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SYNTHESIS AND STEREOCHEMISTRY OF PERHYDROACRIDINES (REVIEW)

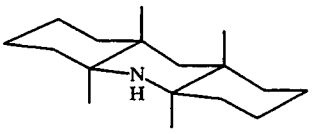
T. G. Nikolaeva, P. V. Reshetov, and A. P. Kriven'ko

Methods for the synthesis of isomeric perhydroacridines are reviewed. Their configurational and conformational features are discussed.

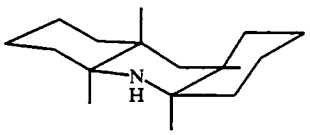
Saturated heterocycles of the series of piperidine and its condensed analogs (decahydroquinoline and decahydroisoquinoline) form the structural base of numerous natural alkaloids and synthetic drugs. A large number of papers and a series of reviews, e.g., [1, 2], have been devoted to questions relating to the synthesis, properties, and stereochemical structure of this type of compound. Another condensed analog of piperidine (perhydroacridine) has been studied to a significantly lesser degree, and the results of the investigations have not been reviewed. At the same time, perhydroacridine and its derivatives have a series of configurational and conformational features that distinguish them from decahydroquinolines and decahydroisoquinolines.

In the present review we analyze published data and our own data on the synthesis and stereochemical investigation of compounds of the perhydroacridine series.

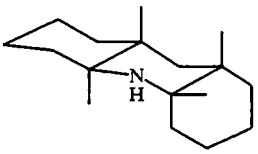
Unlike its carbocyclic analog perhydroanthracene [3], perhydroacridine can exist in the form of six isomers with various types of fusion of the hetero- and carbocycles:



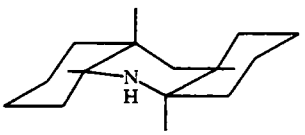
trans-syn-trans (α)



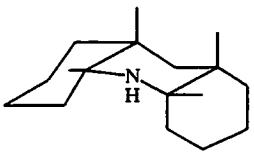
trans-anti-cis (β)



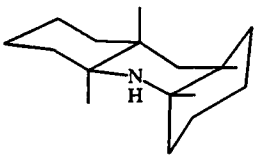
trans-syn-cis (γ)



cis-anti-cis (δ)



cis-syn-cis



trans-anti-trans

The formation of the perhydroacridines in one or the other form is determined by various factors and in particular by the structure of the reagents and the reaction conditions.

Among familiar methods for the production of perhydroacridines, it is possible to single out two main groups, i.e., syntheses based on (hydro)acridines and the reductive amination δ-diketones, β-cycloketols, and pyrylium salts.

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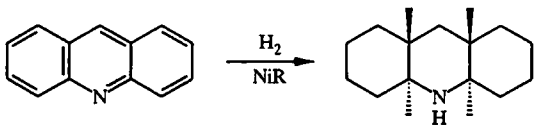
1. SYNTHESES OF PERHYDROACRIDINES BASED ON ACRIDINE AND ITS ISOLOGS

1.1. Reduction of (Hydro)acridines and *sym*-Octahydroacridinium Salts

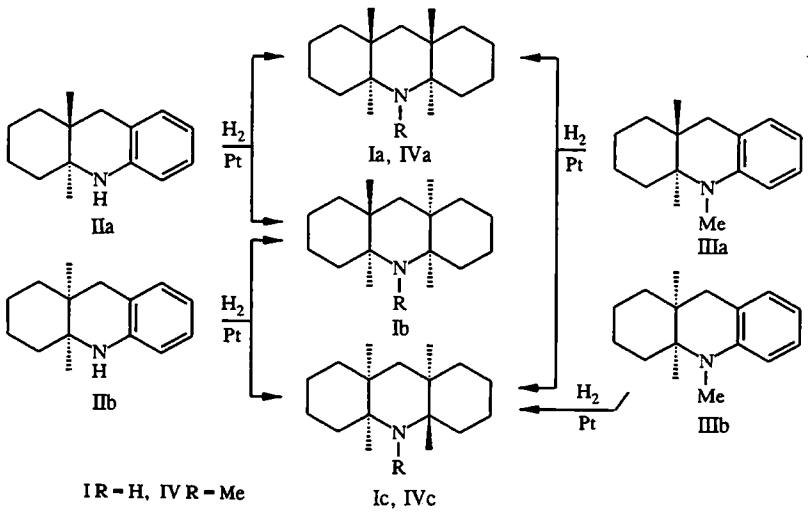
The traditional method for the synthesis of saturated heterocycles is the reduction of the corresponding heteroaromatic compounds with various reducing agents.

Adkins and Coonradt isolated perhydroacridine (I) with an 88% yield as a result of the catalytic hydrogenation of acridine over Raney nickel under rigorous conditions (240°C, hydrogen pressure 25-30 MPa) [4]:



Ia

The stereochemical structure of compound (Ia) was not investigated. However, the melting point of the obtained sample (90-91°C) corresponds to the melting point of the *trans-syn-trans* isomer, which was characterized more recently [5]. If the temperature is reduced to 100°C in the presence of a nickel or copper–chromium catalyst, the hydrogenation of acridine takes place nonselectively. The reaction products are a mixture of hydroacridines with various degrees of saturation — *sym*-octahydroacridine (16%), benzo[*b*]decahydroquinoline (38%), and $\Delta^{8a,10a}$-dodecahydroacridine (22%) [4]. The latter were also used as starting materials in the synthesis of perhydroacridine. Study of the catalytic hydrogenation of benzo[*b*]decahydroquinoline as a platinum catalyst set the foundation for a stereochemical investigation into a series of perhydroacridines [5, 6]. By using the *cis* and *trans* isomers of benzo[*b*]decahydroquinoline (II) and its N-methyl homolog (III) it was possible to trace the relation between the direction of the reaction and the structure of the substrate and to isolate and characterize the various isomers of N-R-perhydroacridines.



