FISCHER SYNTHESIS OF INDOLES FROM 2,6-DISUBSTITUTED ARYLHYDRAZONES

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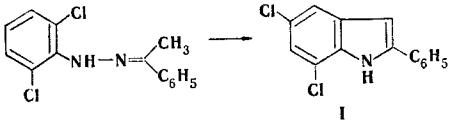
UDC 547.759.1.3.07

A review of the literature data on the Fischer synthesis of indoles from 2,6-disubstituted arylhydrazones is given. As a result of their own experimental studies of the indolization of hydrazones from 8-R-N-amino-1,2,3,4-tetrahydroquinolines the authors established that no less than five different transformations of the cyclohexadienoneimine intermediate, including 1,2 and 1,4 shifts and splitting out of the substituent, may follow attack on the 8 position of the tetrahydroquinoline ring. Attack in the 10 position of the tetrahydroquinoline ring leads to another cyclohexadienoneimine, which undergoes indolization with the loss of a propylamine chain via a different mechanism. It was proved by experiments with labeled compounds that 1,3 migration of the methyl group (R = CH_3) is the result of a double 1,2 shift, while the 1,4 shift is a direct reaction.

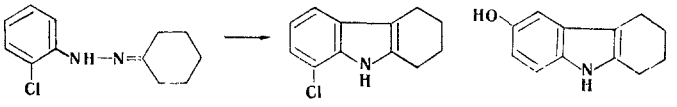
The Fischer synthesis of indoles is one of the most complex and diversfied reactions [1-3]. In the case of o,o'-disubstituted arylhydrazones indolization proceeds with the simultaneous shift and elimination or replacement of groups, but relatively little study has been devoted to the effect of the character of the substituents in the 2 and 6 positions on the course of the reaction.

It is known that 2,6-dihalophenylhydrazones form indoles with a halogen in the "meta" position relative to the starting compound [4, 5].



I

Substitution products may be formed in some cases [6, 7].



II

These, as well as other results [8, 9], are in agreement with the mechanism in [10], which assumes the initial formation of a cyclohexadienoneimine intermediate via the well-known Robinson scheme [11, 12].

Dichloroindole I is obtained by allylic migration of the chlorine atom with subsequent ring closure, while 6-hydroxy-1,2,3,4-tetrahydrocarbazole (II) may be formed due to simultaneous nucleophilic attack by the hydroxy group and loss of a chlorine atom in the allyl position.

The production of 4-aminoindole VI [13, 14] can also be explained by the formation of intermediate structure IV, which can be reduced by III and undergo cyclization to give indole V or can be converted to aminoindole VI.

Institute of Industrial Chemistry, Center for the Study of Methods for the Synthesis and Stereochemistry of Special Organic Systems, Milan, Italy. Translated from Khimiya Geterotsiklicheskikh Soedinenii, No. 2, pp. 200-216, February, 1978. Original article submitted January 25, 1977.

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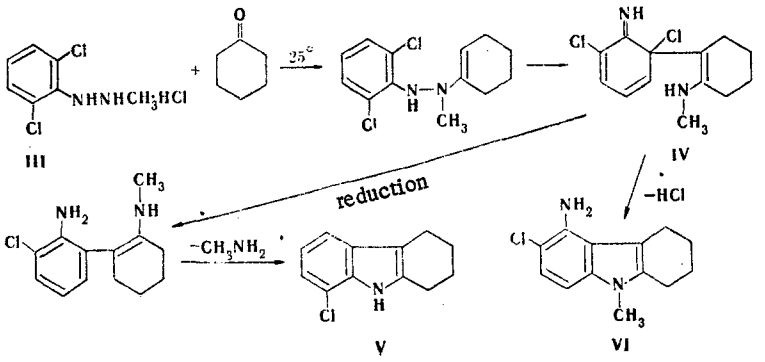
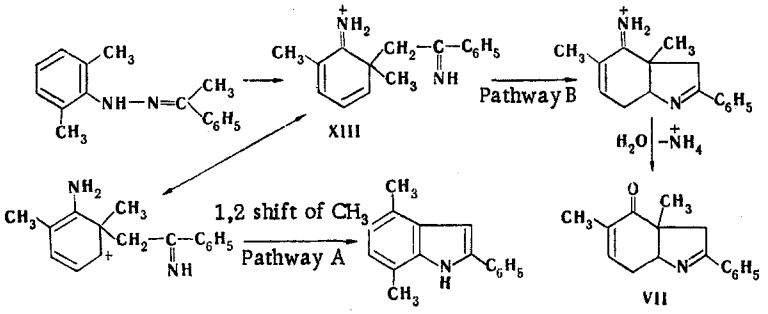
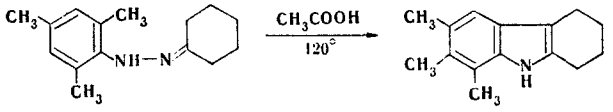


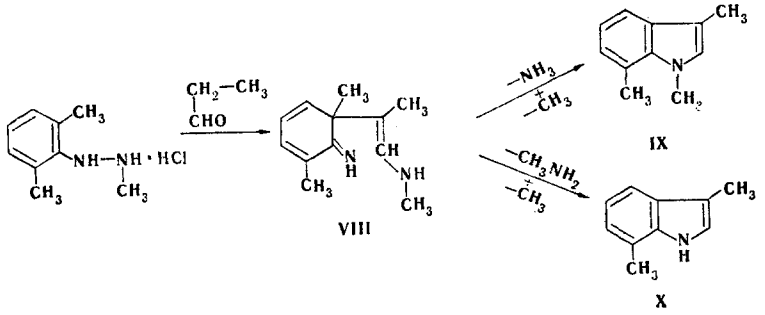
A 1,2 shift of the methyl group [15, 16], which may be a consequence of isomerization of the carbonium ion (pathway A) [8, 17], is usually noted in the case of methyl-substituted phenylhydrazones. The formation of nonaromatized structure VII proceeds simultaneously (pathway B).



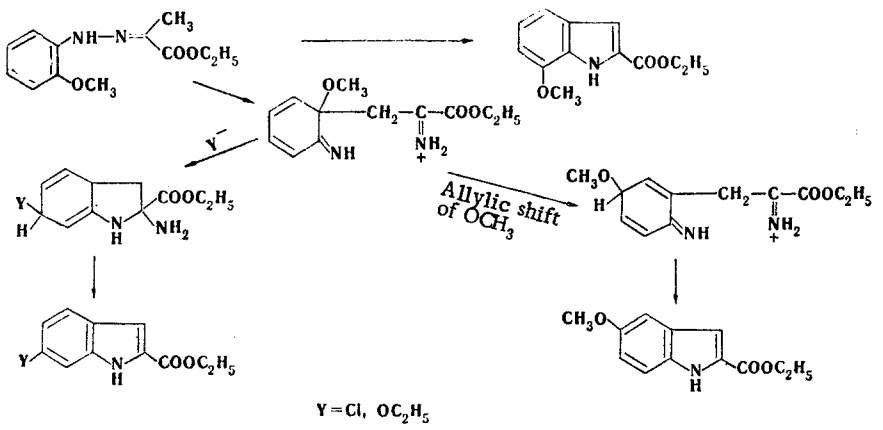
A rearrangement occurs in only one case, which was studied in detail by Carlin and Moores [18, 19]; they explained this rearrangement as a 1,4 shift of the methyl group.



Instances of indolization with the loss of a methyl group have been frequently mentioned in the literature [20-23], but the fate of the detached group has never been ascertained. For example, in the case pointed out by Bajwa and Brown [24] indoles IX and X are formed by splitting out of a methyl group and ammonia or methylamine, respectively, from intermediate VIII.



Other rearrangements that can be explained by attack on the position initially occupied by the methoxy group also take place in addition to the usual reaction in the indolization of ethyl pyruvate o-methoxyphenylhydrazone. The nature and relative properties of the products depend on the experimental conditions (the catalyst and the solvent).

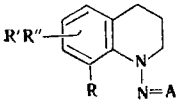


Y=Cl, OC_2H_5

Active methylene compounds (acetylacetone, acetoacetic ester, and indole) can also participate as nucleophiles (in place of anion Y) in this reaction [30-31], and this may lead to the formation of diindolyl compounds.

