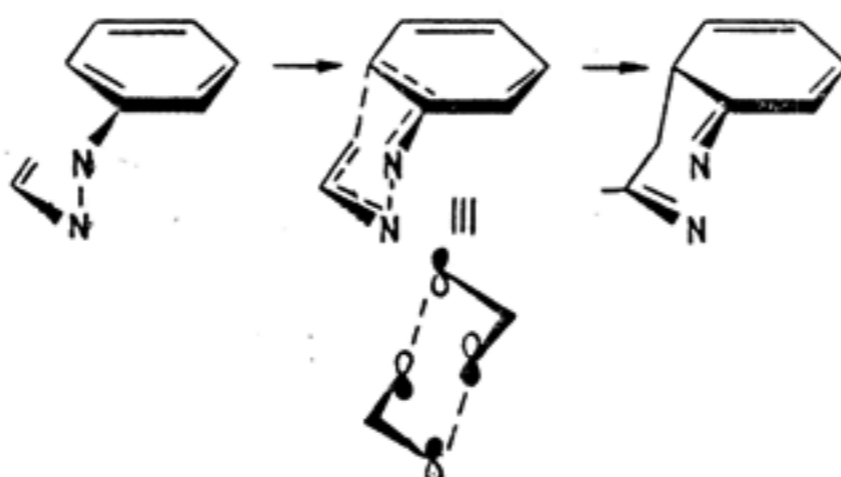
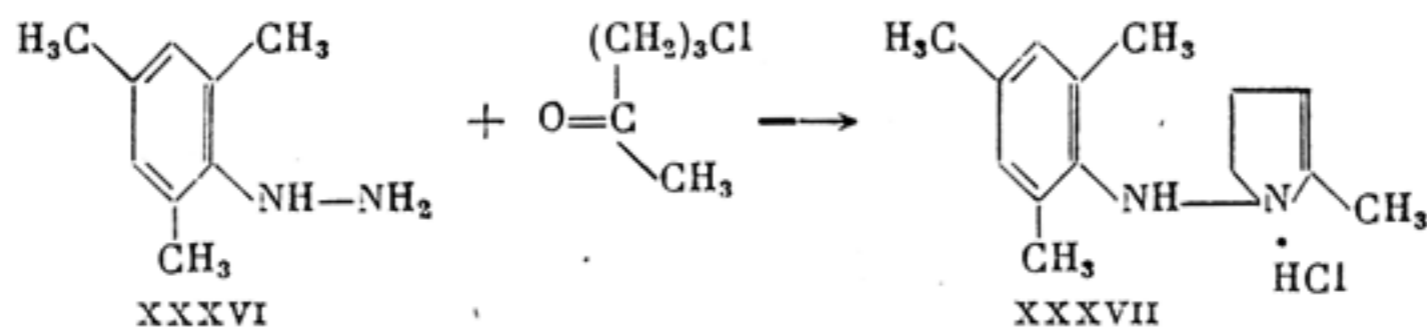


Fig. 2. The stage of the formation of the C-C bond in the Fischer synthesis of indoles as a sigmatropic [3,3]-shift.

determines the direction of the process, i.e., the intramolecular quaternization stage (III  $\rightarrow$  IV).

During a detailed investigation of the formation of tryptamines it was possible to isolate all the intermediate compounds and to establish their structures [52, 57, 58]. As it is easy to see, the above-mentioned hydrazone (XXXII) represents an intermediate product of type (III). It proved possible to synthesize  $\gamma$ -chloropropyl methyl ketone phenylhydrazone by realizing the reaction in benzene (and not in alcohol, as usual), without heat [57]. Compound (XXXVII), similar in structure to the intermediate product (V), was obtained from mesitylhydrazine (XXXVI) [57].



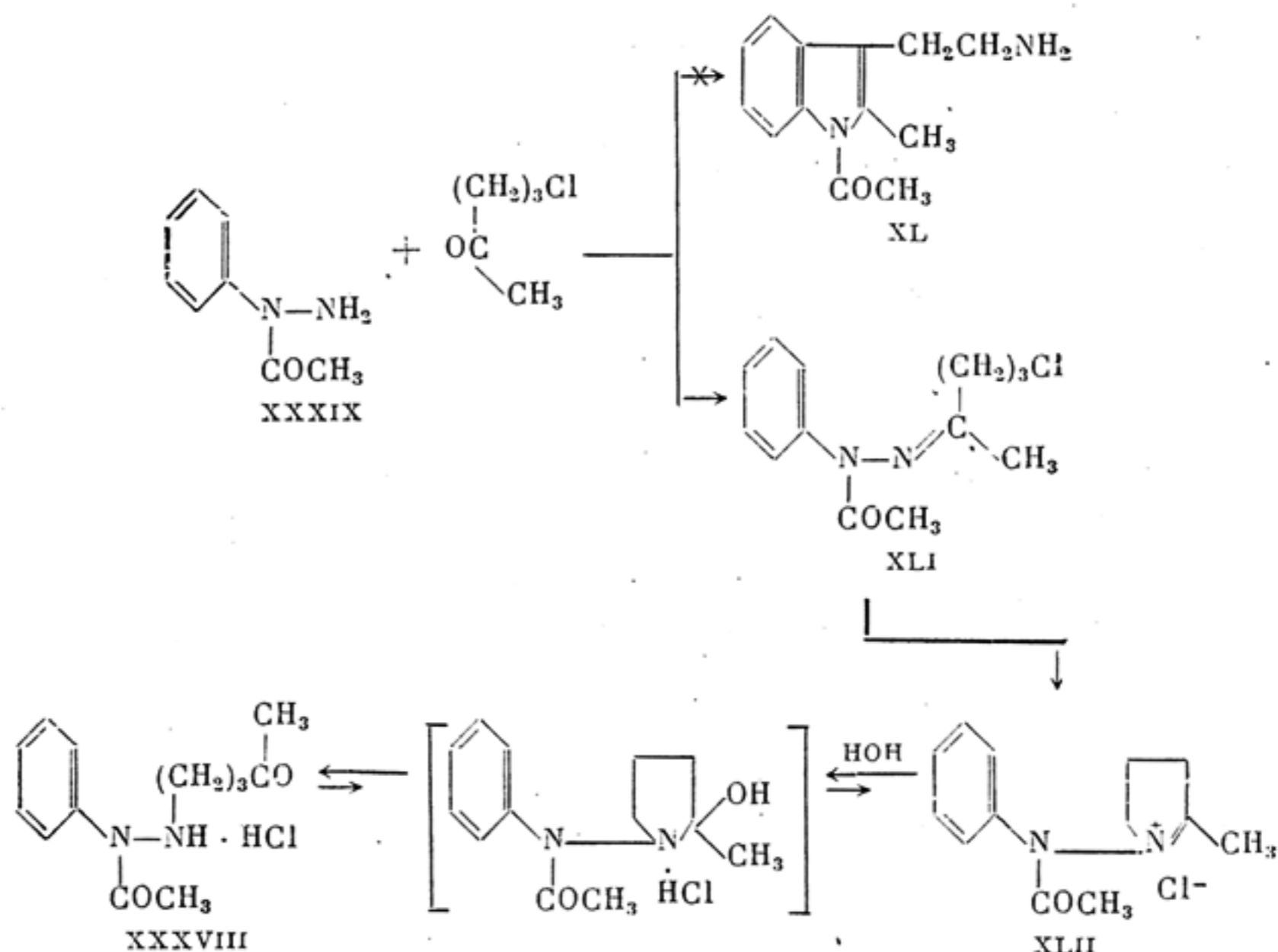
We proposed to regard the most important stage of the process, i.e., the formation of the C-C bond (V  $\rightarrow$  VI), as a sigmatropic [3,3]-rearrangement [5]. From the standpoint of the general principle of Woodward and Hoffmann the approach considered below has already been applied successfully to the Claisen rearrangement. The transition state is four-center (with the chair conformation) and has the form of two highest occupied molecular orbitals of the allyl radicals, in which the 3-4 bond had not yet been finally broken while the 1-6 bond has not been finally formed. The realization of the chair conformation (and not the boat conformation) is determined by its greater favorability on account of the smaller repulsion of the nonbonding molecular orbitals in the transition state [5] (Fig. 2).

