INDOLYLALKYLAMINES FROM ARYLHYDRAZINES AND γ- OR δ-HALOCARBONYL COMPOUNDS (REVIEW)

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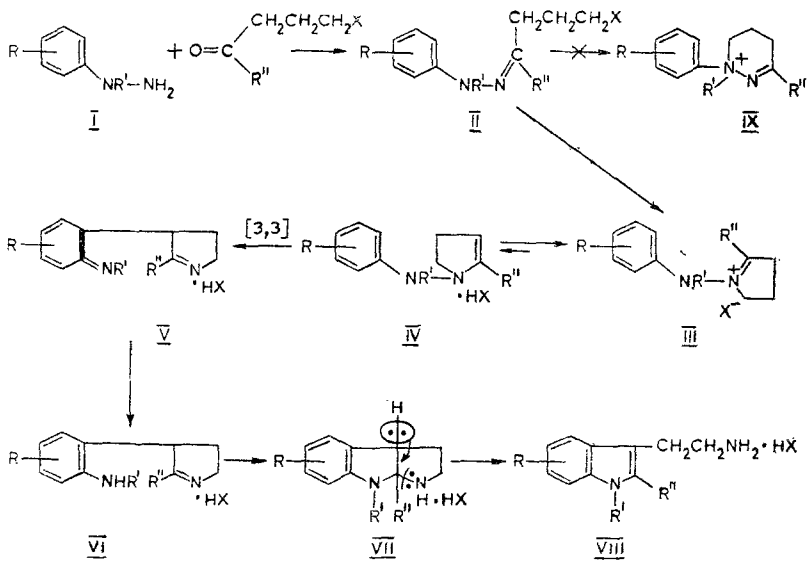
A series of papers devoted to the synthesis of tryptamines and related structures (tryptophols, homotryptamines, eserines, azatryptamines, etc.) from halocarbonyl compounds and arylhydrazines are correlated. The data on the mechanism of the reaction can be successfully applied to the Fischer indole synthesis.

In 1966 it was observed that phenylhydrazine, on heating in alcohol solution with γ-chlorobutyraldehyde [1, 2], forms tryptamine in quite a high yield instead of the expected 1-phenyltetrahydropyridazine. In the following six years a detailed study of the mechanism of the process, which leads to the formation of the most important biogenetic amines, made it possible not only to ascertain the details of this interesting reaction but also to obtain extremely important results related to the Fischer indole synthesis. The goal of this review is a correlation of all of the data on this most promising method at present for the synthesis of tryptamine and other similar structures.

Several arylhydrazines and γ-halocarbonyl compounds have reacted like phenylhydrazine and γ-chlorobutyraldehyde, but the formation of tryptamines did not seem very clear, especially since Sletzinger had previously obtained 3-(β-chloroethyl)indoles from 5-chloro-2-pentanone under the usual conditions of the Fischer reaction [3, 4]. The scheme for the process that had already been proposed in one of the first papers [5] satisfactorily explained all of the experimental facts and was then confirmed in detail (see below). According to this scheme, arylhydrazine I reacts with a γ-halo ketone or γ-halo aldehyde to give hydrazone II, which is cyclized to 1-anilinopyrroline salt III.



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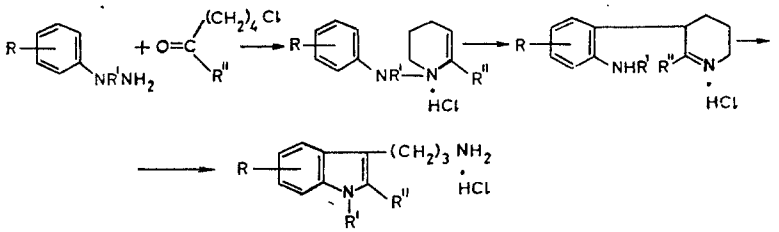
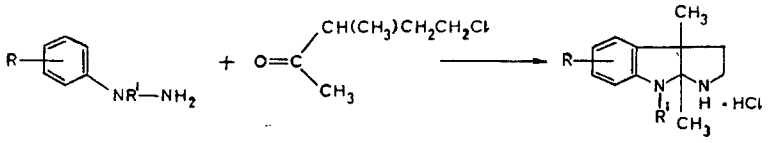
The latter, because of its weak basicity, exists partially in the form of unprotonated enamine IV, which forms structure V via a scheme involving a sigmatropic [3, 3] shift with cleavage of the N—N bond and formation of a C—C bond. Stabilization to an aromatic system leads to ortho-substituted aniline VI, which through addition of a NHR' group to the C=N double bond gives eserine derivative VII, which is stabilized by β-elimination with ejection of a proton and opening of the pyrrolidine ring to the aromatic structure of tryptamine salt VIII. This scheme proved to be extremely promising for subsequent studies in this field.