Recent Results

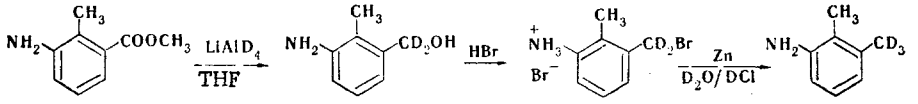
Taking the above material into account, we investigated arylhydrazones XII obtained from N-amino-1,2,3,4-tetrahydroquinolines (see Table 1).



XII a-n

The synthesis of the compounds was carried out via the following scheme: aromatic amine $\xrightarrow{\text{Skraup synthesis}}$quinoline $\xrightarrow{\text{reduction}}$tetrahydroquinoline derivative $\xrightarrow{HNO_2}$N-nitrosotetrahydroquinoline $\xrightarrow{\text{reduction}}$N-aminotetrahydroquinoline $\xrightarrow{\text{carbonyl compound}}$arylhydrazone.

The 2-methyl-3-trideuteromethylaniline necessary for the synthesis of XIIe was obtained in good yield via the following scheme:

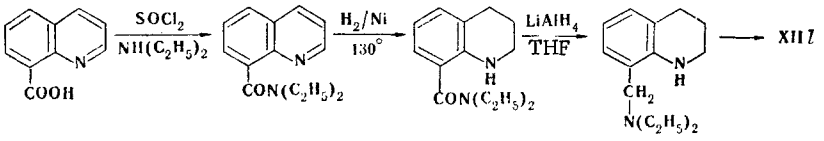


Trideuteroxylidine was obtained in satisfactory yield in one step by reduction of 4-carbomethoxy-2-methylaniline with lithium aluminum deuteride.

The Skraup reaction was carried out under the usual conditions, but the quinoline ring was reduced catalytically over Raney nickel or with sodium in butanol.

The conversion of the nitroso derivatives to hydrazine required selection of the reaction conditions for each compound. Satisfactory results were obtained with $LiAlH_4$ in ether at 25°C, but some of the nitroso derivatives with bulky substituents in the 8 position were reduced only by zinc in dilute acetic acid with the simultaneous formation of the hydrazone in the presence of excess carbonyl compound.

Hydrazone XIIℓ was obtained from quinoline-8-carboxylic acid via the following scheme:

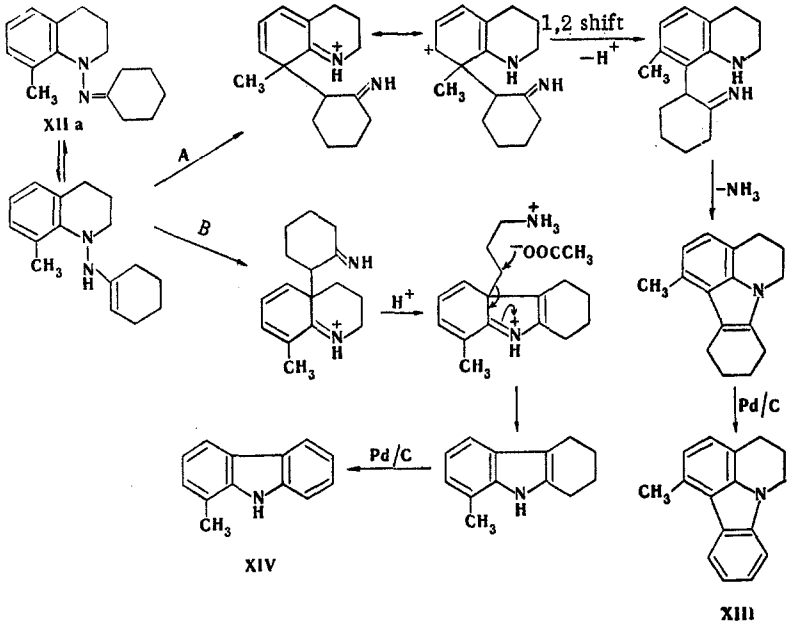


The indole rearrangement of these substances does not require severe conditions: Brief refluxing with HCl or H_2SO_4 in methanol is sufficient for completion of the reaction with acetoacetic acid hydrazones, whereas brief heating with glacial acetic acid is required for cyclohexanone hydrazones.

TABLE 1. Arylhydrazones

Compound	Position and character of the substituent			*
	6	7	8	
XIIa	H	H	CH_3	a
XIIb	H	H	CH_3	b
XIIc	H	CH_3	CH_3	a
XIId	H	CH_3	CH_3	b
XIIe	H	CD_3	CH_3	b
XIIf	CH_3	H	CH_3	a
XIIg	CD_3	H	CH_3	a
XIIi	CH_3	—	CH_3	b
XIIj	H	$-(CH_2)_4-$		b
XIIk	H	$-(CH_2)_3-$		b
XIIl	H	H	$CH_2N(C_2H_5)_2$	b
XIIm	H	H	$CH_2C_6H_5$	b
XIIn	H	H	C_6H_5	b

*The hydrazones were obtained from: a) acetoacetic ester (usually the methyl ester) and b) cyclohexanone.



Indolization of hydrazone XIIa with subsequent aromatization* over Pd/C led to the formation of XIII and XIV, which were isolated by chromatography.

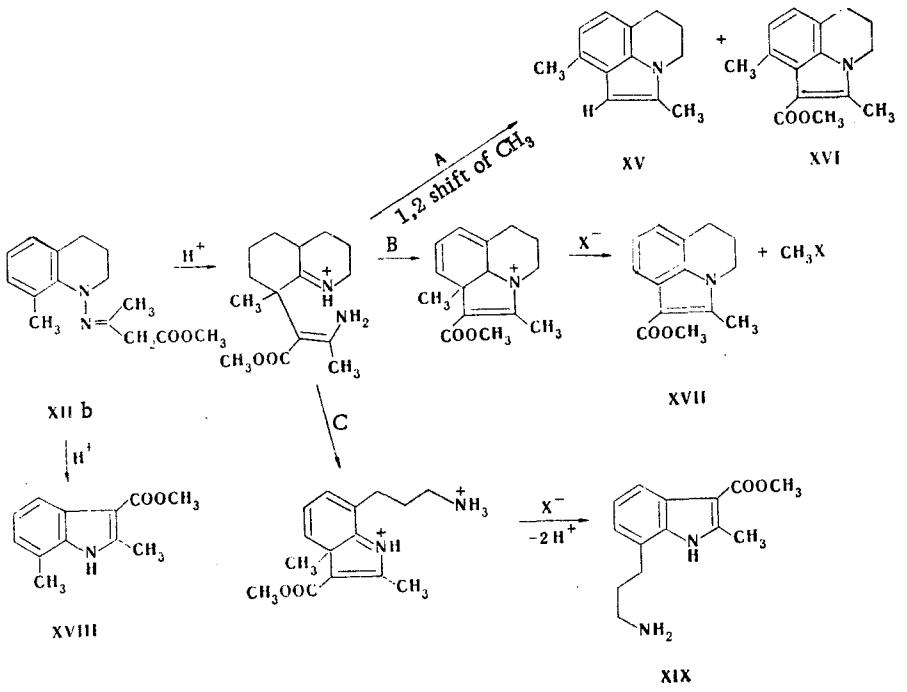
The fate of the propylamino fragment was studied in detail in the case of hydrazone XIIk (see [35]). Indolization of hydrazone XIIb in a methanol solution of HCl or in glacial acetic acid leads to a mixture of five substances (XV-XIX) (see scheme on the following page).

The formation of indoles XV and XVI is related to scheme A in the preceding case (attack in the 8 position and 1,2 shift of the methyl group). A $COOCH_3$ group may be split out (to give XV) in the step preceding the formation of the indole ring, since XVI is extremely resistant to acidic or alkaline hydrolysis.

The formation of indole XVII proceeds with splitting out of a methyl group. This type of reaction has been previously noted, but the fate of the methyl group was unknown [20-24].

We repeated the synthesis using the ethyl ester rather than the methyl ester and by carrying out the reaction in benzene in the presence of dry HCl; we were able to trap and identify the methyl chloride formed in the demethylation in this case.

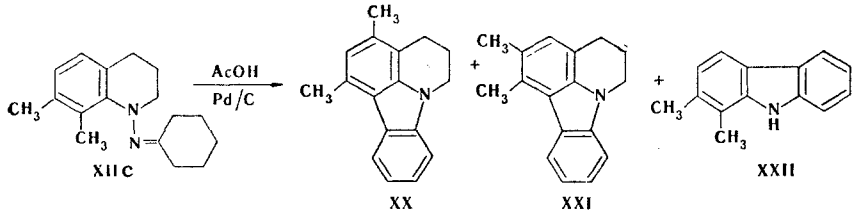
*The tetrahydrocarbazoles obtained by indolization of cyclohexane arylhydrazones were dehydrogenated to avoid rapid oxidation [32-34].