During the hydrogenation of the *trans* isomer (IIa), *trans-syn-trans*-perhydroacridine (Ia) (called the α isomer) and the *trans-anti-cis* (β) isomer (Ib) were isolated. During reduction the *cis* isomer (IIb) forms *cis-syn-trans*-perhydroacridine (Ic) (γ) in addition to the isomer (Ib).

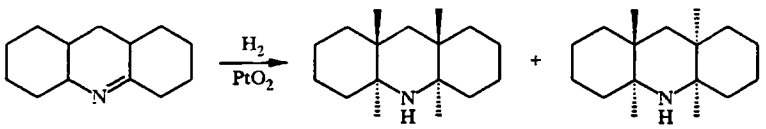
Under the same conditions, N-methylbenzo[*b*]decahydroquinolines (III) behave somewhat differently. Hydrogenation of the *trans* isomer (IIIa) gives a mixture of *trans-syn-trans*- and *cis-syn-trans*-N-methylperhydroacridines (IVa, IVc). The *cis* isomer (IIIb) is converted almost completely into the isomer (IVc). In all the investigated cases, the hydrogenation of the isomeric benzo[*b*]decahydroquinolines (II, III) takes place with retention of the configuration of the chiral centers in the initial compounds.

TABLE 1. ^{13}C Chemical Shifts of N-R-Perhydroacridines (δ, ppm, deutero-chloroform)

R	Configuration	$C_{(1)}$ $C_{(8)}$	$C_{(2)}$ $C_{(7)}$	$C_{(3)}$ $C_{(6)}$	$C_{(4)}$ $C_{(5)}$	$C_{(9)}$	$C_{(8a)}$ $C_{(9a)}$	$C_{(4a)}$ $C_{(10a)}$
CH_2CH_2OH*	*cis-anti-cis*	28,39	22,35	22,35	23,34	30,24	33,87	55,38
C_6H_5	*cis-anti-cis*	29,87	22,06†	23,79†	35,72†	27,07	32,29	55,71
p-$CH_3OC_6H_4$	*cis-anti-cis*	29,42	23,18	23,64	24,31	30,40	33,98	56,82
CH_3	*cis-syn-cis*	32,26	22,70	25,89	25,89	26,89	37,58	60,95
CH_2CH_2OH	*cis-syn-cis*	32,34	22,06	26,57†	26,77†	26,29	37,71	58,80
C_6H_5	*cis-syn-cis*	32,46	21,62	26,11	26,11	26,02	37,49	53,53
H	*cis-syn-cis*	30,54	27,22	21,81	33,83	36,21	35,91	57,15
H	*trans-anti-cis*	26,93	26,40	20,72	32,69	38,98	36,70†	55,37
		33,83	26,47	25,76	33,15		37,63†	63,19
C_6H_5	*trans-anti-cis*	26,87	26,87	19,92	30,46	39,04	37,33	60,83
		33,16	25,47	25,85	32,45		37,33	68,85
CH_3	*trans-anti-cis*	27,47	27,07	19,80	30,70	39,47	37,08†	63,55
		33,81	25,89	26,15	30,97		30,76†	70,19
H	*trans-syn-trans*	32,34	26,21	25,50	33,66	39,91	43,25	62,10
C_6H_5	*trans-syn-trans*	32,90	25,47	25,86	31,98	40,13	42,23	67,82
CH_3	*trans-syn-trans*	33,46	25,83	26,10	31,03	40,69	40,99	69,28
o-$NH_2C_6H_4$	*trans-syn-cis*	29,66	20,86	27,00	20,14	31,70	31,05	49,25
		31,05	25,92	27,00	18,28		37,40	59,40

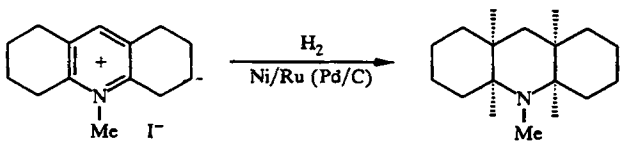
*In DMSO at 100°C, the signal of the solvent at 39.60 ppm was used as standard.
†Equally probable assignments.