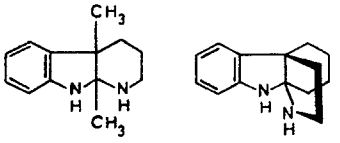
Tryptamines and Homotryptamines. No difficulties whatsoever were observed when the substituents in the benzene ring and those attached to the α-nitrogen atom of the arylhydrazine were varied and different 1,4-halocarbonyl compounds were used. The yields in most cases were quite high and reached 90% [5-13]. It was found that δ-halocarbonyl compounds react with arylhydrazines via a similar scheme to give 3-(γ-aminopropyl)indoles (homotryptamines) [9, 12-14].



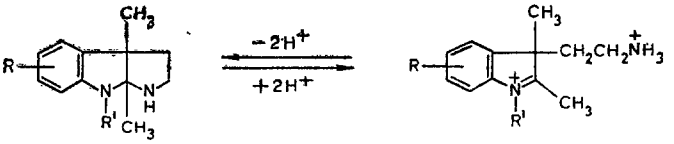
Eserine Systems. α-Alkyl-substituted γ-halo ketones have formed tricyclic eserine systems in high



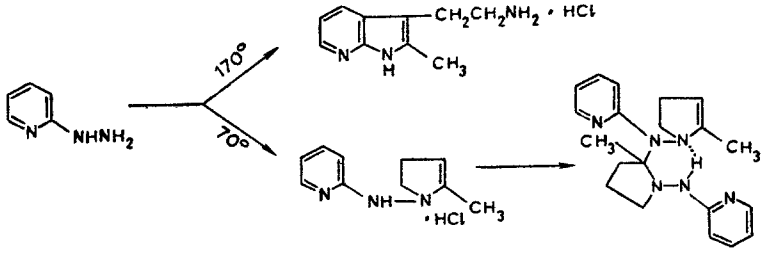
yields [15-18]. Homoeseroline systems and echiboline derivatives [17, 18] could be obtained when the corresponding halocarbonyl compounds were used.



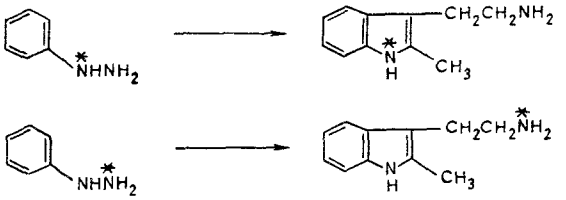
The ring-chain tautomerism of salts of such systems with the establishment of the regions of existence of tautomers as a function of the pH and structure of the compounds was investigated in detail in a number of papers [19, 20].



Azatryptamines. α-Pyridylhydrazine has formed the corresponding 7-azatryptamines in this reaction under somewhat more severe conditions [21]. However, under the usual conditions (at 70°C in methanol) the reaction stopped at the step involving a compound similar to form IV, and pyridylaminopyrrole existed as a dimer in neutral media [22].