The mechanism of the formation of indole XVIII is evidently the same as the mechanism for indole XIV, whereas in the case of aminopropylindole XIX the reaction proceeds through a different type of cleavage of the intermediate (see the scheme above).

An alternative mechanism for the formation of XVII and XIX suggests splitting out of a methyl group to give a five-membered ring.

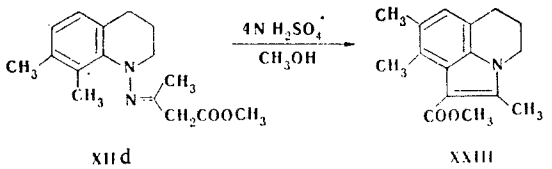
Indolization of hydrazone XIIc after dehydrogenation led to a mixture of three carbazoles, from which XX and XXII were isolated in the individual state.



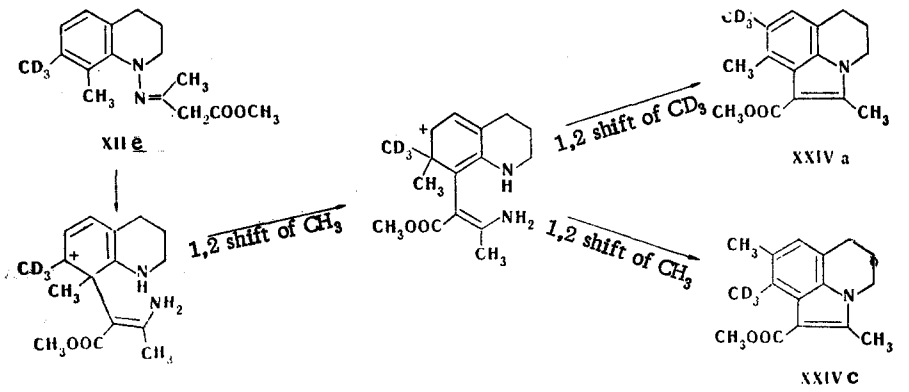
We established the structure of XXI by comparing the PMR spectrum of the mixture with the spectra of the pure isomers synthesized by another method.

Compound XX is evidently formed by a 1,3 shift of the methyl group, whereas XXI is formed by a 1,4 shift of the methyl group. The mechanism of this rearrangement will be subsequently discussed in detail. Carbazole XXII is formed via a scheme similar to the previously examined scheme.

Indolization of hydrazone XIId led to only indole XXIII in good yield. Its structure was confirmed by alternative synthesis [36].

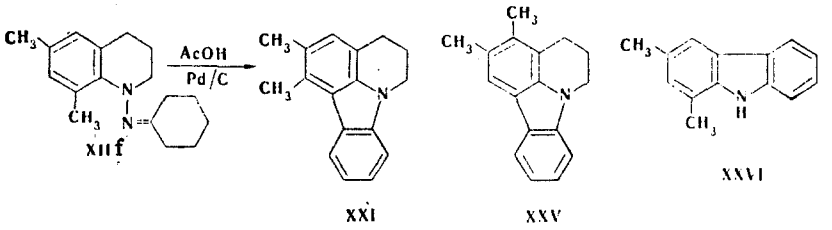


Even in this case indolization occurred with a shift of the methyl group. In order to establish whether this rearrangement is the result of a double 1,2 shift of the methyl group or a direct 1,3 shift we carried out the rearrangement of hydrazone XIIe with a labeled methyl group. The PMR spectrum showed that a mixture (1:1) of isomers XXIVa and XXIVb, which can be formed only through a step involving an intermediate structure with methyl and trideuteromethyl groups attached to the same carbon atom, is formed. Consequently, a 1,2 shift occurs in this case.



Indolization of hydrazone XIIf and subsequent dehydrogenation led to carbazoles XXI, XXV, and XXVI, which were isolated by means of chromatography.

The XXI and XXV structures were confirmed by alternative synthesis.



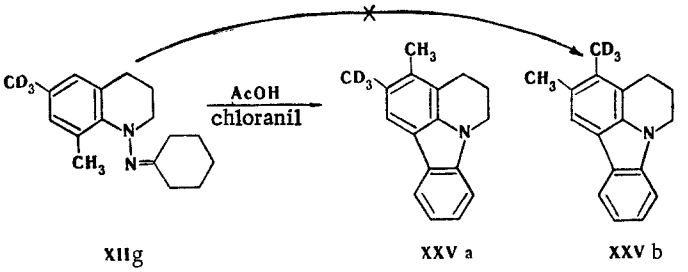
The formation of XXI can be explained by a 1,2 shift of the methyl group [15, 16], whereas the formation of carbazole XXVI proceeds through attack at the 10 position of the quinoline ring with splitting out of a propylamine chain. Carbazole XXV is produced by 1,4 migration of the methyl group similar to the migration mentioned for hydrazone XXd.

Since carbazole XXV was isolated in pure form in this case, we used this reaction to study the mechanism of the 1,4 shift, which is seldom encountered in the chemical literature. Some authors feel that a mechanism of this sort is unlikely and prefer a triple 1,2 shift of the methyl group [37, 38].

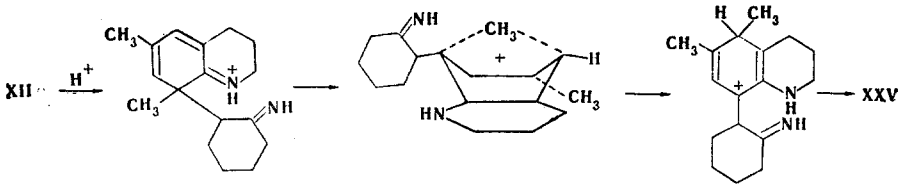
We subjected a labeled hydrazone to indolization [39], during which aromatization of the tetrahydrocarbazoles was effected with chloranil rather than with Pd/C, since it was established in a preliminary experiment that splitting out of deuterium occurs in the presence of Pd/C.

Signals of only the XXVa isomer were observed in the PMR spectra, and the XXVb isomer was absent. This provides solid evidence that the 1,4 migration of a methyl group does not include the formation of new bonds between the migrating component and the carbon atoms of the aromatic ring at the level of the intermediates (see scheme on the following page). The experimental data on 1,4 migration are in agreement with the hypothesis of a transition state in which the migrating methyl group is located between the 1 and 4 carbon atoms in the cyclohexadiene system in the boat form, in conformity with the Carlin hypothesis.*

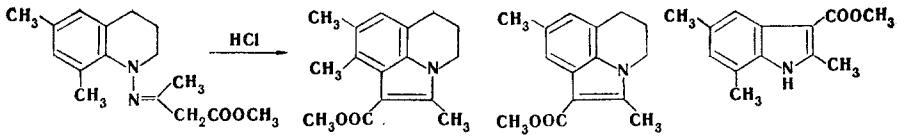
*However, a hypothesis regarding counterclockwise migration of the methyl group was recently expressed [40].



XIIg XXV a XXV b

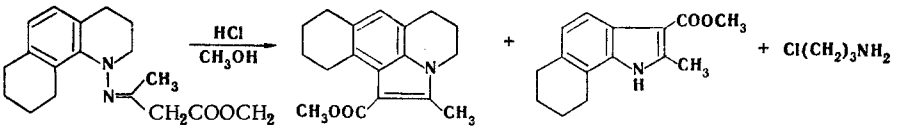


Indolization of XIIi gave XXIII, XXVII, and XXVIII; the mechanisms of their formation are in agreement with the mechanisms already mentioned above.