A mixture of the α and β isomers of perhydroacridines (Ia, Ib) was obtained during the hydrogenation of $\Delta^{4a,10}$-dodecahydroacridine in dioxane at platinum dioxide at atmospheric pressure [7]:



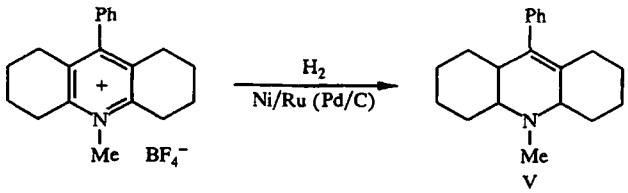
Ia Ib

In contrast to hydroacridines, the hydrogenation of *sym*-octahydroacridinium salts takes place selectively. During the hydrogenation of N-methyl-*sym*-octahydroacridinium iodide in an alcohol solution saturated with methylamine at 100°C and a hydrogen pressure of 10 MPa in the presence of Raney nickel, modified with ruthenium or palladium, on charcoal the reaction product was *cis-syn-cis*-N-methylperhydroacridine (IVd). It was isolated with a 73% yield [8, 9]:



IVd

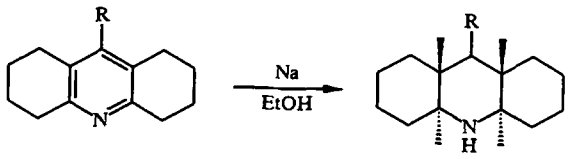
The introduction of a phenyl substituent at position 9 of the initial salt prevents complete hydrogenation, and the reaction stops at the formation of 9-phenyl-10-methyl-$\Delta^{9,9a}$-dodecahydroacridine (V) with a yield of 53% [8]:



Retention of the olefinic bond in the heterocycle is probably favored by conjugation with the phenyl radical.

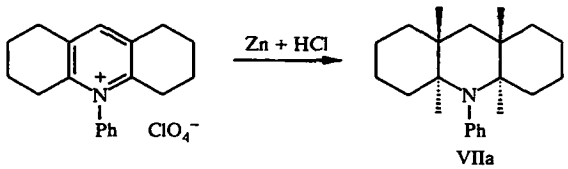
As a rule, the reduction of hydroacridines with various degrees of saturation leads to the formation of the most thermodynamically stable isomers (α, more rarely β).

During reduction with sodium in alcohol 9-R-*sym*-octahydroacridines are transformed with high yields into the corresponding α-perhydroacridines (Ia, VIa) [10, 11]:

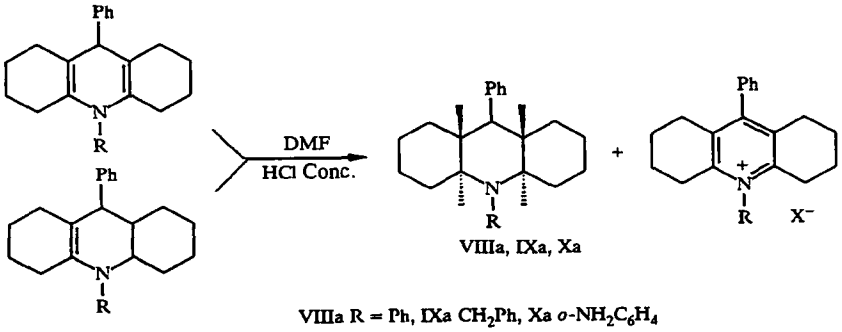


Ia R = H, VIa R = Me

N-Phenyl-*sym*-octahydroacridinium perchlorate is reduced by zinc in an acidic medium also with the formation of α-N-phenylperhydroacridine (VIIa) [12]:

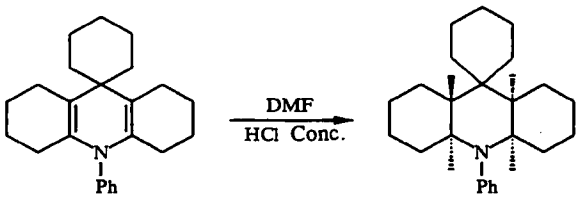


Dimethylformamide in concentrated hydrochloric acid was used for the reduction of 9,10-substituted $\Delta^{4a,8a,9a,10a}$-decahydro- and $\Delta^{8a,10a}$-dodecahydroacridines [13]. Here, high yields of the *trans-syn-trans* isomers of 9,10-substituted perhydroacridines (VIIIa, IXa, Xa) were obtained. The reaction is complicated by disproportionation as side process, as demonstrated by the isolation of small amounts of 9-phenyl-10-R-*sym*-octahydroacridinium salts:



VIIIa R = Ph, IXa CH_2Ph, Xa *o*-$NH_2C_6H_4$

In the case of 9,9-pentamethylene-10-phenyl-$\Delta^{4a,8a,9a,10a}$-decahydroacridine, the main product (yield 89%) was the β isomer of 9,9-pentamethylene-10-phenylperhydroacridine (XIb) [14]:



XIb

In the case of decahydroacridines the use of formic acid (85 or 100%) as reducing agent promotes the disproportionation side reaction, while 9-phenyl-10-R-dodecahydroacridines are not reduced at all by formic acid [13].

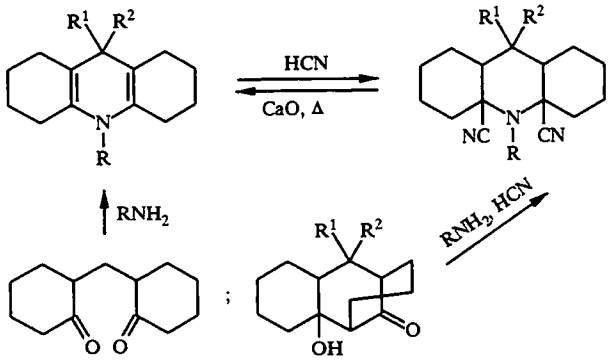
Unlike the 9,10-substituted decahydroacridines, which are resistant to the action of complex metal hydrides ($LiAlH_4$, KBH_4) even under drastic conditions [13], 9-R-10-phenyl-4a-cyano-$\Delta^{8a,10a}$-dodecahydroacridines are reduced by KBH_4 with great difficulty to the respective perhydroacridines (VII) (α) and (VIII) (α, γ) [15]. It is supposed that slow disproportionation of the initial compounds takes place under the given conditions with subsequent reduction of the dicyanides.