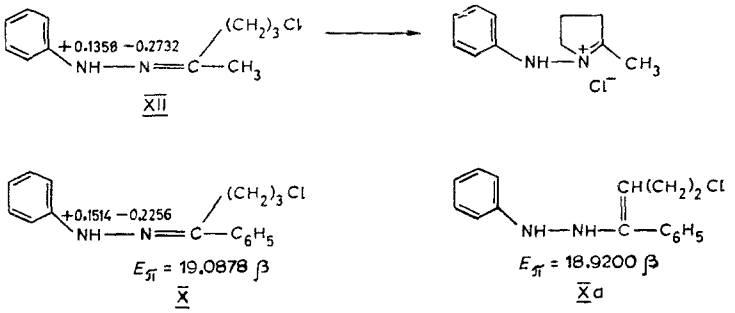


Reaction Mechanism. According to the reaction scheme, the β-nitrogen atom of the arylhydrazine participates in the formation of the amino group of the aminoethyl portion of the tryptamine molecule. In order to confirm this assumption, α-^{15}N-phenylhydrazine was converted to 2-methyltryptamine by heating under the usual conditions with γ-chloropropyl methyl ketone. If the scheme is valid, the 2-methyltryptamine formed should contain the ^{15}N isotope in the 1 position, while the 2-methyltryptamine obtained from β-^{15}N-phenylhydrazine should contain the ^{15}N isotope in the amino group of the side chain of the indole. In fact, mass-spectral analysis of the tryptamines proved the presence of the label at the sites of the molecules corresponding to the scheme below [23].



When one examines the scheme, a question naturally arises regarding the prevailing direction of the cyclization, i.e., regarding the quaternization of the α- or β- nitrogen atoms in the hydrazone molecule. This question was solved partially by calculations of several systems by the MO LCAO method within the Huckel approximation [24].

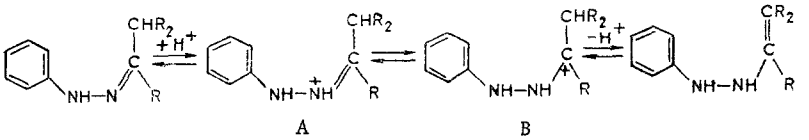
A comparison of the π-electron densities on the α- and β-nitrogen atoms of the hydrazones shows distinctly that the β-nitrogen atom is always more basic, although the basicity of hydrazones is less than the basicity of hydrazines, on the average by two orders of magnitude [25].



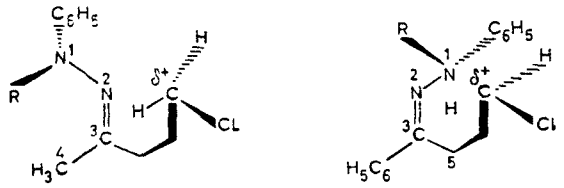
The formation of 1-anilinopyrroline III rather than a tetrahydropyridazine system of the IX type during quaternization is in complete conformity with the established rule [26].

Despite the fact that the "hydrazone" form for the resulting anilinopyrroline salt (III ⇌ IV) is more favorable from an energy point of view (see E_π for X and Xa and [24]), the tautomeric and, apparently, unprotonated enehydrazine form (IV), in which the atoms in the 1 and 6 positions are situated closely enough for formation of a C—C bond, naturally undergoes reaction [24].

One should especially note the following fact. According to the general scheme for the Fischer indole synthesis, the rate-determining step of the process is the formation of the enamine form as a result of prototropic catalysis [27] (see also [28] for the role of enamines in the Fischer reaction).



However, not every act of protonation should lead to the enamine form, and, in connection with the "energic disadvantageousness" of the enamine form, the time during which it exists may be so short that there is not enough time for the next step – a sigmatropic [3,3] shift – to be realized (see below). The situation differs sharply for the analogous 1-anilinopyrroline fragment in the scheme of the synthesis of tryptamines. Unprotonated form IV cannot exist in the hydrazone form but exists only in the enamine form; this sharply increases the possibility for the occurrence of the next step – sigmatropic [3,3] shift.