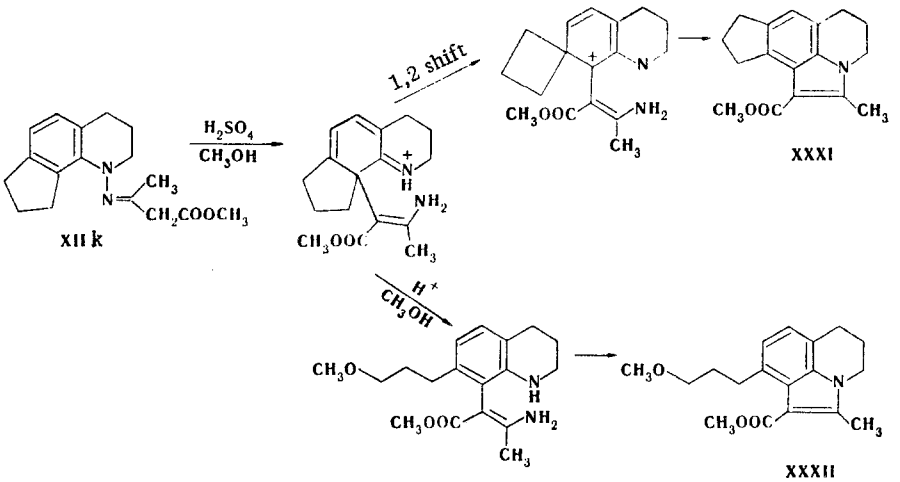
XIIi XXIII XXVII XXVIII

Hydrazone XIIj, in which the 7 and 8 positions are connected by a tetramethylene chain, behaved like XIId [41]. Compound XXIX is formed by a double 1,2 shift through a spiran intermediate, and XXX is formed by attack of the 10 position of the tetrahydroquinoline ring with splitting out of a propylamine fragment in the form of γ-chloropropylamine.



XII j XXIX XXX

We therefore decided to study whether a similar substance with a trimethylene chain would undergo a double 1,2 shift, which in this case should occur through a spirocyclobutane carbonium ion that is quite strained and is formed with great difficulty. Compounds XXXI and XXXII were obtained by indolization of XIIk by refluxing with H_2SO_4 in methanol [42].



XII k XXXI XXXII

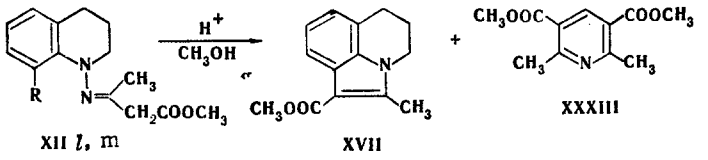
The formation of the first of these compounds as the principal product indicates that the reaction proceeds through a spirocyclobutane intermediate, but the presence of XXXII shows that it is formed with greater difficulty than the corresponding spirocyclopentane.

In addition to this reaction one observes competitive splitting out of the group in the 8 position upon reaction with the nucleophile that is present in the solution.

Since the splitting out of substituents has been previously mentioned [20-23] in the Fischer indole synthesis and has also been noted in the course of our research, we planned experiments with compounds in which the nature of the substituents would promote splitting out of substituents rather than migration.

We assumed that these groups would be capable of forming particularly stable carbonium ions. With the above in mind, we studied the indolization of XIIl [43] and XIIm.

The only indole compound obtained from XIIl and XIIm was XVII; i.e., the side chain was split out during the reaction.

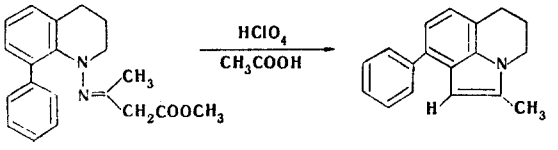


XII l, m XVII XXXIII

XII l R=$CH_2N(C_2H_5)_2$; m R=$CH_2C_6H_5$

The isolation of pyridine XXXIII (in the case of XIIl) can be explained by reaction of the β-aminocrotonic ester with formaldehyde (or its functional derivative) via the scheme of the Hantzsch synthesis. In this case the initially formed dihydro structure should undergo oxidation and can consequently reduce the N–N bond of the starting hydrazone. In fact, when benzophenone N-methylphenylhydrazone is refluxed briefly with H_2SO_4 in methanol in the presence of the Hantzsch ester, it is reduced quantitatively to acetophenone and methylaniline.

If there is a phenyl group (hydrazone XIIn) rather than an alkyl group in the 8 position, indole XXXIV, which is formed by a 1,2 shift of the phenyl group [43], is obtained in low yield.



XII n XXXIV

Thus we have observed different pathways for the indolization reaction (see scheme on the following page).

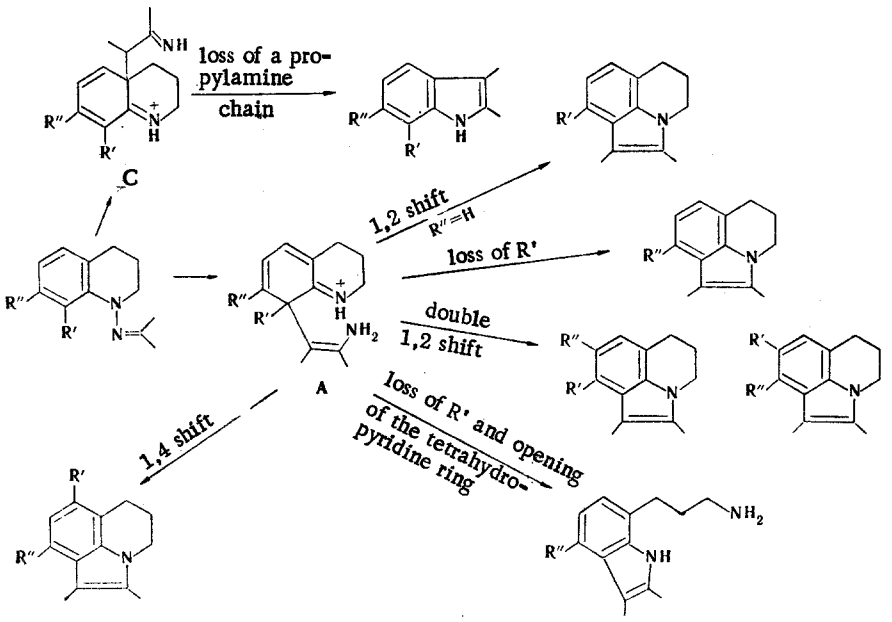
No less than five different transformations of the cyclohexadienoneimine intermediate may follow attack on the 8 position of the tetrahydroquinoline ring. Only 1,2 migration, splitting out of a substituent (only for the methyl group), and 1,4 migration (observed only in a single case without any proof for the mechanism) were previously known.

Attack at the 10 position of the tetrahydroquinoline ring leads to the formation of a different cyclohexadienoneimine, which undergoes indolization with the loss of a propylamine chain via a different mechanism.

By means of experiments with labeled compounds we proved that 1,3 migration of the methyl group is the result of a double 1,2 shift, while 1,4 migration is the result of a direct reaction.

EXPERIMENTAL

The melting points were determined with a Büchi apparatus and were not corrected. The IR spectra were recorded with a Perkin-Elmer 137 spectrometer. The PMR spectra of solutions of the compounds in CCl_4 (if no other solvent is indicated) were recorded with Varian 60 and 100 MHz spectrometers with tetramethylsilane as the internal standard. Satisfactory analytical results were obtained for all of the new compounds.



2-Chloro-5,6-dimethylacetanilide. Satisfactory results could not be obtained by the method indicated in [44] for the chlorination of 3,4-dimethylacetanilide with hydrochloric and chloric acids. It is more convenient to use the following method. A 25-g (~0.15 mole) sample of 3,4-dimethylacetanilide was treated with 35 g (~0.26 mole) of SO_2Cl_2 in 200 ml of dry chloroform at 0-5°C. The reaction mixture was allowed to stand for 15 min, after which it was treated with ice water and worked up to give 14 g (47%) of 2-chloro-5,6-dimethylacetanilide with mp 155°C (from diisopropyl ether).

2-Methyl-4-trideuteromethylaniline. A solution of 35.8 g (0.2 mole) of methyl 4-amino-3-methylbenzoate [45] in 160 ml of dry diglyme was added dropwise with stirring to a suspension of 17 g $LiAlD_4$ in 340 ml of diglyme, after which the mixture was heated on an oil bath. An exothermic reaction took place at 80°, and heating was continued after this reaction ceased. The mixture was then heated at 140°C for 10 min, after which it was cooled in a stream of nitrogen, 230 ml of 10% NaOH was added carefully, and the mixture was diluted with 450 ml of water and subjected to steam distillation. The distillate was acidified with 35% HCl and evaporated to dryness at reduced pressure. The residue was dissolved in water, and the solution was treated with 33% NaOH. The liberated base was extracted with ether, the ether was removed from the extract by evaporation, and the residue was vacuum distilled to give 18 g (73%) of product. PMR spectrum: 7.50 (3H, m, aromatic protons), 3.20 (2H, broad s, NH_2), and 2.06 ppm (3H, s, CH_3).