Thus, perhydroacridines with the *trans-syn-trans* and *trans-anti-cis* configuration are formed during the catalytic and chemical reduction of hydroacridines with various degrees of saturation. Only catalytic hydrogenation of *sym*-octahydroacridinium salts leads to perhydroacridines with *cis-syn-cis* fusion of the hetero- and carbocycles. However, there are few such examples.

1.2. Addition Reactions in the Series of Decahydro- and Dodecahydroacridines

The ability of decahydro- and dodecahydroacridines to undergo addition reactions (HCN, H_2O_2, H_2S_2) has made it possible to obtain from them perhydroacridines containing substituents at the bridgehead carbon atoms $C_{(4a)}$ and $C_{(10a)}$.

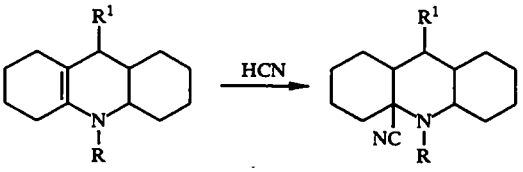
The addition of hydrogen cyanide to decahydroacridines leads to 10- or 9,10-substituted 4a, 10a-dicyano-perhydroacridines [1, 16, 17].



R = CH_3, Ph, CH_2CH_2OH, CH_2COOH, $CH_2COOC_2H_5$, $C_6H_4OCH_3$-*p*, $C_6H_4COOCH_3$-*p*, $CH_2C_6H_5$,
$R^1 = R^2 = H$; $R^1 = H$, $R^2 = CH_3$, Ph, CH_2Ph; $R^1 + R^2 = -(CH_2)_5-$

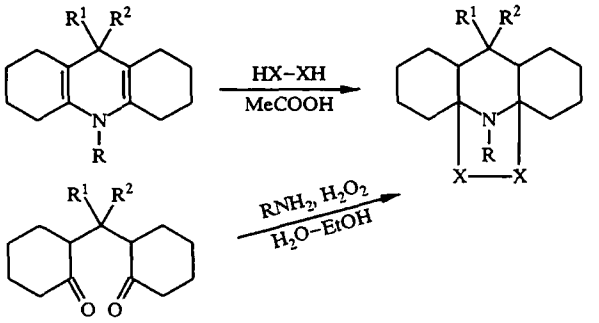
The latter are also formed during the reaction of methylenedicyclohexanone and tricyclic β-ketols with amines in the presence of hydrogen cyanide [7, 14, 16, 18, 19]. The intermediates of this reaction are the corresponding decahydroacridines [14, 16].

The reaction of hydrogen cyanide with dodecahydroacridines gave high yields (80-96%) of 10- and 9,10-substituted 10a-cyanoperhydroacridines [13, 20]:



R = Ph, CH_2Ph, C_6H_4OH-*o*, $C_6H_4NH_2$-*o*, α- and β-naphthyl $C_6H_4OCH_3$; R^1 = H, Ph

Apart from hydrogen cyanide, hydrogen peroxide [17, 21] and hydrogen disulfide [22] have also been used in addition reactions at the double bonds of decahydroacridines. It is possible to pass directly to the peroxidation products from methylenedicyclohexanone by reacting the latter with amines in the presence of hydrogen peroxide [17, 23]. The yields of the final products range from 15 to 70%

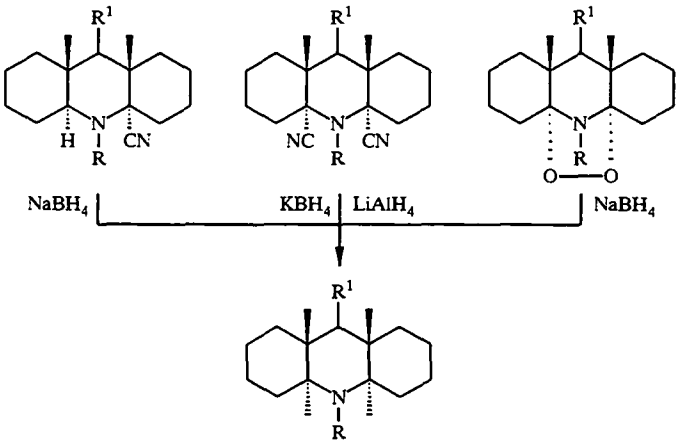


R = H, Ph, CH_2Ph, $C_6H_4COOCH_3$-*p*, $C_6H_4OCH_3$-*p*; R^1 = H, R^2 = Ph, CH_2Ph, CH_3; R^1+R^2 = $-(CH_2)_5-$; X = O, S

9-Phenyl-10-R-4a,10a-epoxy(dithio)perhydroacridines are formed exclusively in the form of the *trans-syn-trans* isomers. Although low-temperature synthesis (−10°C) leads to the preferential formation of the *trans-anti-cis* isomers, the latter change irreversibly into the *trans-syn-cis* isomers if the temperature is raised to 20°C in the presence of acetic acid. Exceptions are 9,9-pentamethylene- and 9-benzyl-10-phenyl-4a,10a-epidioxyperhydroacridines, which exist in the form of the β isomers under any conditions [17]. The aminoperoxidation of methylenedicyclohexanone takes place in a water–alcohol medium and does not affect the chiral centers. Two isomers of epidioxyperhydroacridine are formed from a mixture of the *threo* and *meso* forms; one *trans-syn-trans* isomer is formed if the pure *threo* form is used [23].