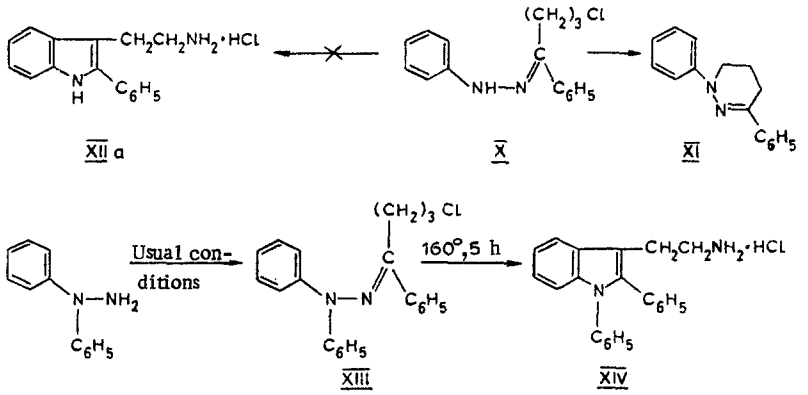


anti-form syn-form

Fig. 1. Conformations of hydrazone molecules (Dreiding models).

Results that attest to the significant effect of conformational factors as well on the trend of the process were obtained in a more detailed study of the reaction. For example, the reaction of phenylhydrazine with γ-chloropropyl phenyl ketone, which proceeds through a step involving the formation of hydrazone X, gives tetrahydropyridazine XI instead of the expected tryptamine (XII). Moreover, cyclization occurred at the α-nitrogen atom even during the reaction with α-benzylphenylhydrazine and the formation of the same pyridazine (XI) due to splitting out of benzyl chloride from the unstable quaternary salt. The differences in the π-electron densities of the nitrogen atoms in the molecules of hydrazones X and XII are not so significant as to induce reorientation during intramolecular cyclization. A conformational analysis of the hydrazone molecules successfully explained the reason for the change in the course of the reaction [24].

According to the general concepts regarding the configuration of molecules with a multiple bond, the 1-5 atoms should lie in a single plane (Fig. 1). The steric prerequisites for convenient attack of the C—Cl fragment are present in the anti form only on the most basic β-nitrogen atom (Dreiding model). In addition, the distance between the 2 and 7 atoms is close to the length of the C—N bond (~2 Å).



XII a X XI

XIII XIV

In the case of hydrazone X by virtue of π,π conjugation, the phenyl ring attached to the carbon atom strives to position itself in the plane of the 1,2,3 fragment (Fig. 1), as a consequence of which the presence of the anti form becomes sterically impossible, and the hydrazone can exist in the syn form. The relative position of the nitrogen atoms and the C—Cl fragment in it is such that only the α atom rather than the β atom can undergo electrophilic attack, although the latter is also more basic.

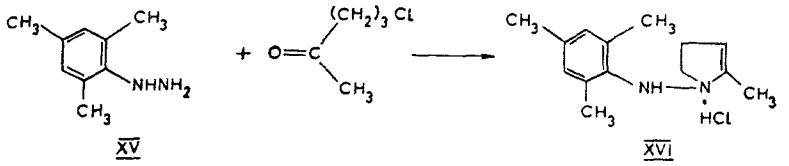
The correctness of these concepts was confirmed by the isolation of phenyl γ-chloropropyl ketone diphenylhydrazone (XIII) under the usual conditions of the reaction [24]. In this case, pyridazine was not formed because of the markedly increased basicity of the α-nitrogen atom, but the tryptamine was formed because of the fact that the hydrazone exists in the syn form. Isomerization of the syn form to the anti form occurred only under considerably more severe conditions (160° for 5 h), and the corresponding tryptamine (XIV) was formed.

Thus, calculation of the π-electron density of hydrazone molecules, their conformational analysis, and the directed change of the basicity of the α- and β-nitrogen atoms of the hydrazones made it possible to explain one of the basic steps that determines the direction of the process – the step involving intramolecular quaternization (II → III).

All of the intermediates were isolated and their structures were established during a detailed study of the reaction to form the tryptamines [24, 29, 30]. It is easy to note that hydrazone XII (mentioned above) is intermediate II (R=H, R'=R"=C_6H_5, X=Cl).