Only the structure of the transition state which permits supra-supra migration of the  $\sigma$  bond in the ground state is possible for the planar structure of the N-allyl fragment.

It was extremely interesting from the standpoint of investigating the detailed mechanism of the process to use  $\alpha$ -acylarylhazines in the reaction. During an attempt at the synthesis of tryptamine acylated at position 1 of the indole ring it was unexpectedly found that  $\alpha$ -acetyl- $\beta$ -acetopropylphenylhydrazine (XXXVIII), i.e., the product from alkylation of the  $\alpha$ -acetylphenylhydrazine (XXXIX) by the chloro ketone, and not the expected tryptamine (XL) was formed when equimolar amounts of the initial compounds were boiled [58].

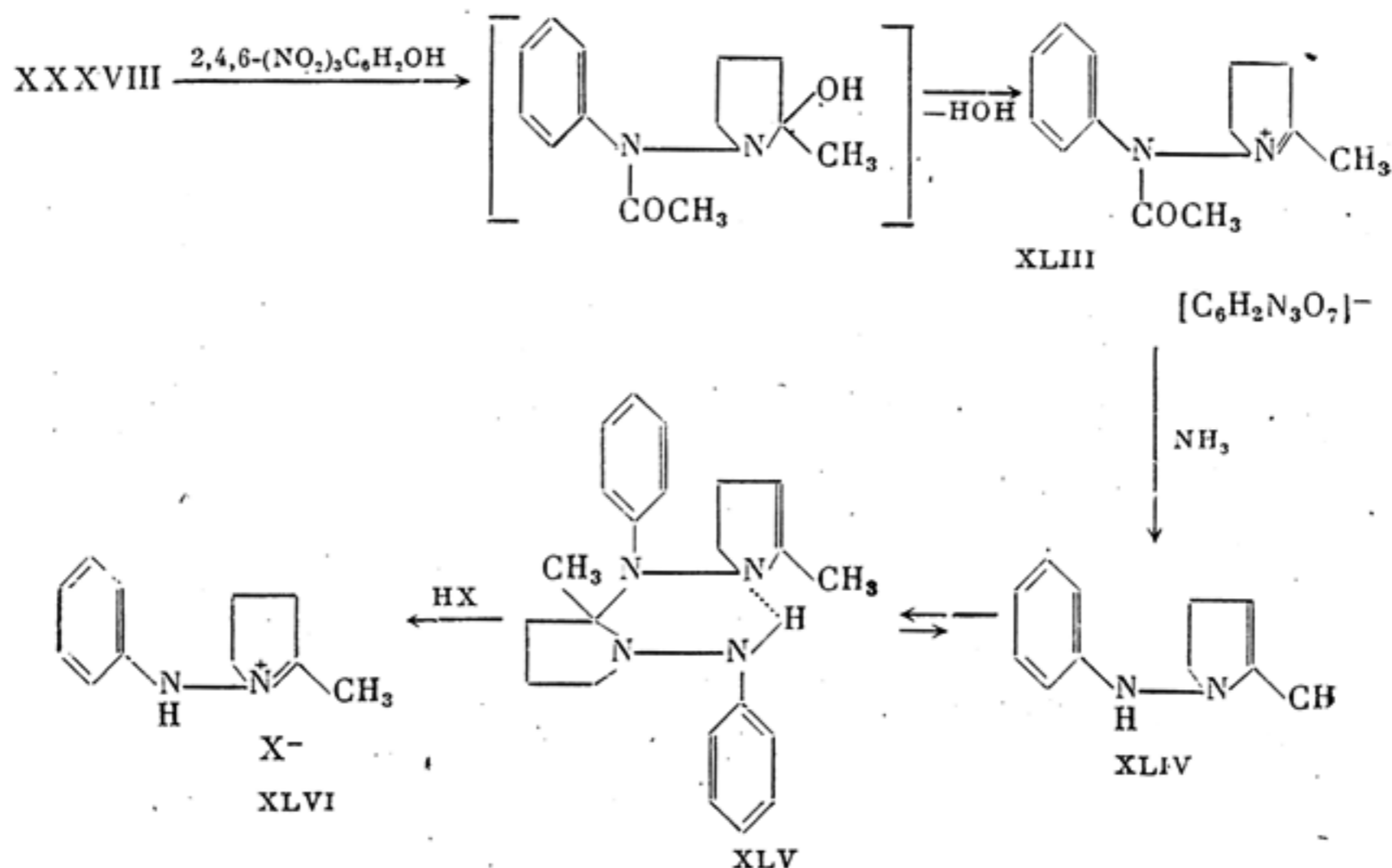
A thorough investigation of this reaction showed that compound (XXXVIII) is not formed by direct alkylation of the hydrazine (XXXIX). The hydrazine (XXXIX) reacts with the chloro

ketone, forming the phenylhydrazone (XLI). The hydrazone then undergoes cyclization to 1-anilinopyrroline hydrochloride (XLII), which undergoes hydrolytic cleavage of the ring with the formation of the hydrazine (XXXVIII). The evidence for this scheme was based on a study of the dynamics of variation in the intensity of the absorption band for the carbonyl group of the ketone in the IR spectrum [58].