Thus, 4a,10a-substituted perhydroacridines appear in the form of the most thermodynamically stable α and β isomers.

The mono- and dicyanoperhydroacridines are transformed readily and with good yields, and the 4a,10a-epidioxyperhydroacridines are transformed with considerably greater difficulty by the action of complex metal hydrides (KBH_4, $NaBH_4$, $LiAlH_4$) into 9,10-substituted perhydroacridines as a result of nucleophilic attack by the hydride ion [24]. In most cases the reaction takes place without change in the configuration of the chiral centers:



R = Me, Ph, C_6H_4OH-*o*, CH_2Ph; R^1 = H, Ph

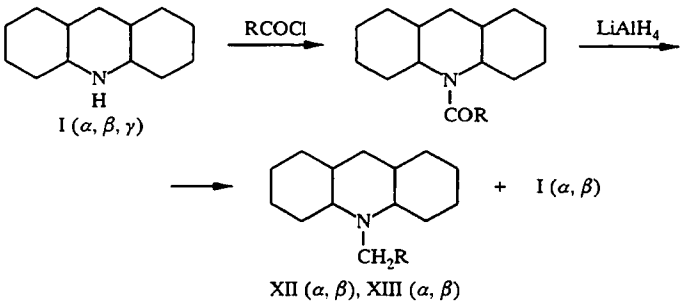
1.3. Reactions of Perhydroacridines at the Nitrogen Atom

The reactions of perhydroacridines involving the nitrogen atom (nitrosation, acylation, alkylation, salt formation, etc.) have now been studied fairly well.

TABLE 2. ^{13}C Chemical Shifts of 9-R-10-Methylperhydroacridines (δ, ppm, deuterochloroform)

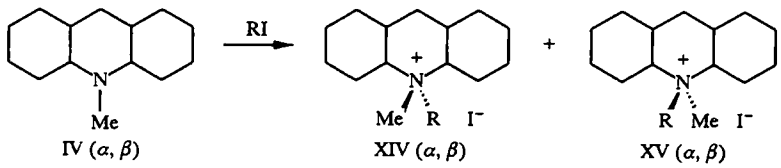
R	Configuration	$C_{(1)}$ $C_{(8)}$	$C_{(2)}$ $C_{(7)}$	$C_{(3)}$ $C_{(6)}$	$C_{(4)}$ $C_{(5)}$	$C_{(9)}$	$C_{(8a)}$ $C_{(9a)}$	$C_{(4a)}$ $C_{(10a)}$	$C_{(11)}$
CH_3	*cis-syn-cis*	25,27	27,73	21,27	31,20	38,89	43,82	66,11	35,69
CH_3	*trans-anti-cis*	21,33	27,05	20,39	30,08	40,11	43,06	64,62	35,52
		31,29	26,07	26,07	30,90		44,43	70,06	
CH_3	*trans-syn-trans*	30,40	26,05	26,26	31,47	41,54	45,91	68,08	34,89
C_2H_5	*cis-syn-cis*	25,31	27,82	21,32	31,29	46,11	41,79	66,22	35,82
C_2H_5	*trans-anti-cis*	21,09	27,08	20,51	31,05	46,60	39,24	64,68	36,66
		29,80	26,01	26,19	31,55		42,33	70,20	
C_2H_5	*trans-syn-trans*	29,82	26,12	26,50	31,56	46,41	41,50	68,34	35,38
C_6H_5	*cis-syn-cis*	25,78	27,73	21,31	31,39	50,37	41,98	66,72	35,58
C_6H_5	*trans-anti-cis*	23,03	26,71	20,12	30,97	53,96	39,41	64,80	36,48
		30,97	25,86	26,22	31,25		44,78	70,41	
C_4H_3O	*cis-syn-cis*	25,81	26,46	21,13	31,16	45,67	36,49	65,91	35,64

During the acylation of the α, β, and γ isomers of perhydroacridine (I) good yields of the N-acyl derivatives were obtained [25-28]. Reduction of the α and β isomers of N-acetyl(benzoyl)perhydroacridines led to the corresponding α- and β-N-alkylperhydroacridines (XII, XIII) with the preferential equatorial orientation of the N-alkyl group [29]. The formation of the N-benzylperhydroacridines (XIII) was accompanied by dealkylation side processes.