It proved to be possible to synthesize γ-chloropropyl methyl ketone phenylhydrazone (XIIa) by carrying out the reaction in benzene (rather than in alcohol as is usually done) without heating [29].

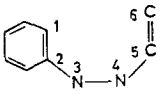
Compound XVI, which is similar in structure to intermediate III, was obtained from 1,3,5-trimethylphenylhydrazine (XV) [29].



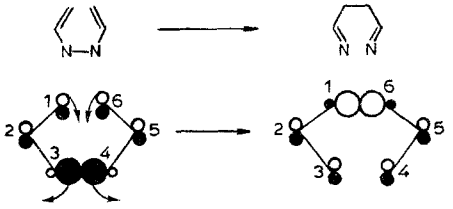
XV XVI

It has been proposed that the most important step of the process – formation of the C–C bond (IV → V) – be considered to be a sigmatropic [3,3] rearrangement [31]. The approach from the point of view of the Woodward–Hoffmann general principle, which is considered below, had already been successfully applied in the examination of the Claisen rearrangement [32]. In [31] it is proposed that the principal step in the Fischer indole synthesis (formation of the C–C bond) and in a number of other related processes (for example, the benzidine rearrangement) be considered to be a sigmatropic [3,3] shift.

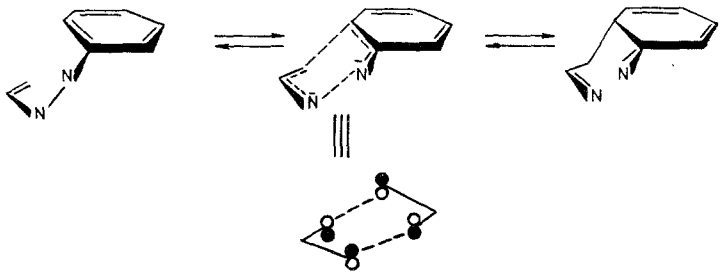
As applied to the step under consideration, it is proposed that the sigmatropic [3,3] shift occurs in the following manner. Simplifying, it is necessary to examine only the fragment of the molecule consisting of the six atoms of the IV form that participate directly in the process. The nitrogen atoms can be formally considered to be carbon atoms and, consequently, it can be supposed that their p electrons do not participate in the process.



Under the condition of retention of the orbital symmetry, within a rough approximation, the sigmatropic [3,3] shift occurs approximately in this manner for the 1,5-hexadiene fragment. The lobes of the N–N σ bond in the 3,4 position swing around and become further away from one another, while the terminal lobes of the π bonds in the 1-6 position begin to approach one another as they swing around. In this case, rehybridization of the atoms ($sp^3 \rightarrow sp^2$ for the 3 and 4 atoms and $sp^2 \rightarrow sp^3$ for the 1 and 6 atoms) also gradually takes place.



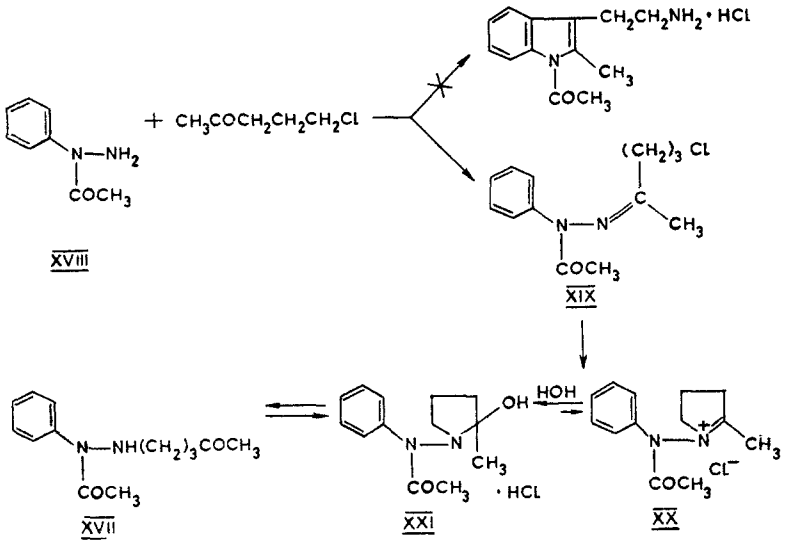
The transition state is a four-center state – chair conformation – and has the form of the two upper occupied molecular orbitals of allyl radicals, for which the 3-4 bond is not yet definitely broken and the 1-6 bond is not yet definitely formed. The development of the chair conformation (rather than the boat conformation) is determined by its greater advantageousness because of lower repulsion of the nonbonding molecular orbitals in the transition state [31].