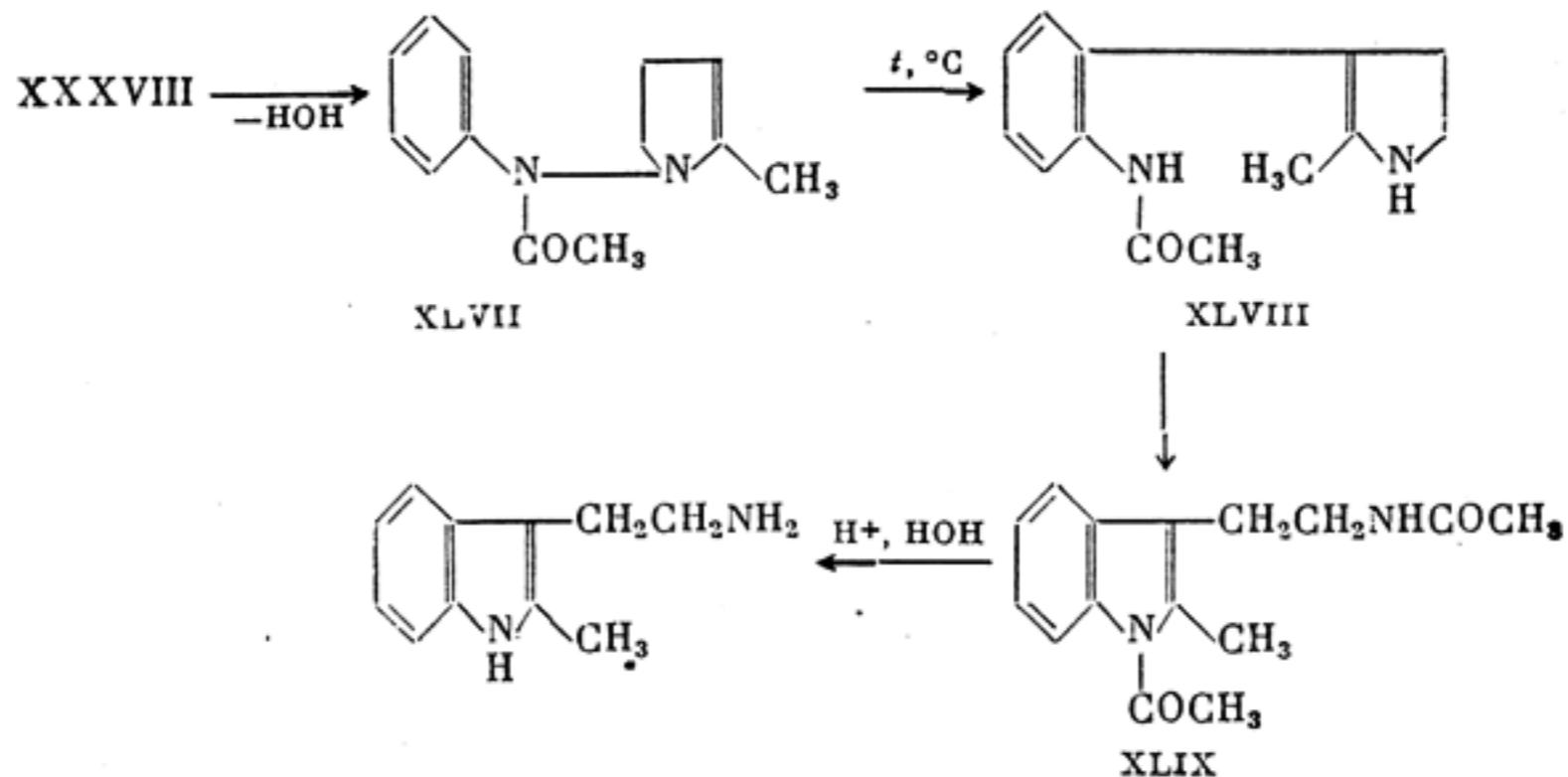


Compound (XXXVIII) very readily loses a molecule of water. Thus, it undergoes cyclization with the elimination of water even during treatment with picric acid with the formation of 1-acetylanilino-2-methyl-2-pyrroline picrate (XLIII), i.e., an intermediate compound of type (V).

When the picrate (XLIII) is treated with liquid ammonia with simultaneous removal of the acetyl group the base (XLIV), which under these conditions exists in the form of the dimer (XLV), is isolated. In an acidic medium (at pH < 1.6) the dimer is converted into the salt of the monomer (XLVI) [16, 58].