Quinolines

The quinolines were obtained by the Skraup synthesis from the corresponding anilines. Nitrobenzenesulfonic acid was used as the dehydrating agent in all cases in which the boiling point of the resulting quinoline and unsubstituted quinoline were very close; nitrobenzene was used in the other cases. All of the quinolines have been described in the literature [43, 46], except for 8-chloro-5,6-dimethylquinoline, 8-methyl-6-trideuteromethylquinoline, and 8-benzylquinoline.

8-Chloro-5,6-dimethylquinoline. This compound, with mp 80°C (from hexane), was obtained in 15% yield.

8-Methyl-6-trideuteromethylquinoline. PMR spectrum: 8.40 (1H, q, 2-H), 7.85 (1H, q, 4-H), 7.25 (3H, m, aromatic protons), and 2.72 ppm (3H, s, CH_3).

8-Benzylquinoline. This compound was obtained in 63% yield as white crystals with mp 55°C (from hexane) and bp 144°C (0.1 mm).

Tetrahydroquinolines. These compounds are usually obtained by hydrogenation of the corresponding quinolines in the presence of Raney nickel at 80-100°C and 50-70 atm in a saturated alcohol solution. 6-Methyl- [47], 7-methyl- [48], 8-methyl- [48], 5,6-dimethyl- [36], 6,7-dimethyl- [36], 6,8-dimethyl- [49-51], and 7,8-dimethyl-1,2,3,4-tetrahydroquinoline [36] have been described in the literature.

6,8-Dimethyl-1,2,3,4-tetrahydroquinoline. We will present the characteristics of this compound, since it is mentioned in the literature only in a few patents [49-51]. It was obtained as an oil with bp 100-105°C (0.1 mm). PMR spectrum: 6.51 (2H, s, aromatic protons), 3.23 (3H, one of which undergoes exchange with D_2O, t, NH—CH_2), 2.65 (2H, t, benzyl), and 2.10 ppm (8H, m, two s, 2.12 and 1.93, CH_2 attached to a saturated carbon atom; two CH_3 groups).

8-Methyl-6-trideuteromethyl-1,2,3,4-tetrahydroquinoline. PMR spectrum: 6.50 (3H, s, aromatic protons), 6.69 (3H, one of which undergoes exchange with D_2O, t, NH—CH_2), 2.68 (2H, t, benzyl), and 2.1 (5H, m, with a singlet at 1.97 ppm, CH_2 attached to a saturated carbon atom; CH_3 group).

8-Benzyl-1,2,3,4-tetrahydroquinoline. This compound was obtained in 77% yield and had mp 65°C and bp 140°C (0.2 mm).

N-Nitroso-1,2,3,4-tetrahydroquinolines. These compounds were obtained in almost quantitative yields by treatment of a solution of the tetrahydroquinoline in H_2SO_4 with the calculated amount of $NaNO_2$ at 0-5°C. The nitroso compounds were extracted with ethyl acetate and used subsequently without purification if they were oily. The crystalline products were crystallized from hexane.

6-Methyl-1-nitroso-1,2,3,4-tetrahydroquinoline [52] and 8-methyl-1-nitroso-1,2,3,4-tetrahydroquinoline [48] are known compounds. 7-Methyl-1-nitroso-1,2,3,4-tetrahydroquinoline was used without additional purification, and was not subjected to elementary analysis or PMR spectroscopy. We have previously described [36] 5,7-, 6,7-, and 7,8-dimethyl-N-nitroso-1,2,3,4-tetrahydroquinolines.

5,6-Dimethyl-1-nitroso-1,2,3,4-tetrahydroquinoline. This compound was obtained as yellow crystals with mp 49°C. PMR spectrum: 7.69 and 7.00 (each 1H, dd of the AB type, aromatic protons), 3.75 (2H, t, NH—CH_2), 2.71 (2H, t, benzyl), 2.27 and 2.18 (each 3H, two s, two CH_3 groups), and 1.90 ppm (2H, m, CH_2 attached to a saturated carbon atom).

6,8-Dimethyl-1-nitroso-1,2,3,4-tetrahydroquinoline. This compound was obtained as an oil with bp 150°C (0.8 mm, slight decomposition). PMR spectrum: 6.89 and 6.76 (each 1H, two s, aromatic protons), 3.75 (2H, t, N—CH_2), 2.55 (2H, t, benzyl), 2.31 and 2.25 (6H, two s, two CH_3 groups), and 1.84 ppm (2H, m, CH_2 attached to a saturated carbon atom).

8-Methyl-1-nitroso-6-trideuteromethyl-1,2,3,4-tetrahydroquinoline. PMR spectrum: 6.92 and 6.81 (each 1H, two s, aromatic protons), 3.84 (2H, t, N—CH_2), 2.65 (2H, t, benzyl), 2.38 (3H, s, CH_3), and 1.93 ppm (2H, m, CH_2 attached to a saturated carbon atom).

8-Benzyl-1-nitroso-1,2,3,4-tetrahydroquinoline. This compound was obtained in 79% yield as yellow crystals with mp 75°C (from hexane).

N-Amino-1,2,3,4-tetrahydroquinolines. These compounds were obtained by reduction of 0.1 mole of the N-nitroso derivative with 0.1 mole of $LiAlH_4$ in dry tetrahydrofuran (THF) (~180 ml) at 20-25°C by the method described for similar compounds [36, 40].

When the starting compound vanished from the reaction mixture according to the results of thin-layer chromatography (TLC), it was worked up by the usual method. The resulting hydrazines were either vacuum distilled or were more frequently used with purification. The 6-methyl [52] and 5,7-, 6,7-, and 7,8-dimethyl derivatives are described in the literature [36]. Data for the 6,7-dimethyl derivative, which has not been isolated in pure form, are also presented in [36].

1-Amino-7-methyl-1,2,3,4-tetrahydroquinoline. This compound was obtained as an oil with bp 92-95°C (0.8 mm).

1-Amino-8-methyl-1,2,3,4-tetrahydroquinoline. This compound was obtained as white crystals with mp 50°C. PMR spectrum ($CDCl_3$): 6.91 (3H, m, aromatic protons), 3.57 (2H, broad s, undergoes exchange with D_2O, NH_2), 3.28 (2H, m, NCH_2), 2.77 (2H, t, benzyl), 2.38 (3H, s, CH_3), 1.88 ppm (2H, m, CH_2 attached to a saturated carbon atom).

1-Amino-5,6-dimethyl-1,2,3,4-tetrahydroquinoline. This compound was obtained as an oil that slowly crystallized on standing. PMR spectrum: 6.77 (2H, s, aromatic protons), 3.33 (2H, broad s, undergoes exchange with D_2O, NH_2), 3.13 (2H, t, N—CH_2), 2.58 (2H, t, benzyl), and 2.10 ppm (8H, m, from two s at 2.15 and 2.02, two CH_3, and CH_2 attached to a saturated carbon atom).

1-Amino-6,7-dimethyl-1,2,3,4-tetrahydroquinoline. This compound was obtained in 56% yield as crystals with mp 72°C and bp 140°C (0.3 mm). PMR spectrum: 6.73 and 6.54 (each 1H, two s, aromatic protons), 3.32 (2H, s, undergoes exchange with D_2O, NH_2), 3.13 (2H, m, N—CH_2), 2.61 (2H, t, benzyl), 2.15 and 2.08 (6H, two s, two CH_3), amd 1.90 ppm (2H, m, CH_2 attached to a saturated carbon atom).

1-Amino-6,8-dimethyl-1,2,3,4-tetrahydroquinoline. This compound was obtained in 81% yield as an oil with bp 100°C (0.8 mm). PMR spectrum: 6.62 and 6.51 (each 1H, two m, aromatic protons), 3.33 (2H, s, undergoes exchange with D_2O, NH_2), 3.06 (2H, m, NCH_2), 2.57 (2H, t, benzyl), 2.20 and 2.15 (6H, two s, two CH_3), and 1.70 ppm (2H, m, CH_2 attached to a saturated carbon atom).

1-Amino-8-methyl-1,2,3,4-tetrahydro-6-trideuteromethylquinoline. PMR spectrum: 6.65 and 6.54 (each 1H, two m, aromatic protons), 3.38 (2H, s, undergoes exchange with D_2O, NH_2), 3.16 (2H, m, NCH_2), 2.66 (2H, t, benzyl), 2.25 (3H, s, CH_3), and 1.75 ppm (2H, m, CH_2 attached to a saturated carbon atom).