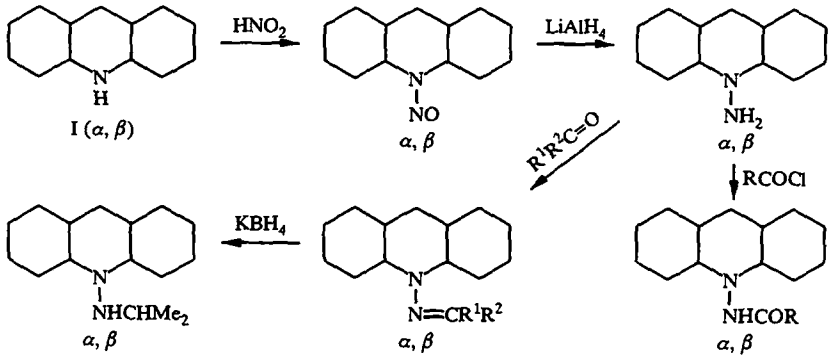
XII (α,β), XIII (α,β), XII R = CH_3, XIII R = Ph

The quaternization of *trans-syn-trans*- and *trans-anti-cis*-N-methylperhydroacridines (α-IV, β-IV) with methyl iodide or CD_3I gave the salts α- and β-XIV and α- and β-XV as mixtures of isomers differing in the orientation of the substituting groups at the nitrogen atom, the ratio of which is determined by the temperature conditions of the reaction [30, 31]:



R = CH_3, CD_3

A series of α and β isomers of N-nitroso-, N-amino(aminoisopropyl)-, N-amido-, and N-iminoperhydroacridines, among which the *trans-syn-trans*- and *trans-anti-cis*-N-aminoperhydroacridines were active inhibitors of monoamineoxidase, were synthesized in the search for biologically active substances [32]:



R = Ph, $C_6H_4NH_2$-*p*, β-pyridyl $COOC_2H_5$; R^1 = Ph, *p*-$(CH_3)_2NC_6H_4$, $C_6H_5CH_2CH_2$, *p*-$NH_2C_6H_4$, *p*-$NO_2C_6H_4$, 2-(5-nitrofuryl) with R^2 = H; $R^1 = R^2 = CH_3$

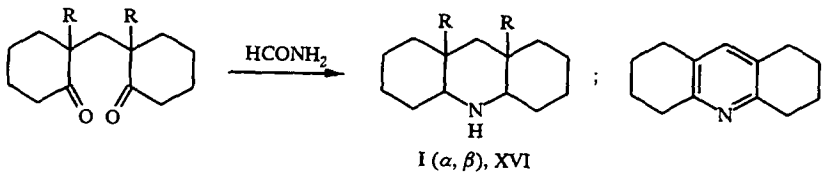
2. REDUCTIVE AMINATION OF δ-DIKETONES, β-CYCLOKETOLS, AND PYRYLIUM SALTS

The reductive amination of carbonyl compounds is widely used for the synthesis of amines, including those with cyclic structures [33]. Formic acid and its derivatives (the Leuckart reaction), complex metal hydrides (hydride amination), and catalytically excited hydrogen (catalytic hydroamination) have been used as reducing agents. This method was used successfully for the synthesis of perhydroacridines.

2.1. Synthesis of Perhydroacridines by the Leuckart Reaction

The Leuckart reaction is an important method for the synthesis of saturated azaheterocycles based on δ-diketones and β-cycloketols.

When methylenedicyclohexanone is heated with formamide, a 2:1 mixture of perhydroacridine (I) and *sym*-octahydroacridine is formed [10, 25, 34, 35]. Methylenebis-2,2′-(2-methylcyclohexanone) is only converted into 8a,9a-dimethylperhydroacridine (XVI) with a yield of 50% [36].

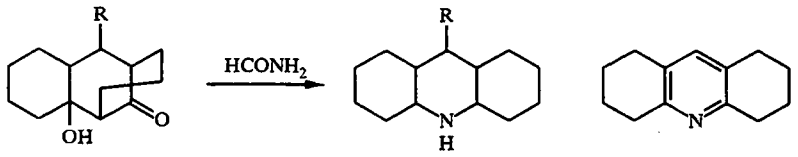


I (α, β), XVI

I R = H, (α,β); XVI R = CH_3

Perhydroacridine can be represented in the form of a mixture of *trans-syn-trans* and *trans-anti-cis* isomers [25, 37].

The 9-R-perhydroacridines (I, VI, XVII, XVIII) were isolated by the reaction of formamide with tricyclic ketones, which under these conditions undergo decyclization to the corresponding α-R-methylenedicyclohexanones [10, 35, 38-40]. The exception is unsubstituted β-cycloketol, which like methylenedicyclohexanone is transformed into a 2:1 mixture of the α,β isomers (I) and *sym*-octahydroacridine [35, 38]:

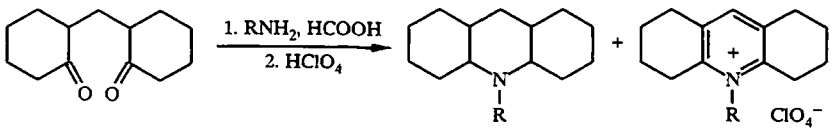


I (α, β); VI (α, β, γ); XVII, XVIII

I R = H; VI R = CH_3; XVII R = Ph; XVIII R = 2-furyl

9-Methylperhydroacridine (VI) is formed in three isomeric forms (α, β, γ) in ratios of 5:2:3 [40]; the stereoisomeric composition of compounds (XVII, XVIII) was not investigated.