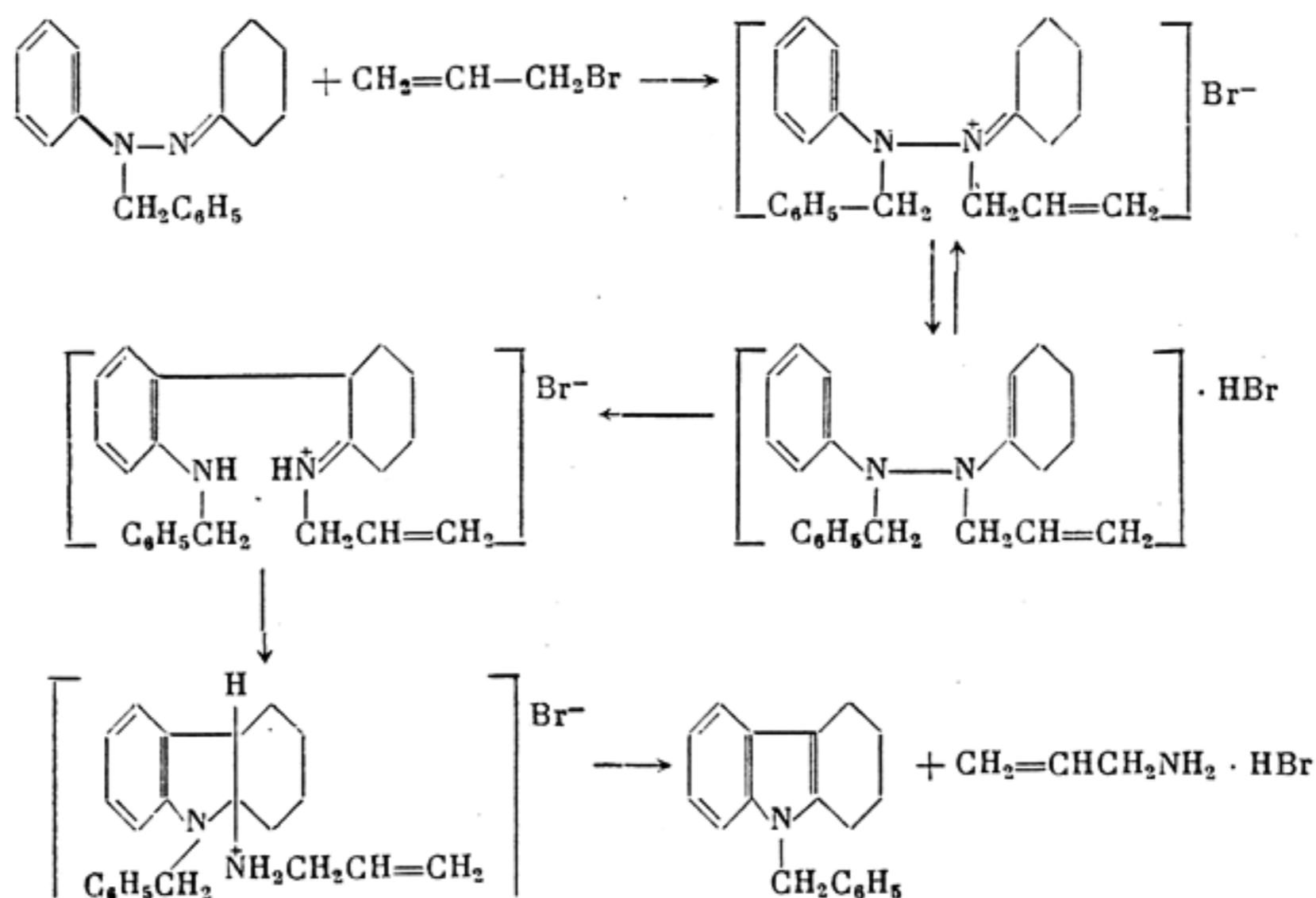


The base (XLVII), which corresponds to 1-anilinopyrroline (V), was obtained by boiling compound (XXXVIII) in xylene with distillation of an equimolar amount of water. During the distillation of compound (XLVII) the crystalline compound (XLVIII), similar in structure to the intermediate product (VII), was isolated. Treatment of the intermediate product (XLVIII) with boiling acetic anhydride gave the diacetylated 2-methyltryptamine (XLIX), which was easily converted into 2-methyltryptamine by acid hydrolysis [58].



The last intermediate product of type (VIII) in the scheme was obtained as a result of the reaction of phenylhydrazine with 5-chloro-3-methyl-2-pentanone [see (XIII)] [19].

The structures of all the intermediate compounds described above were proved rigorously by IR, UV, PMR, and mass-spectrometric methods [59-63].



An attempt was made to study the kinetics of the formation of tryptamines [64]. Two reactions were chosen as models, i.e., the synthesis of 9-benzyltetrahydrocarbazole [65] and 2-methyltryptamine. The mechanism of these reactions is similar except that in the case of the formation of 2-methyltryptamine the quaternization of the  $\beta$ -nitrogen atom of the arylhydrazine is intramolecular and in the case of the formation of N-benzyltetrahydrocarbazole it is intermolecular. According to data from a series of authors [66, 67], the rate of the Fischer reaction corresponds approximately to a first-order equation. Investigation of the kinetics of the formation of 9-benzyltetrahydrocarbazole also gave an order close to unity for this reaction [65].

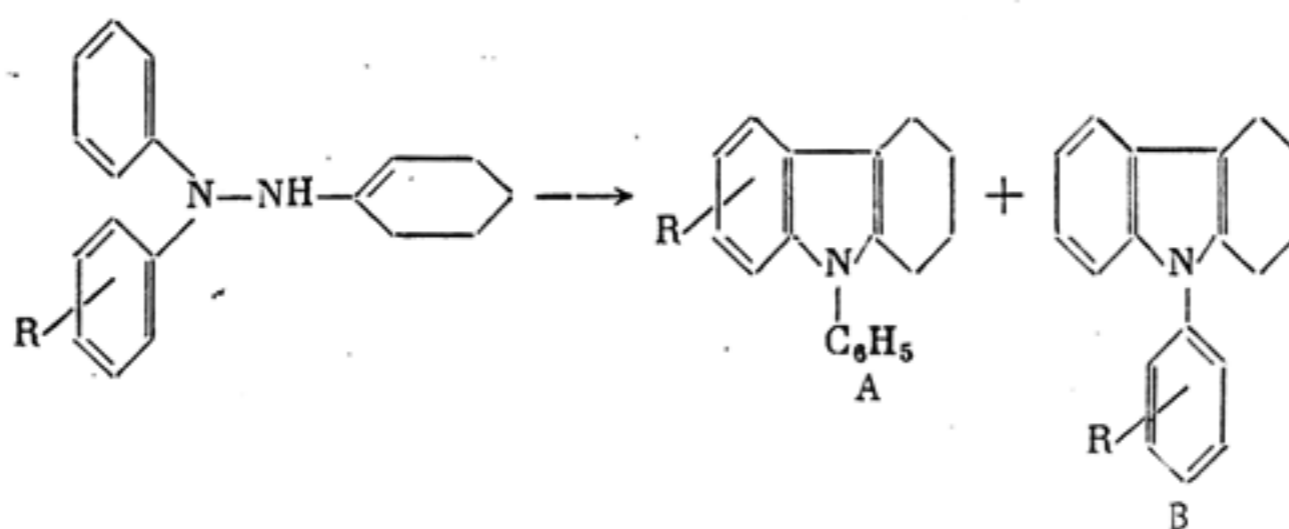
Ionic halogen (in the present case bromine) appears at the stage of quaternization of the  $\beta$ -nitrogen atom of the hydrazone. If the concentration of  $\text{Br}^-$  at each moment coincides with the concentration of the final product (allylamine hydrobromide), the suggestion that the stage which determines the rate of the whole reaction is quaternization is correct. In fact, such agreement was observed in the concentrations [64].