Cyclohexanone Hydrazones. These compounds were synthesized by the reaction of equimolar amounts of cyclohexanone and the corresponding 1-amino-1,2,3,4-tetrahydroquinoline at 50-60°C without a solvent. The water formed in the reaction was removed by vacuum evaporation, and the residue, which, according to the TLC data, is the almost pure hydrazone, was used directly in the indolization reaction. The hydrazone was not isolated only in those cases in which cyclohexanone and the hydrazine undergo the Fischer reaction directly.

N-[1-(8-Methyl-1,2,3,4-tetrahydroquinolyl)]cyclohexanoneimine (XIIa). PMR spectrum: 6.77 (3H, s, aromatic protons), 3.08 (2H, m, NCH_2), 2.70 (4H, m, benzyl, and CH_2 attached to an unsaturated carbon atom), 1.98 (3H, s, CH_3), and 1.70 ppm (8H, m, CH_2 attached to a saturated carbon atom).

N-[1-(6,7-Dimethyl-1,2,3,4-tetrahydroquinolyl)]cyclohexanoneimine. PMR spectrum: 6.56 and 6.24 (each 1H, two s, aromatic protons), 3.00 (2H, t, NCH_2), the remaining portion of the spectrum (12H) is made up of the superimposition of several groups of signals that cannot be individually integrated. Only some of the signals were identified: 2.68 (t, benzyl), 2.42 (broad t, CH_2 attached to an unsaturated carbon atom), 2.10 (s, two CH_3), and 1.60 (m, CH_2 attached to a saturated carbon atom).

N-[1-(5,7-Dimethyl-1,2,3,4-tetrahydroquinolyl)]cyclohexanoneimine. PMR spectrum: 6.32 and 6.12 (each 1H, two s, aromatic protons), 3.00 (2H, t, NCH_2); the remainder of the spectrum (14H) is made up of the superimposition of three principal groups of signals at 2.50 (m, CH_2 attached to an unsaturated carbon atom), 2.16 and 2.09 (two s, two CH_3), and 1.70 ppm (m, CH_2 attached to a saturated carbon atom).

N-[1-(7,8-Dimethyl-1,2,3,4-tetrahydroquinolyl)]cyclohexanoneimine (XIId). PMR spectrum: 6.65 (2H, s, aromatic protons), 3.10 (m, NCH_2) 2.65 (t, benzyl), 2.18 (m with a singlet, CH_2 attached to an unsaturated carbon atom, and CH_3), 1.86 and 1.70 ppm (s and m, CH_3, and CH_2 attached to a saturated carbon atom).

N-[1-(6,8-Dimethyl-1,2,3,4-tetrahydroquinolyl)]cyclohexanoneimine (XIIf). PMR spectrum: 7.63 (2H, s, aromatic protons), 3.03 (2H, m, NCH_2), 2.60 (4H, m, benzyl, and CH_2 attached to an unsaturated carbon atom), 2.17 (5H, m including a singlet, CH_3 and CH_2 attached to an unsaturated carbon atom), 1.91 (3H, s, CH_3), and 2.60 ppm (8H, m, CH_2 attached to a saturated carbon atom).

Acetoacetic Ester Hydrazones. These compounds were synthesized by reaction of equimolar amounts of methyl or ethyl acetoacetate with the corresponding hydrazine in 50% aqueous acetic acid. The hydrazones were almost always solids that crystallized after a few minutes; they were purified by crystallization from methanol or ethanol. In some cases, particularly when there was no substituent in the 8 position of the tetrahydroquinoline ring, the hydrazones were not isolated, and the reaction of acetoacetic ester with the hydrazone was carried out by the Fischer method [1-3, 18, 19]. Hydrazone XIIm was obtained by reduction of the nitroso compound with Zn in dilute acetic acid in the presence of excess methyl acetoacetate (see below).

Methyl N-[1-(6-Methyl-1,2,3,4-tetrahydroquinolyl)]acetoacetate Imine [52]. This compound was obtained as white crystals with mp 90°C (from methanol). According to the PMR spectral data, it exists in the enehydrazine form: 6.70 (3H, m, aromatic protons), 4.48 (1H, s, vinyl), 3.58 (3H, s, OCH_3), 3.32 (2H, t, NCH_2), 2.70 (2H, m, benzyl), and 2.20 and 1.92 (8H, two s,

separate from the multiplet, two CH_3, and CH_2 attached to a saturated carbon atom).

Methyl N-[1-(8-Methyl-1,2,3,4-tetrahydroquinolyl)]acetoacetate Imine (XIIb). This compound was obtained as white crystals with mp 98°C. According to the PMR spectral data ($CDCl_3$), hydrazone XIIb exists at least partially in the tautomeric enehydrazine form: 6.93 (3H, s, aromatic protons), 4.51 (s, vinyl), 3.70 (m, OCH_3), 3.25 (m, NCH_2), 2.83 (t, benzyl), 2.25 and 2.20 (two s, CH_3), and 2.00 (m, CH_2 attached to a saturated carbon atom).

Ethyl N-[1-(8-Methyl-1,2,3,4-tetrahydroquinolyl)]acetoacetate Imine. This compound was obtained as a syrupy oil that exists in solution in the form of a mixture of isomers of the enehydrazine form. PMR spectrum ($CDCl_3$): 9.19 (1H, s, NH), 6.88 (3H, m, aromatic protons), 5.47 and 4.47 (1H, two s, vinyl), 4.00 (2H, m, $COOCH_2CH_3$), 3.20 (2H, m, NCH_2), 7.19 (2H, t, benzyl), 2.00 (8H, m with a distinct singlet at 2.21 and 2.19, two CH_3, and CH_2 attached to a saturated carbon atom), and 1.20 ppm (3H, m, CH_2CH_3).

Methyl N-[1-(6,8-Dimethyl-1,2,3,4-tetrahydroquinolyl)]acetoacetate Imine (XIIi). This compound was obtained as white crystals with mp 90°C (from hexane). According to the PMR spectral data, it is present in solution in the enehydrazine form: 9.23 (1H, s, NH), 6.66 (2H, m, aromatic protons), 4.35 (1H, s, vinyl), 3.50 (3H, s, OCH_3), 3.18 (2H, m, NCH_2), 2.76 (2H, t, benzyl), 2.18 and 2.13 (6H, two s, two CH_3), 2.10 (2H, m, CH_2 attached to a saturated carbon atom), and 1.20 ppm (3H, m, CH_2CH_3).

Methyl N-[1-(8-Benzyl-1,2,3,4-tetrahydroquinolyl)]acetoacetate Imine (XIIm). A total of 7.5 g of zinc dust (washed with 5% HCl solution) was added in portions to a stirred solution of 11.8 g (0.05 mole) of 8-benzyl-1-nitroso-1,2,3,4-tetrahydroquinoline in 170 ml of 60% acetic acid while maintaining the temperature of the mixture at 20°C. A small amount of ethyl acetate was added to increase the solubility of the nitroso compound. After 3 h, the mixture was filtered, and the clear filtrate was diluted with an equal volume of water and extracted several times with ether. The combined ether extracts were washed with 5% $NaHCO_3$, and evaporated to dryness. The residue was purified by chromatography with a column filled with silica gel (elution with benzene) to give 2.1 g (14%) of the hydrazone with mp 85°C (from 80% ethanol).

Fischer Synthesis

The cyclohexanone hydrazones were refluxed in glacial acetic acid for 15 min. The acetoacetic ester hydrazones were usually indolized in 4 N H_2SO_4 or HCl by refluxing for 40 min. At the end of the reaction, the solvent was removed by vacuum evaporation, and the residue was treated with ether and 5% HCl solution. The organic layer was washed with 5% $NaHCO_3$ solution, dried over $MgSO_4$, and evaporated. The indole fraction was purified by chromatography with a column filled with silica gel.

Because of the instability of the tetrahydrocarbazoles formed in the indolization of the cyclohexanone hydrazones, they were atomized by refluxing in xylene or mesitylene in the presence of 5% Pd/C. Chloranil was used as the dehydrogenating agent in only a few cases. In the case of indolization of hydrazones without substituents in the 8 position of the tetrahydroquinoline ring, the reaction products were crystallized from a suitable solvent without chromatographic purification.