Only a transition-state structure that permits supra-supra migration of the σ bond in the ground state is possible for the planar structure of the N-aryl fragment.

The use of α-acylarylhydrazines in the reaction proved to be extremely interesting from the point of view of the elucidation of the detailed mechanism of the process. In an attempt to synthesize a tryptamine arylated in the 1 position of the indole ring it was unexpectedly observed that α-acetyl-β-(3-acetylpropyl)-phenylhydrazine (XVII) – the product of alkylation of α-acetylphenylhydrazine (XVIII) with a chloro ketone –

rather than the expected tryptamine [30] is formed when equimolar amounts to the starting compounds are refluxed.



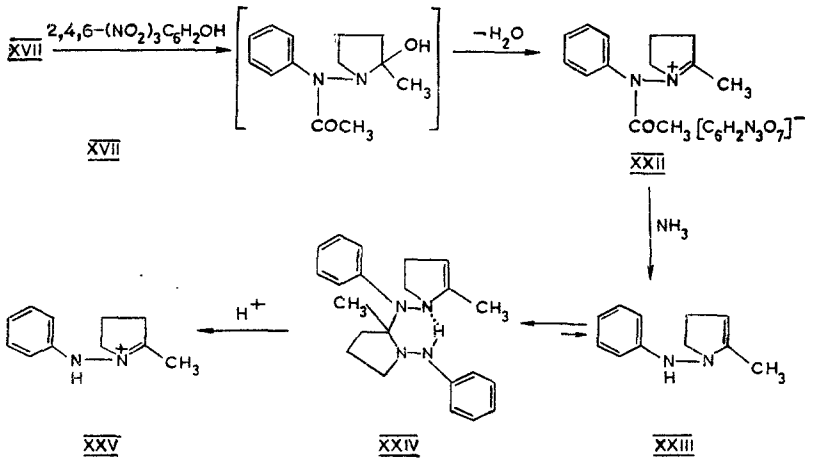
A thorough study of this reaction showed that XVII is not formed by direct alkylation of hydrazine XVII.

α-Acetylphenylhydrazine (XVIII) reacts with the carbonyl group of the chloro ketone to give phenylhydrazone XIX. The hydrazone then cyclizes to 1-anilinopyrroline hydrochloride (XX), which undergoes hydrolytic opening of the ring to give hydrazine XVII. The proof of this scheme was based on a study of the dynamics of the intensity of the absorption band of the ketone carbonyl group in the IR spectrum [30].

Compound XVII very readily loses a water molecule. Thus, even during treatment with picric acid, it cyclizes with splitting out of water to form the picrate of 1-acetylanilino-2-methyl-Δ^2-pyrroline (XXII) – an intermediate of the IV type (R=H, R'=$COCH_3$, R"=CH_3).

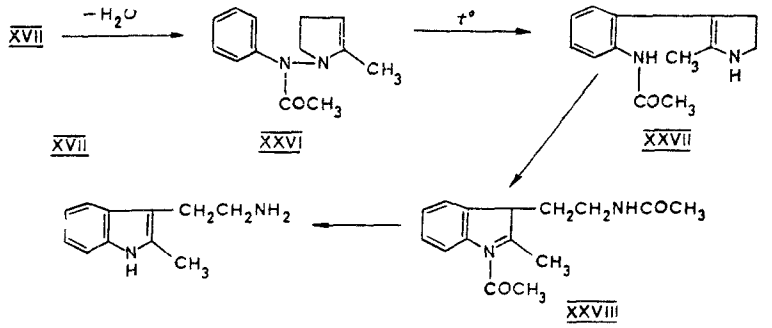
Base XXIII, which exists as dimer XXIV under these conditions, is isolated on treatment of picrate XXII with liquid ammonia with simultaneous removal of the acetyl group. Dimer XXIV is converted to the salt of monomer XXV in acidic media (at pH < 1.6) [30] (see also [22]).