As expected, the slowest stage in the formation of 2-methyltryptamine must also be quaternization of the nitrogen atom, which leads the formation of 1-anilinopyrrolidine (III  $\rightarrow$  IV). It was possible to prove this in the following way. First, it was established that the stage of the formation of the hydrazone is not limiting. For this purpose the dependence of the intensity of absorption of the carbonyl group in the  $\gamma$ -chloropropyl methyl ketone during its reaction with phenylhydrazine on time was investigated by spectrophotometry. It was



found that the reaction is complete (90%) after only 2 min, whereas the same degree of conversion of the initial compounds in 2-methyltryptamine (under the same conditions) requires 300 min. Second, the concentration of  $\text{Cl}^-$  at any moment coincided with the concentration of tryptamine. As in the case of the formation of the carbazole, this demonstrated the correctness of the choice of quaternization stage as limiting stage. Third, a marked increase in the reaction rate was observed when the alcohol was diluted with water. This confirmed the idea that the quaternization stage determines the rate of the process. There are similar examples which describe the acceleration of such a type in the cyclization of  $\omega$ -aminoalkyl halides in the literature [68]. In spite of the fact that the formation rate of 2-methyltryptamine, as shown by direct and indirect data, was determined by the rate of the second stage (quaternization of the  $\beta$ -nitrogen atom), it was not possible to assign this reaction any specific order, and the order proved to be equal to 1.28. The difference between this value and unity evidently indicated that other intermediate stages also affect the rate of the process.

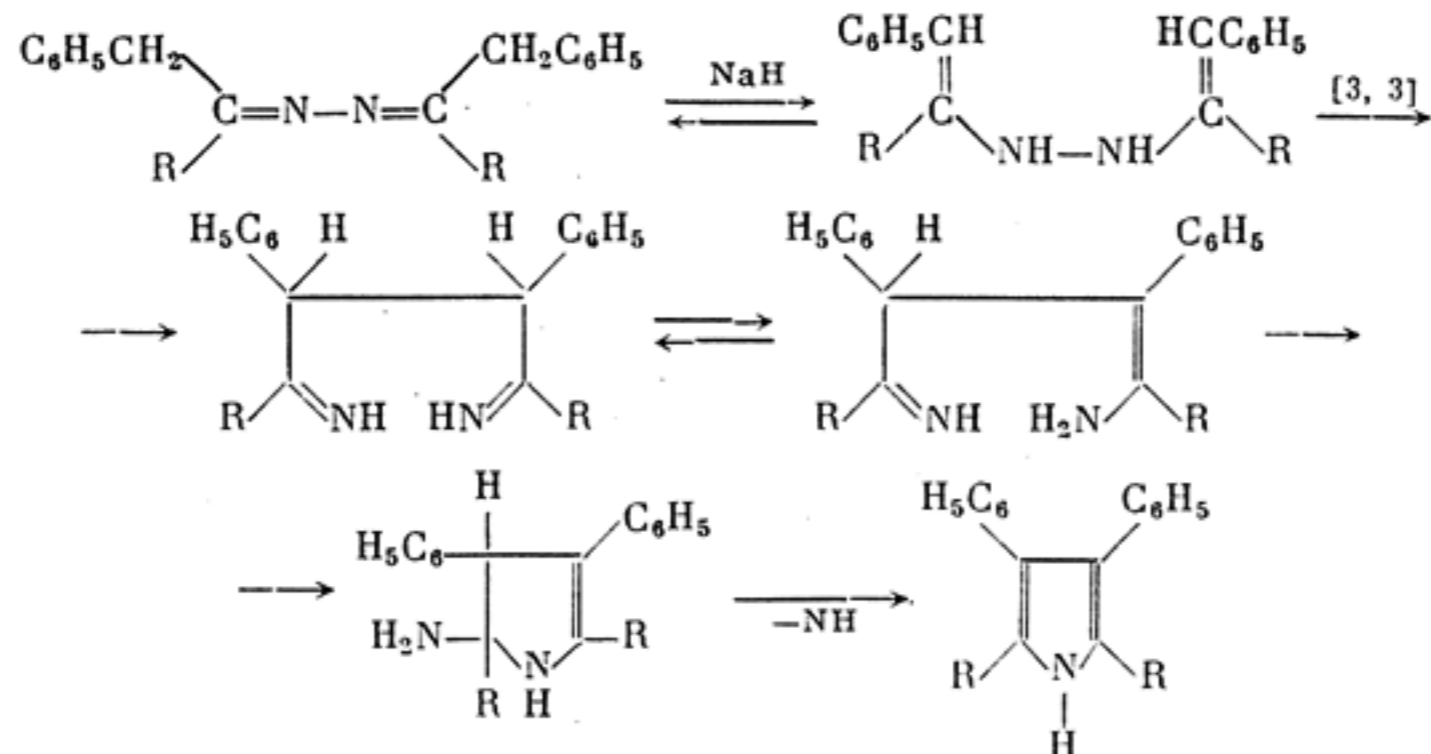
As already mentioned, in [5] we put forward general arguments about the principal stage (the formation of the C-C bond) in the Fischer synthesis of indoles as sigmatropic [3,3]-rearrangement. In connection with the fact that the action of electronic effects is insignificant in sigmatropic reactions, we investigated the possibility of the formation of isomers during the reaction of 1,1-diarylhydrazines with symmetrical ketones where one of the allyl groups contained electron-donating or electron-withdrawing substituents.



It was found that the effect of the substituent R (irrespective of its nature) on the ratio of the isomers A and B is extremely small. From our standpoint this is direct evidence for the fact that the stage of the formation of the C-C bond is a sigmatropic reaction [69-71, 98]. To generalize the developed ideas about the Fischer synthesis of indoles as a sigmatropic [3,3]-rearrangement, we proposed to examine a whole series of similar syntheses from these standpoints (the Brunner synthesis of hydroxyindoles, the Kost synthesis of  $\alpha$ -aminoindoles, the Bucherer synthesis of benzocarbazoles) [5]. We consider that the synthesis of pyrroles from oximes and acetylene worked out in detail by Trofimov's group (e.g., see [72]), like the previously described syntheses of Sheradsky [73] and House and Richey [74], take place similarly, although the authors themselves (to some extent, it is true, without evidence) hold different views.