Fischer Synthesis from Hydrazone XIIa. A 7.4-g (0.03 mole) sample of hydrazone XIIa was refluxed in 16 ml of acetic acid for 30 min. The indole fraction (0.85 g) was dissolved in 50 ml of xylene, and the solution was refluxed for 3 h in the presence of 0.3 g of 5% Pd/C. The catalyst was removed by filtration, and the solvent was removed by vacuum evaporation. Thin-layer chromatography of the residue demonstrated the presence of two substances, which were separated by chromatography [elution with hexane–benzene (8:2)]. Workup of the first fraction gave 0.18 g of 1-methyl-4,5,6,7-tetrahydropyrido[3,2,1-j,k]carbazole (XIII) with mp 85°C (from hexane). PMR spectrum (CS_2): 7.90 and 7.00 (1H and 5H, two m, aromatic protons), 4.12 (2H, t, NCH_2), 2.99 (2H, t, benzyl), 2.73 (3H, s, CH_3), and 2.23 ppm (2H, m, CH_2 attached to a saturated carbon atom). Workup of the second fraction gave 0.2 g of 1-methylcarbazole (XIV) [53] with mp 116°C. Reaction of 0.6 g of cyclohexanone with 1 g of 1-amino-7-methyl-1,2,3,4-tetrahydroquinoline in glacial acetic acid gave a product that was slightly soluble in acetic acid. It was dehydrogenated over 5% Pd/C to give carbazole XIII in 60% yield.

Fischer Reaction with Hydrazone XIIb. A) A solution of 4 g (0.015 mole) of hydrazone XIIb in 40 ml of a 4 N methanol solution of HCl was refluxed for 30 min, after which the solvent was removed by vacuum evaporation, and the residue was treated with water and extracted several times with ether. The combined organic layers were washed with 5% $NaHCO_3$ solution and dried over $MgSO_4$. The solvent was removed by evaporation to give 1.6 g of an oily mixture of four compounds, which were separated with a column filled with silica gel (elution with $CHCl_3$). Workup of the first fraction gave 0.045 g of 2,9-dimethyl-3,4,5,6-tetrahydropyrrolo[3,2-i,j]quinoline (XV) with bp 110° (0.3 mm). The product darkened under the influence of air and light. PMR spectrum ($CDCl_3$): 6.75 (2H, s, aromatic protons of the benzene ring), 6.17 (1H, s, pyrrole ring), 4.00 (2H, t, NCH_2), 2.95 (2H, t, benzyl), 2.47 and 2.40 (6H, two s, two CH_3), and 2.25 ppm (2H, m, CH_2 attached to a saturated carbon atom). Indole XV was obtained in good yield by refluxing 0.1 g of ester XVI with 0.1 g of KOH in 5 ml of ethylene glycol for 10 h. The next fraction yielded 0.16 g of 2,9-dimethyl-1-methoxycarbonyl-3,4,5,6-tetrahydropyrrolo[3,2-i,j]quinoline (XVI) with mp 86-88°C (from hexane). PMR spectrum ($CDCl_3$): 6.83 (2H, s, aromatic protons), 3.97 (2H, t, NCH_2), 3.86 (3H, s, OCH_3), 2.92 (2H, t, benzyl), 2.65 and 2.62 (6H, two s, two CH_3), and 2.15 ppm (2H, m, CH_2 attached to a saturated carbon atom). The product was identical to the product obtained by refluxing equimolar amounts of N-amino-7-methyl-1,2,3,4-tetrahydroquinoline and methyl acetoacetate in a 4 N methanol solution of HCl for 1 h. The next fraction yielded 1.13 g of a mixture (2:3) of XVI and 2-methyl-1-methoxycarbonyl-3,4,5,6-tetrahydropyrrolo[3,2-i,j]quinoline (XVII) [43]; the latter was isolated in pure form (0.24 g) in the subsequent fractions. Elution was continued with a mixture of chloroform and ethyl acetate (9:1) to give 2,7-dimethyl-3-methoxycarbonylindolylhexane. PMR spectrum ($CDCl_3$): 8.30 (1H, broad s, NH), 7.94 (1H, m, 4-H), 7.10 (2H, m, 5-H and 6-H), 3.92 (3H, s, OCH_3), 2.75 (3H, s, 2-CH_3), and 2.47 ppm (3H, s, 7-CH_3). The acidic fractions formed in the Fischer synthesis were made alkaline with 33% NaOH and subjected to steam distillation. The distillate was treated with benzoyl chloride, and the resulting amides were extracted with ether. N-(γ-Chloropropyl)benzamide was identified by comparison with an authentic sample [35].

B) A 5-g (0.02 mole) sample of hydrazone XIIb was refluxed in 100 ml of a 0.4 N benzene solution of HCl for 20 min, during which nitrogen was passed slowly into the solution, and the gases evolved from the flask were collected in a trap containing CS_2 cooled to −50°C. Gas-chromatographic analysis and the PMR spectrum of the solution demonstrated the formation of CH_3Cl. When methyl acetoacetate was treated under the same conditions, CH_3Cl was not detected. The benzene solution was shaken with 50 ml of 10% HCl solution, and the precipitate (0.9 g) was removed by filtration. The precipitate was dissolved in boiling water, and the solution was filtered through charcoal. The filtrate was made alkaline with 33% NaOH solution, and the 7-(γ-aminopropyl)-3-methoxycarbonyl-2-methylindole (XIX) was extracted with $CHCl_3$. The solvent was removed from the extract by evaporation, and the residue was crystallized from diisopropyl ether to give a product with mp 117°C and M^+ (by mass spectrometry) 246. PMR spectrum ($CDCl_3$): 7.90 (1H, m, 4-H), 7.00 (2H, m, aromatic protons), 3.93 (3H, s, OCH_3), 2.70 (7H, m including a singlet at 2.72, N—CH_2, benzyl, and CH_3), and 1.80 ppm (3H, m, CH_2 attached to a saturated carbon atom, and NH). The benzene solution was washed with 5% $NaHCO_3$, dried with $MgSO_4$, and evaporated to dryness to give 2.8 g of residue containing a mixture of indoles XVI, XVII, and XVIII, which can be isolated by the method indicated above.

Fischer Reaction with Ethyl N-[1-(8-Methyl-1,2,3,4-tetrahydroquinolyl)]acetoacetate Imine. This reaction was carried out under the same conditions as those previously indicated (dry HCl in benzene) for hydrazone XIIb. The following compounds were isolated in pure form. 1-Ethoxycarbonyl-2-methyl-3,4,5,6-tetrahydropyrrolo[3,2-i,j]quinoline with mp 109°C. PMR spectrum ($CDCl_3$): 7.85 (1H, m, 4-H), 7.00 (2H, m, aromatic protons), 4.40 (2H, q, OCH_2CH_3), 4.00 (2H, t, NCH_2), 2.95 (2H, t, benzyl), 2.70 (3H, s, CH_3), 2.26 (2H, m, CH_2 attached to a saturated carbon atom), and 1.44 (3H, t, OCH_2CH_3). 7-(γ-Aminopropyl)-3-ethoxycarbonyl-2-methylindole with mp 120°C (from diisopropyl ether) and M^+ 260. PMR spectrum ($CDCl_3$): 7.95 (1H, m, 4-H), 7.00 (2H, m, aromatic protons), 4.38 (2H, q, OCH_2CH_3), 2.90 (7H, m including a singlet at 2.70, N—CH_2, benzyl, and CH_3), 2.90 (2H, m, CH_2 attached to a saturated carbon atom), and 1.42 ppm (4H, t, OCH_2CH_3, and NH). A 0.5-g sample of the crude product was refluxed with 10 ml of acetic anhydride for 30 min, after which the solvent was removed by vacuum evaporation, and the residue was chromatographed with a column filled with silica gel to give 0.15 g of white crystals of the N,N-diacetyl derivative with mp 112-115°C (from methanol) and M^+ 344. PMR spectrum ($CDCl_3$): 8.82 (1H, broad s, NH), 8.00 (1H, m, 4-H), 7.00 (2H, m, aromatic protons), 4.40 (2H, q, OCH_2CH_3), 3.60 (2H, t, NCH_2), 2.85 (5H, t and s, benzyl, and CH_3 attached to a pyrrole ring), 2.30 (6H, s, two $COCH_3$), 2.00 (2H, m, CH_2 attached to a saturated carbon atom), and 2.45 ppm (3H, t, OCH_2CH_3).