Base XXVI, which corresponds to 1-anilinopyrroline IV, was obtained by refluxing XVII in xylene with removal of an equimolar amount of water by distillation.



Crystalline substance XXVII, which is similar in structure to intermediate VI (R=H, R'=$COCH_3$, R"=CH_3), was isolated on distillation of XXVI.

Treatment of intermediate XXVII with boiling acetic anhydride gives diacetylated 2-methyltryptamine XXVIII, which readily converted to 2-methyltryptamine during acid hydrolysis [30].

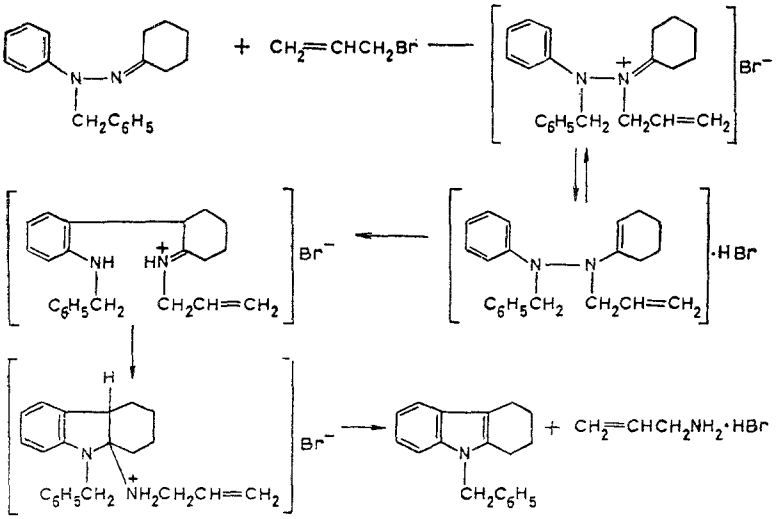


The latter intermediate of the VII type was obtained as a result of the reaction of phenylhydrazine with 5-chloro-3-methyl-2-pentanone [17] (see the scheme on p. 502).

The structure of all of the intermediates described above was proved rigorously by IR, UV, and PMR spectroscopy and mass spectrometry [33-37].

An attempt has been made to study the kinetics of the formation of tryptamines [38]. Two reactions – the synthesis of 9-benzyltetrahydrocarbazole [39] and the synthesis of 2-methyltryptamine – have been selected as model reactions. The mechanisms of these reactions are similar, but in the case of the formation of 2-methyltryptamine, quaternization of the β-nitrogen atom of the arylhydrazine occurs intramolecularly, while quaternization occurs intermolecularly in the case of the formation of N-benzyltetrahydrocarbazole.

According to the data obtained by McLean and co-workers [40] and Pausacker and Schubert [41], the rate of the Fischer reaction corresponds approximately to a first-order equation. A study of the kinetics of the formation of 9-benzyltetrahydrocarbazole also gave a first-order equation for this reaction [39].

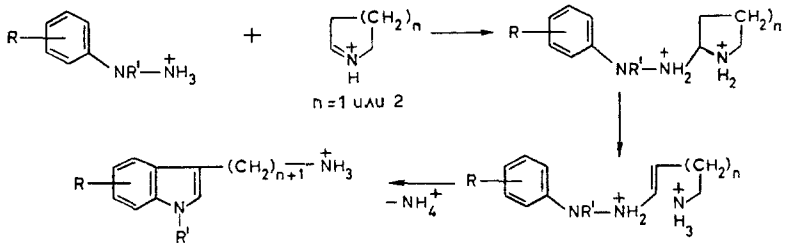


Ionic halogen (bromine in this case) appears in the step involving quaternization of the β-nitrogen atom of hydrazine. If the Br concentration at each given instant coincides with the concentration of the final product – allylamine hydrobromide – the assumption that the step that determines the rate of the overall reaction is quaternization is valid. In fact, this sort of coincidence of the concentrations has been observed [38].