The replacement of formamide by a mixture of amine and formic acid leads to the formation of N-substituted perhydroacridines (IV, VII) (yields 40-46%) and N-R-*sym*-octahydroacridinium salts (34-40%), isolated in the form of the perchlorates [12, 26, 41]:



IV (α, β, γ, δ), VII (α, β, δ)

IV R = CH_3, VII R = Ph

The base (IV) is formed as a mixture of four isomers (α, β, γ, δ) [26]. For identification, the mixture of isomers was converted into the familiar perhydroacridines (I) by dealkylation through the N-nitroso derivatives and their subsequent hydrolysis [12]. Here it was only possible to isolate the α, β, and γ isomers of (I). The loss of the δ isomer is explained by its small content in the initial mixture. N-Phenylperhydroacridine (VII) is formed as three isomers, one of which is the α isomer [41]; the stereochemical structure of the other isomers (β, γ) was established more recently [42].

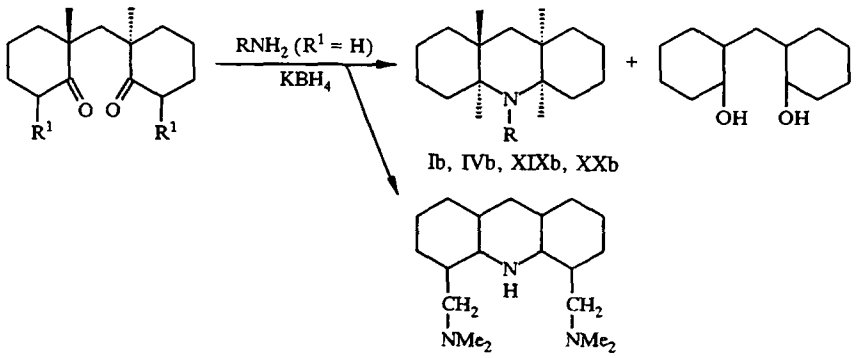
The mechanism of the formation of perhydroacridines in the Leuckart reaction has not yet been determined. It was suggested that decahydroacridine intermediates are formed initially and subsequently undergo disproportionation with hydride transfer from the decahydroacridine molecule, which acts as donor, to its protonated form, acting as hydride-ion acceptor [10, 41]. Since the yields of the saturated bases usually exceed the theoretically possible values, it was suggested that reduction of the intermediates by the formic acid takes place in addition to disproportionation [41]. It is also impossible to rule out the formation of N-formyl intermediates during the reaction, especially as cases of their isolation and hydrolysis to the free bases are known [36, 43].

Thus, the Leuckart reaction makes it possible to synthesize perhydroacridines with fairly high yields (40-100%). However, the application of this reaction is limited considerably by the rigorous conditions, the need in a number of cases to separate the saturated and unsaturated azaheterocycles, and the absence of stereospecificity.

2.2. Hydride Amination of Methylene-2,2-dicyclohexanones

Reductive amination with complex metal hydrides as a rule has an advantage over the Leuckart method, since it is carried out under mild conditions and is stereoselective.

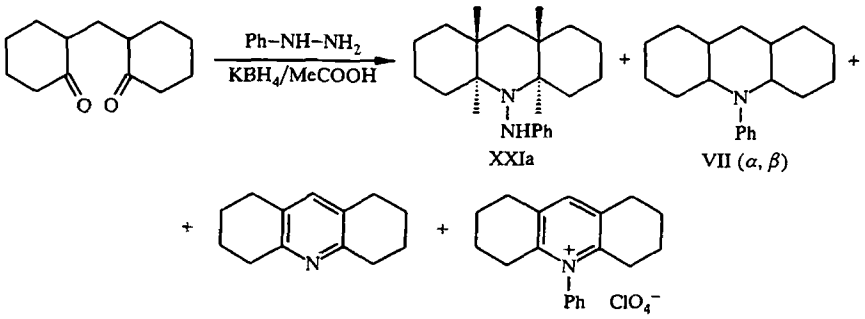
The hydride amination of methylenedicyclohexanones in the presence of KBH_4 was conducted in an alcohol medium at 30-35°C [44, 45]. If *threo*-methylenedicyclohexanone and ammonia are used, *trans-anti-cis*-perhydroacridine (Ib) is formed with an 80% yield [44]. The asymmetric centers of the substrate are not affected in the reaction, since when a mixture of the *threo* and *erythro* forms is used a mixture of α- and β-perhydroacridines (Ia, Ib) with the same overall yield is obtained [45]. This conclusion was also confirmed in the case of the synthesis of the β isomers of N-methyl-, N-(β-aminoethyl)-, and N-(β-hydroxyethyl)perhydroacridines (IVb, XIXb, XX), isolated with yields of 25-40% [45].



R^1 = H, $CH_2N(CH_3)_2$; Ib R = H; IVb R = CH_3; XIXb R = $(CH_2)_2NH_2$; XXb R = $(CH_2)_2OH$

A side reaction is the reduction of the initial oxo compounds to the corresponding diols [44, 45]. The intermediate compounds during hydride amination may be imino ketones and cycloimmonium salts [46].

The reaction of methylenedicyclohexanone with phenylhydrazine in the presence of hydride reducing agents (KBH_4 in alcohol, acetic acid, and their mixtures, $LiAlH_4$ in ether) takes place unambiguously [47]. Thus, N-phenylamino-perhydroacridine (XXIa) was obtained with a 40% yield in the form of the α isomer only when KBH_4 in dilute acetic acid was used.



In addition, the α and β isomers of N-phenylperhydroacridine (VII) (~4%) in a ratio of 3:1, *sym*-octahydroacridine (27%), and an N-phenyl-*sym*-octahydroacridinium salt (10%) were isolated.