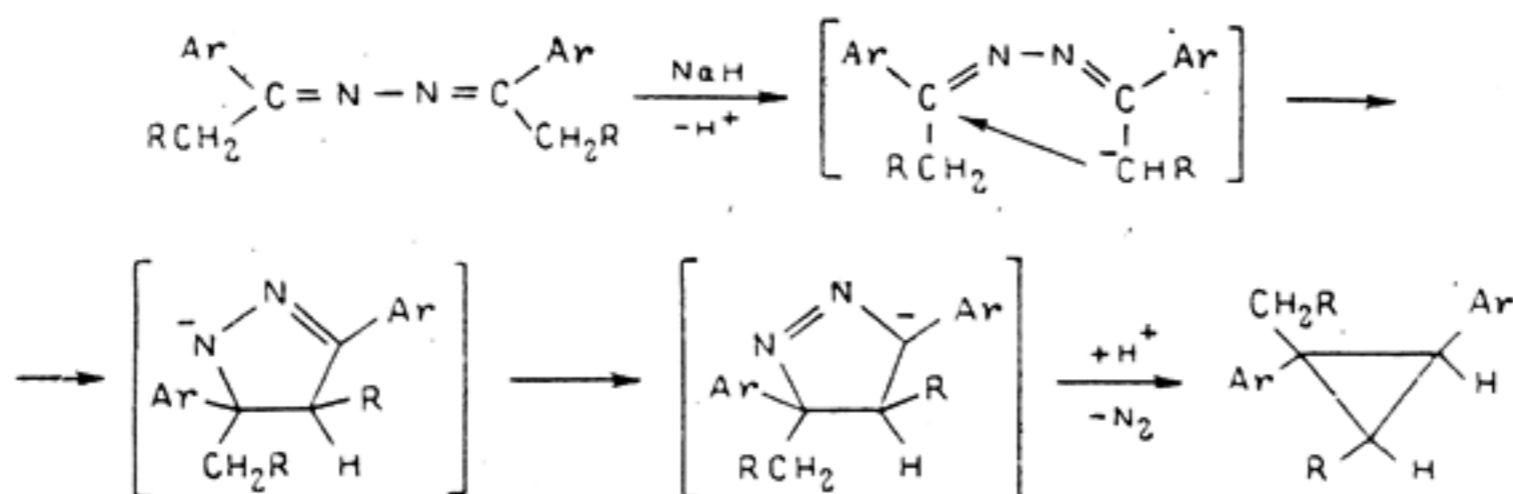
The concept of sigmatropic [3,3]-shift at the stage of formation of the C-C bonds in the Fischer reaction naturally suggested alkaline catalysis in this process, since alkaline catalysts could also increase the rate of the tautomeric hydrazone  $\rightleftharpoons$  enehydrazine transformation. In a number of cases [75] we were able to obtain indoles during alkaline catalysis, but in general alkaline catalysis was clearly inferior to acid catalysis. On the other hand, extremely interesting results were obtained during alkaline thermolysis of azines containing the readily enolized benzyl group [76, 77]. In this reaction we observed the formation of pyrroles.

As in the case of the Fischer reaction, at the first stage of cyclization the azine is converted into a dienehydrazine. This transformation is reversible, and the equilibrium is shifted toward the azine, for it is known that in compounds capable of forming tautomeric forms of the ketone-enol and lactim-lactam types the tautomeric equilibrium under normal conditions is largely shifted toward the form in which the proton is attached to the less electronegative atom of the tautomeric triad. While not shifting the equilibrium itself, the alkaline catalyst appreciably increases the rate of the tautomeric transformation. A phenyl group also helps to increase the acidity of the hydrogen in the adjacent methylene group and increases the probability of the formation of the enehydrazine tautomer. The formation of the dienehydrazine evidently takes place by an E1 elimination mechanism similar to the enolization of O-phenyloximes of unsymmetrical carbonyl compounds to benzofurans by the mechanism of the Fischer reaction [78].



At the next stage a sigmatropic [3,3]-shift occurs, and a pyrrole derivative is then formed (through several stages, accompanied by the elimination of ammonia). The probability of the formation of the carbon-carbon bond as a sigmatropic [3,3]-shift is confirmed by the very fact that a pyrrole compound is formed during thermolysis without a catalyst but at 300°C. In all cases pyrazoles, evidently formed by a carbanionic mechanism, were isolated in addition to the pyrroles [77].

During an attempt to realize the process for azines of aliphatic-aromatic ketones we were able to detect their rearrangement into pyrazolines, which immediately dissociate to cyclopropanes [79-81] with high yields.



At the first stage of the reaction during the action of the alkali-metal hydride on the ketazine a carbanion is formed which undergoes intramolecular cyclization to the 2-pyrazoline anion. The latter isomerizes to the 1-pyrazoline anion, which loses nitrogen under the reaction conditions and forms the cyclopropane anion. At some state (most likely the last) the intermediate anions or the cyclopropane anion deprotonate a new molecule of the ketazine. In [82] it was proposed to treat the cyclization of azines to pyrazolines as a disrotatory electrocyclic reaction. From this standpoint the alkali-metal hydride promotes the formation of the 1,4-heterodiene structure.

Physicochemical Investigations. The dissociation of indole structures under electron impact has been studied specially [83-89]. The obtained relationships made it possible to distinguish between isomeric ring-substituted indoles. It was also possible to develop a method for semiquantitative analysis of the 4- and 6-substituted isomers. Detailed analysis of the PMR spectra made it possible to assign all the signals of the indole and tryptamine structures, and this was also used in the analysis of isomeric mixtures [90, 91]. Determination of the Kovats indices in the GLC of indoles, indolines, and tryptamines [92-97] made it possible to undertake a quantitative analysis of mixtures of isomeric indoles with accurate assignment of the chromatographic peaks. The rational application of these three methods enabled us to analyze reliably fairly complex mixtures of indole structures.

#### LITERATURE CITED

1. I. I. Grandberg, T. I. Zuyanova, and N. I. Afonina, Inventor's Certificate No. 192818 (1966); Byull. Izobr., No. 6 (1967).
2. I. I. Grandberg, Izv. Akad. Nauk SSSR, Ser. Khim., 1966, 1682.
3. I. I. Grandberg and T. I. Zuyanova, Khim. Geterotsikl. Soedin., 1968, 875.
4. I. I. Grandberg, Khim. Geterotsikl. Soedin., 1974, 579.
5. I. I. Grandberg, Izv. Timiryazevsk. S-Kh. Akad., No. 5, 188 (1972).
6. I. I. Grandberg, T. I. Zuyanova, N. I. Afonina, and T. A. Ivanova, Dokl. Akad. Nauk SSSR, 176, 583 (1967).