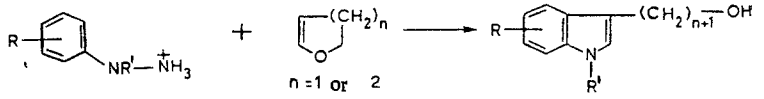
As one should have expected, the slowest step in the formation of 2-methyltryptamine also should be quaternization of the nitrogen atom, which leads to the formation of 1-anilinopyrroline (II → III). This was shown in the following way. First, it was established that the step involving the formation of the hydrazone is not the limiting step. With this in mind, the dependence of the intensity of the absorption of the carbonyl group of γ-chloropropyl methyl ketone on time during its reaction with phenylhydrazine was studied spectrophotometrically. It was found that the reaction is complete (~90%) after 2 min, while the same degree of conversion of the starting compounds to 2-methyltryptamine (under the same conditions) requires > 300 min. Second, the Cl^- concentration at any instant coincided with the tryptamine concentration; as in the

case of the formation of the carbazole, this indicated the correctness of the selection of the step involving quaternization as the limiting step. Third, a sharp increase in the reaction rate was observed when the alcohol was diluted with water. This confirmed the point of view that the step involving quaternization determines the rate of the process. There are similar examples that describe this sort of acceleration during the cyclization of ω-aminoalkyl halides in the literature [42]. Despite the fact that the rate of formation of 2-methyltryptamine was determined, as attested to by direct and indirect data, by the rate of the second step – quaternization of the β-nitrogen atom – no definite order could be assigned to this reaction; the reaction order was found to be 1.28. The deviation of this value from unity apparently indicated the effect of other intermediate steps also on the rate of the process.

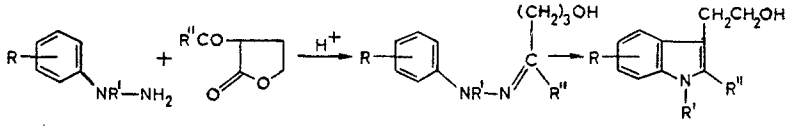
Indolylalkylamines from Cyclic Enamines. In attempts to further extend the range of application of the reaction it was found that arylhydrazine salts react with the salts of cyclic enamines via the scheme below to give the corresponding tryptamines or homotryptamines [43-48].



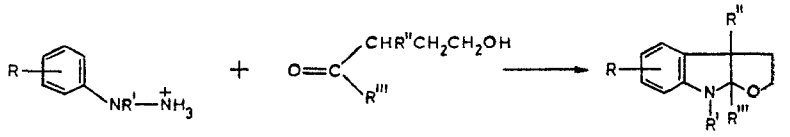
Tryptophols and Homotryptophols from Cyclic Vinyl Ethers. Similarly, participation of cyclic vinyl ethers in place of cyclic enamines led to the corresponding tryptophols [49, 50] and homotryptophols [49-54].



The method was later modernized, and the tryptophols were obtained from α-acylbutyrolactones, which formed the tryptophols in a one-step process after hydrolysis and decarboxylation [55].



Physovenine Structures. The use of theoretical representations of the Fischer synthesis and some modified methods for its realization [56-58] have made it possible to work out an important (in a practical sense) scheme for the preparation of physovenine structures [36, 59-63].



Ring-chain tautomerism, which was investigated in detail in [36], is characteristic for salts of the latter and for salts of eserines in acidic media [36].

Physicochemical Investigations. The investigation of the indole derivatives described above by means of physicochemical methods is partially reflected in the papers already cited. In addition, one may familiarize himself with mass-spectra data [64-69], with PMR spectroscopic data [34, 35], and gas–liquid chromatographic analysis [70-74] in special papers.

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