Fischer Reaction with Hydrazone XIIc. The neutral fraction (2.0 g) obtained in the indolization of 8.0 g of hydrazine XIIc was refluxed with 4.5 g of chloranil in 40 ml of xylene for 3 h, after which the mixture was filtered, and the filtrate was washed with 10% NaOH and dried over K_2CO_3. The solvent was removed by vacuum evaporation, and 1.5 g of the residue was chromatographed with a column filled with 30 g of silica gel [elution with chloroform–hexane (1:1)]. Two principal fractions were collected: the second fraction consisted of 1,2-dimethylcarbazole (XXII) [54], with mp 148°C (from hexane), and the first fraction consisted of a mixture of 1,2-dimethyl-4,5,6,7-tetrahydropyrido[3,2,1-j,k]carbazole (XXI) and 1,3-dimethyl-4,5,6,7-tetrahydropyrido[3,2,1-j,k]carbazole (XX) (4:1). Crystallization from hexane gave almost pure carbazole XXI with mp 116°C. PMR spectrum (CS_2): 7.95 (1H, m, 8-H), 6.75 (1H, s, 3-H), 7.10 (3H, m, aromatic protons), 4.05 (2H, t, NCH_2), 2.92 (3H, t, benzyl), 2.65 and 2.35 (3H each, two s, two CH_3), and 2.20 (2H, m, CH_2 attached to a saturated carbon atom). Carbazole XXI (2 g) was also obtained by indolization of 7 g of N-[1-(6,7-dimethyl-1,2,3,4-tetrahydroquinolyl)]cyclohexanoneimine and subsequent dehydrogenation of the intermediate 1,2-dimethyl-4,5,6,7,8,9,10,11-octahydropyrido[3,2,1-j,k]carbazole (3 g, mp 120°C) by refluxing in xylene with chloranil. The product was isolated in pure form by chromatography with a column filled with silica gel [elution with benzene–hexane (1:1)].

The mother liquors from the crystallization of carbazole XXI were chromatographed with a column filled with 10 g of silica gel (elution with hexane). The last fraction (0.18 g) was a mixture of XX and XXI (2:1). The PMR spectrum of this mixture coincided with the spectrum of a mixture of authentic samples. Carbazole XX was obtained in 75% yield by indolization of the previously described N-[1-(5,7-dimethyl-1,2,3,4-tetrahydroquinolyl)]-cyclohexanoneimine and subsequent aromatization of the intermediate 1,3-dimethyl-4,5,6,7,8,9,10,11-octahydropyrido[3,2,1-j,k]carbazole [mp 143°C (from hexane)] with chloranil; carbazole XX had mp 120°C. PMR spectrum (CS_2): 7.83 (1H, m, 8-H), 6.84 (1H, s, 2-H), 7.10 (3H, m, aromatic protons), 4.03 (2H, t, NCH_2), 2.83 (2H, t, benzyl), 2.66 and 2.30 (3H each, two s, two CH_3), and 2.20 ppm (2H, m, CH_2 attached to a saturated carbon atom).

Fischer Reaction with Hydrazone XIIf. Indolization of 5 g (0.02 mole) of hydrazone XIIf in 20 ml of refluxing acetic acid gave a mixture of indoles (1.5 g), which was dissolved in 150 ml of benzene. The benzene solution was filtered through a short column filled with 5 g of silica gel, and the filtrate was refluxed with 2.1 g of chloranil for 4 h. The mixture was filtered, the solvent was removed from the filtrate by distillation, and the residue was treated with 10% NaOH solution and ether. The organic layer was dried over K_2CO_3 and evaporated, and 0.5 g of the residue was chromatographed with a column filled with 20 g of silica gel (elution with benzene). Two principal fractions were collected: The first fraction (0.27 g from 80 ml of eluent) was a mixture of carbazoles XXI and XXV, and the second fraction (0.11 g) consisted of XXVI contaminated with a small amount of carbazoles XXI and XXV. 1,3-Dimethylcarbazole (XXVI) [32] was purified by chromatography with a column filled with 8 g of silica gel (elution with benzene) and crystallized from hexane to give a product with mp 95°C [54]. Carbazoles XXI and XXV were separated by very thorough chromatography with a column filled with 15 g of silica gel (with the exclusion of light) by elution with hexane. The first product isolated was 2,3-dimethyl-4,5,6,7-tetrahydropyrido[3,2,1-j,k]-carbazole (XXV), which was purified by two crystallizations from hexane to give a product with mp 126°C. PMR spectrum (CS_2): 7.70 (1H, m, 8-H), 7.39 (1H, s, 1-H), 7.00 (3H, m, aromatic protons), 4.00 (2H, t, NCH_2), 2.89 (2H, t, benzyl), and 2.30 (7H, m including two singlets at 2.35 and 2.22, CH_2 attached to a saturated carbon atom, and two CH_3). Carbazole XXV was obtained in 40% yield by aromatization (with Pd/C) of the tetrahydro derivative obtained by reaction of equimolar amounts of 1-amino-5,6-dimethyl-1,2,3,4-tetrahydroquinoline with cyclohexanone in refluxing acetic acid. The second product eluted was 1,2-dimethyl-4,5,6,7-tetrahydropyrido[3,2,1-j,k]carbazole (XXI), which was identical to an authentic sample (see above).

Fischer Reaction with Hydrazone XIIg. The reaction was carried out as indicated above for unlabeled hydrazone XIIf. PMR spectrum (CS_2) of labeled carbazole XXV: 7.75 (1H, m, 8-H), 7.47 (1H, s, 1-H), 7.00 (3H, m, aromatic protons), 4.06 (2H, t, NCH_2), 2.94 (2H, t, benzyl), 2.30 (5H, m including a singlet at 2.22, CH_2 attached to a saturated carbon atom, and 3-CH_3); the signal at 2.35 ppm (2-CH_3 of the unlabeled compound) was absent. PMR spectrum (CS_2) of the labeled carbazole corresponding to XXI: 7.98 (1H, m, 8-H), 6.80 (1H, s, 3-H), 7.20 (3H, m, aromatic protons), 4.12 (2H, t, NCH_2), 2.95 (2H, t, benzyl), 2.65 (3H, s, 1-CH_3), and 2.20 ppm (2H, m, CH_2 attached to a saturated atom); the signal at 2.35 ppm (2-CH_3 of unlabeled compound) was absent.

Fischer Reaction with Hydrazone XIIi. The neutral fraction (2.9 g) obtained by refluxing 8 g of hydrazone XIIi in 80 ml of a 4 N methanol solution of HCl for 40 min was chromatographed with a column filled with silica gel (elution with benzene). Elution gave initially a mixture (2.0 g) of 2,7,8-trimethyl-1-methoxycarbonyl-3,4,5,6-tetrahydropyrrolo[3,2,1-i,j]quinoline (XXIII) and 2,7-dimethyl-1-methoxycarbonyl-3,4,5,6-tetrahydropyrrolo[3,2,1-i,j]quinoline (XXVII). Indoles XXIII and XXVII could not be isolated in pure form, but the spectrum of the mixture was in agreement with the spectrum of a mixture (8:7) of authentic samples of XXIII [36] and XXVII. The latter was obtained in almost quantitative yield by refluxing equimolar amounts of methyl acetoacetate and 1-amino-6-methyl-1,2,3,4-tetrahydroquinoline in a 4 N methanol solution of HCl; the product had mp 120°C [52] (from hexane). PMR spectrum ($CDCl_3$): 7.62 (1H, s, 8-H), 3.98 (5H, m formed by a triplet and singlet at 3.91, NCH_2, OCH_3), 2.92 (2H, t, benzyl), 2.67 and 2.45 (3H each, two s, two CH_3), and 2.20 ppm (2H, m, CH_2 attached to a saturated carbon atom). Elution was continued with a mixture of benzene and ethyl acetate (9:1), and the resulting 0.36 g of product was chromatographed under similar conditions and crystallized from benzene–hexane to give 3-methoxycarbonyl-2,5,7-trimethylindole (XXVIII) with mp 180°C. PMR spectrum ($CdCl_3$): 8.30 (1H, broad s, NH), 7.74 (1H, s, 4-H), 6.93 (1H, s, 6-H), 3.92 (3H, s, OCH_3), 2.72 (3H, s, CH_3 attached to the pyrrole ring), and 2.42 ppm (6H, s, two CH_3).

Fischer Reaction with Hydrazone XIId in Acetic Acid. This reaction in a 4 N methanol solution of H_2SO_4 has already been described [36]. It was repeated in fluxing acetic acid, but only indole XXIII was formed in this case.

Fischer Reaction with Hydrazone XXIIm. Indolization was carried out in a 4 N methanol solution of HCl in accordance with the general method described above. Workup of the principal fraction yielded 8-benzyl-1,2,3,4-tetrahydroquinoline; the only indole product was 1-methoxycarbonyl-2-methyl-3,4,5,6-tetrahydropyrrolo[3,2,1-i,j]quinoline (XXVII).

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