7. I. I. Grandberg, T. I. Zuyanova, N. I. Afonina, and T. A. Ivanova, Dokl. Timiryazevsk. S-Kh. Akad., 124, 325 (1967).
8. I. I. Grandberg and T. I. Zuyanova, Inventor's Certificate No. 196852 (1966); Byull. Izobr., No. 12 (1967).
9. I. I. Grandberg, N. I. Afonina, and T. I. Zuyanova, Inventor's Certificate No. 201412 (1966); Byull. Izobr., No. 18 (1967).
10. I. I. Grandberg, N. I. Afonina, and T. I. Zuyanova, Khim. Geterotsikl. Soedin., 1968, 1038.
11. I. I. Grandberg, N. M. Przheval'skii, T. A. Ivanova, T. I. Zuyanova, N. I. Bobrova, S. N. Dashkevich, S. B. Nikitina, T. P. Shcherbina, and N. G. Yaryshev, Izv. Timiryazevsk. S-Kh. Akad., No. 5, 208 (1969).
12. I. I. Grandberg and T. I. Zuyanova, Khim. Geterotsikl. Soedin., 1971, 51.
13. I. I. Grandberg and N. I. Bobrova, Khim. Geterotsikl. Soedin., 1973, 213.
14. I. I. Grandberg and T. I. Zuyanova, Khim. Geterotsikl. Soedin., 1970, 1495.
15. I. I. Grandberg and N. G. Yaryshev, Khim. Geterotsikl. Soedin., 1972, 1070.
16. I. I. Grandberg and N. G. Yaryshev, Khim. Geterotsikl. Soedin., 1972, 1702.
17. I. I. Grandberg and T. A. Ivanova, Inventor's Certificate No. 201411 (1966); Byull. Izobr., No. 18 (1967).
18. I. I. Grandberg and T. A. Ivanova, Dokl. Timiryazevsk. S-Kh. Akad., 160, 232 (1970).
19. I. I. Grandberg and T. A. Ivanova, Khim. Geterotsikl. Soedin., 1970, 480.
20. I. I. Grandberg and T. A. Ivanova, Khim. Geterotsikl. Soedin., 1970, 939.
21. I. I. Grandberg, T. A. Ivanova, and N. G. Yaryshev, Khim. Geterotsikl. Soedin., 1970, 1276.
22. I. I. Grandberg and T. A. Ivanova, Khim. Geterotsikl. Soedin., 1970, 1489.
23. I. I. Grandberg, S. N. Dashkevich, and T. A. Ivanova, Inventor's Certificate No. 382968 (1970); Byull. Izobr., No. 23 (1973).
24. I. I. Grandberg and S. B. Nikitina, Khim. Geterotsikl. Soedin., 1971, 54.
25. I. I. Grandberg, S. B. Nikitina, and N. G. Yaryshev, Izv. Timiryazevsk. S-Kh. Akad., No. 2, 196 (1970).
26. I. I. Grandberg and S. B. Nikitina, Dokl. Timiryazevsk. S-Kh. Akad., 162, 374 (1971).
27. I. I. Grandberg and S. B. Nikitina, Khim. Geterotsikl. Soedin., 1971, 1204.
28. I. I. Grandberg and S. B. Nikitina, Khim. Geterotsikl. Soedin., 1972, 1216.
29. I. I. Grandberg, N. M. Przheval'skii, and T. A. Ivanova, Inventor's Certificate No. 248689 (1968); Byull. Izobr., No. 24 (1969).
30. I. I. Grandberg and N. I. Afonina, Inventor's Certificate No. 239341 (1967); Byull. Izobr., No. 11 (1969).
31. I. I. Grandberg and T. P. Moskvina, Khim. Geterotsikl. Soedin., 1972, 1366.
32. I. I. Grandberg and T. P. Moskvina, Khim. Geterotsikl. Soedin., 1970, 942.
33. I. I. Grandberg and T. P. Moskvina, Dokl. Timiryazevsk. S-Kh. Akad., 162, 380 (1971).
34. I. I. Grandberg and T. P. Moskvina, Khim. Geterotsikl. Soedin., 1974, 90.
35. I. I. Grandberg and T. P. Moskvina, Izv. Timiryazevsk. S-Kh. Akad., No. 4, 167 (1973).
36. I. I. Grandberg and G. P. Tokmakov, Khim. Geterotsikl. Soedin., 1974, 205.
37. I. I. Grandberg and D. V. Sibiryakova, Inventor's Certificate No. 199892; Byull. Izobr., No. 16 (1967).
38. I. I. Grandberg, L. V. Brovkin, T. A. Belyakova, and D. V. Sibiryakov, Khim. Geterotsikl. Soedin., 1969, 97.
39. I. I. Grandberg, T. I. Zuyanova, N. I. Afonina, and T. A. Ivanova, Inventor's Certificate No. 242901 (1967); Byull. Izobr., No. 16 (1969).
40. I. I. Grandberg and N. I. Bobrova, Khim. Geterotsikl. Soedin., 1974, 1085.
41. I. I. Grandberg and G. P. Tokmakov, Khim. Geterotsikl. Soedin., 1975, 207.
42. I. I. Grandberg and S. N. Dashkevich, Khim. Geterotsikl. Soedin., 1971, 1194.
43. I. I. Grandberg and S. N. Dashkevich, Inventor's Certificate No. 276062 (1969); Byull. Izobr., No. 23 (1970).
44. I. I. Grandberg and S. N. Dashkevich, Khim. Geterotsikl. Soedin., 1970, 1631.
45. I. I. Grandberg and S. N. Dashkevich, Dokl. Timiryazevsk. S-Kh. Akad., 160, 243 (1970).
46. I. I. Grandberg and S. N. Dashkevich, Khim. Geterotsikl. Soedin., 1971, 342.
47. I. I. Grandberg and S. N. Dashkevich, Khim. Geterotsikl. Soedin., 1971, 782.
48. I. I. Grandberg and G. P. Tokmakov, Inventor's Certificate No. 502883 (1974); Byull. Izobr., No. 6 (1976).
49. G. P. Tokmakov and I. I. Grandberg, Khim. Geterotsikl. Soedin., 1980, 331.
50. I. I. Grandberg and G. P. Tokmakov, Inventor's Certificate No. 523096 (1976); Byull. Izobr., No. 28 (1976).



51. I. I. Grandberg, N. M. Przheval'skii, V. I. Vysotskii, and R. A. Khmel'nitskii, *Khim. Geterotsikl. Soedin.*, 1970, 447.
52. I. I. Grandberg, T. I. Zuyanova, N. M. Przheval'skii, and V. I. Minkin, *Khim. Geterotsikl. Soedin.*, 1970, 750.
53. V. I. Sorokin, Candidate's Thesis, Moscow (1973).
54. I. I. Grandberg and N. M. Przheval'skii, *Khim. Geterotsikl. Soedin.*, 1970, 1273.
55. I. I. Grandberg and V. I. Sorokin, *Khim. Geterotsikl. Soedin.*, 1973, 31.
56. I. I. Grandberg and N. M. Przheval'skii, *Khim. Geterotsikl. Soedin.*, 1969, 943.
57. I. I. Grandberg, N. M. Przheval'skii, and V. I. Vysotskii, *Khim. Geterotsikl. Soedin.*, 1970, 1499.
58. I. I. Grandberg, T. I. Zuyanova, and K. K. Zhigulev, *Khim. Geterotsikl. Soedin.*, 1972, 1708.
59. I. I. Grandberg, T. A. Ivanova, and T. I. Zuyanova, *Izv. Timiryazevsk. S-Kh. Akad.*, No. 3, 212 (1970).
60. V. I. Vysotskii, R. A. Khmel'nitskii, and I. I. Grandberg, *Izv. Timiryazevsk. S-Kh. Akad.*, No. 5, 204 (1970).
61. I. I. Grandberg and S. N. Dashkevich, *Izv. Timiryazevsk. S-Kh. Akad.*, No. 1, 189 (1971).
62. I. I. Grandberg and S. N. Dashkevich, *Khim. Geterotsikl. Soedin.*, 1971, 1194.
63. K. K. Zhigulev, R. A. Khmel'nitskii, I. I. Grandberg, and V. I. Vysotskii, *Khim. Geterotsikl. Soedin.*, 1972, 1065.
64. I. I. Grandberg and N. M. Przheval'skii, *Izv. Timiryazevsk. S-Kh. Akad.*, No. 2, 192 (1972).
65. I. I. Grandberg, D. V. Sibiryakova, and L. A. Brovkin, *Khim. Geterotsikl. Soedin.*, 1969, 94.
66. T. McLean, S. McLean, and R. Reed, *J. Chem. Soc.*, 1955, 2519.
67. K. Pausacker and C. Schubert, *J. Chem. Soc.*, 1950, 1814.
68. H. Freundlich and H. Kroepelin, *Z. Phys. Chem.*, 1926, 122, 39.
69. N. M. Przheval'skii and I. I. Grandberg, *Khim. Geterotsikl. Soedin.*, 1974, 1581.
70. N. M. Przheval'skii, I. I. Grandberg, and N. A. Klyuev, *Khim. Geterotsikl. Soedin.*, 1976, 1065.
71. N. M. Przheval'skii, I. I. Grandberg, N. A. Klyuev, and A. B. Belikov, *Khim. Geterotsikl. Soedin.*, 1978, 1349.
72. B. A. Trofimov, S. E. Korostova, L. N. Sobekina, A. I. Mikhaleva, V. M. Bzhezovskii, M. V. Suchalov, and A. A. Atavan, *Khim. Geterotsikl. Soedin.*, 1982, 1931.
73. T. Sheradsky, *Tetrahedron Lett.*, 1970, 25.
74. H. O. House and F. L. Richey, *J. Org. Chem.*, 25, 1430 (1960).
75. I. I. Grandberg and N. I. Bobrova, *Izv. Timiryazevsk. S-Kh. Akad.*, No. 6, 220 (1978).
76. I. I. Grandberg, L. B. Dmitriev, V. I. Sorokin, and Yu. A. Larshin, *Khim. Geterotsikl. Soedin.*, 1979, 620.
77. N. A. Klyuev, I. I. Grandberg, L. B. Dmitriev, and Yu. A. Larshin, *Zh. Org. Khim.*, 15, 2274 (1979).
78. I. I. Grandberg and V. I. Sorokin, *Usp. Khim.*, 43, 266 (1974).
79. I. I. Grandberg, I. K. Yakushchenko, and L. B. Dmitriev, *Zh. Org. Khim.*, 15, 89 (1979).
80. I. I. Grandberg, I. K. Yakushchenko, and L. B. Dmitriev, *Izv. TSKhA*, No. 4, 170 (1979).
81. I. I. Grandberg and I. K. Yakushchenko, Inventor's Certificate No. 727608 (1977); *Byull. Izobr.*, No. 14 (1980).
82. J. Elquero, R. Jacquier, and C. Marzin, *Bull. Soc. Chim. Fr.*, 1970, 4119.
83. V. I. Vysotskii, R. A. Khmel'nitskii, I. I. Grandberg, and G. V. Fridlyandskii, *Izv. Timiryazevsk. S-Kh. Akad.*, No. 3, 206 (1971).
84. R. A. Khmel'nitskii, E. A. Kunina, S. N. Dashkevich, and I. I. Grandberg, *Izv. Timiryazevsk. S-Kh. Akad.*, No. 4, 214 (1971).
85. R. A. Khmel'nitskii, N. A. Klyuev, A. F. Dolgikh, T. P. Moskvina, and I. I. Grandberg, *Izv. Timiryazevsk. S-Kh. Akad.*, No. 3, 192 (1973).
86. R. A. Khmel'nitskii, V. I. Vysotskii, and I. I. Grandberg, *Zh. Org. Khim.*, 5, 417 (1969).
87. V. I. Vysotskii, R. A. Khmel'nitskii, I. I. Grandberg, and V. A. Budylin, *Izv. Timiryazevsk. S-Kh. Akad.*, No. 4, 221 (1970).
88. R. A. Khmel'nitskii, V. I. Vysotskii, I. I. Grandberg, A. N. Kost., and V. A. Budylin, *Zh. Org. Khim.*, 7, 1514 (1971).
89. N. A. Klyuev, I. I. Grandberg, V. P. Suboch, V. I. Vilochinskaya, and Yu. A. Larshin, *Zh. Org. Khim.*, 15, 2237 (1979).

90. V. I. Vysotskii, R. A. Khmel'nitskii, and I. I. Grandberg, *Izv. Timiryazevsk. S-Kh. Akad.*, No. 5, 204 (1970).
91. I. I. Grandberg and S. N. Dashkevich, *Izv. Timiryazevsk. S-Kh. Akad.*, No. 1, 189 (1971).
92. L. B. Dmitriev and I. I. Grandberg, *Izv. Timiryazevsk. S-Kh. Akad.*, No. 5, 206 (1973).
93. I. I. Grandberg, L. D. Belyaeva, and L. B. Dmitriev, *Khim. Geterotsikl. Soedin.*, 1973, 37.
94. I. I. Grandberg, L. D. Belyaeva, and L. B. Dmitriev, *Khim., Geterotsikl. Soedin.*, 1971, 1204.
95. I. I. Grandberg, L. B. Dmitriev, and L. D. Belyaeva, *Dokl. Timiryazevsk. S-Kh. Akad.*, 162, 398 (1971).
96. I. I. Grandberg, L. D. Belyaeva, and L. B. Dmitriev, *Khim. Geterotsikl. Soedin.*, 1971, 58.
97. L. B. Dmitriev and I. I. Grandberg, *Khim. Geterotsikl. Soedin.*, 1975, 946.
98. N. M. Przheval'skii and I. I. Grandberg, *Khim. Geterotsikl. Soedin.*, 1982, 940.