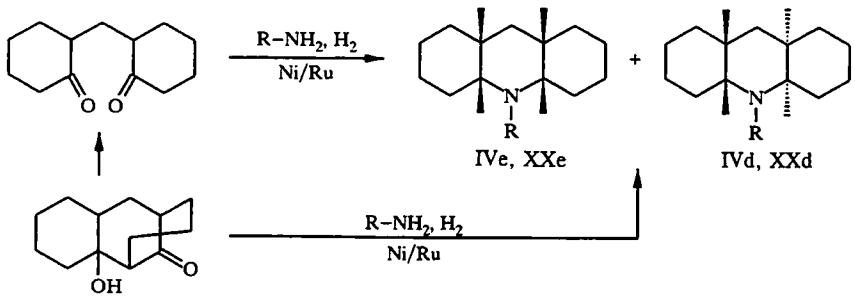
In spite of the mild conditions and the stereoselectivity, the use of hydride amination for the production of perhydroacridines is restricted on account of the formation of side products, the need to separate them, and their comparatively low degree of investigation.

2.3. Catalytic Hydroamination of Methylenedicyclohexanone, β-Cycloketols, and *sym*-Octahydroxanthylium Salts

The catalytic reductive amination of β-diketones, β-cycloketols, and pyrylium salts is promising for the synthesis of saturated six-membered azaheterocycles, including compounds of the perhydroacridine series [33, 48]. The merits of this method include the use of a cheap reducing agent (molecular hydrogen), the selectivity, and the stereoselectivity.

The hydroamination reactions were conducted under hydrogen pressure in the presence of heterogeneous catalysts based on metals of group VIII — Raney nickel modified with ruthenium (Ni/Ru), 5% ruthenium on carbon (Ru/C), and ruthenium dioxide (RuO_2).

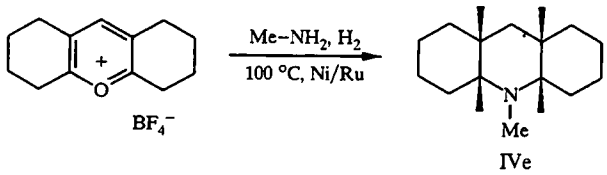
The hydromethyl(hydroxyethyl)amination of methylenedicyclohexanone and its aldolization product (β-cycloketol) takes place stereoselectively with the formation of N-substituted perhydroacridines having the *cis-syn-cis* (IVe, XXe) and *cis-anti-cis* (IVd, XXd) configuration with overall yields of 82-92% [49-51]:



IVd,e R = CH_3, XXd,e R = CH_2CH_2OH

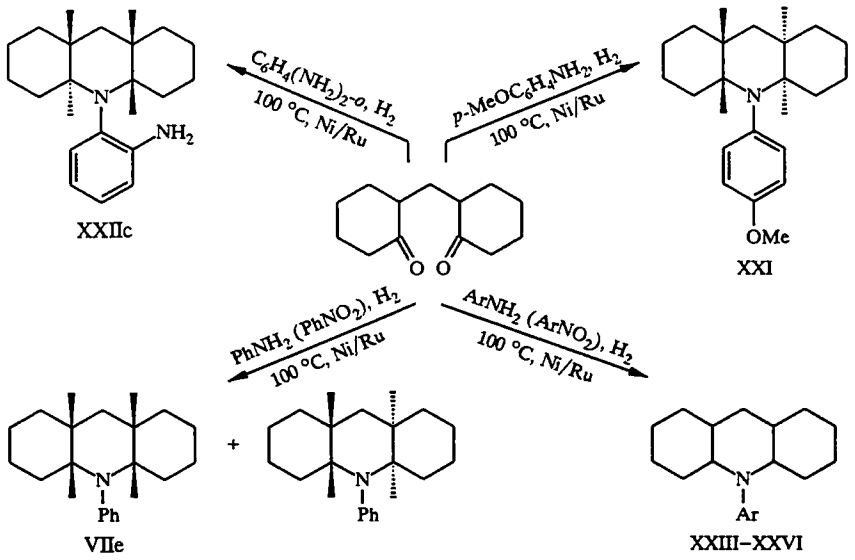
In the presence of Ru/C and Ni/Ru the process takes place at 90-100°C [49, 50, 52], and the most selective is Ni/Ru. With reduced RuO_2 it is possible to reduce the temperature to 20-25°C while retaining the high yields of the desired products. Repeated use of the catalyst is also possible [53].

If the product from O-cyclization of methylenedicyclohexanone (*sym*-octahydroxanthylium tetrafluoroborate) is used in the reaction, the *cis-syn-cis* isomer (IVe) is formed with a yield of 73% [8, 54, 55].



N-Arylperhydroacridines were obtained by the hydroamination of methylenedicyclohexanone by the action of anilines (aniline, *p*-aminophenol, *p*-anisidine, *p*-aminobenzoic acid, *o*- and *p*-phenylenediamines) and nitroarenes (nitrobenzene, *o*- and *p*-nitrophenols, *p*-nitroaniline, *m*-nitrobenzoic acid) [42, 49, 51]. As a rule, the use of nitroarenes in place of the easily oxidized anilines is preferred and makes it possible to obtain N-arylperhydroacridines with yields of up to 76% [42].

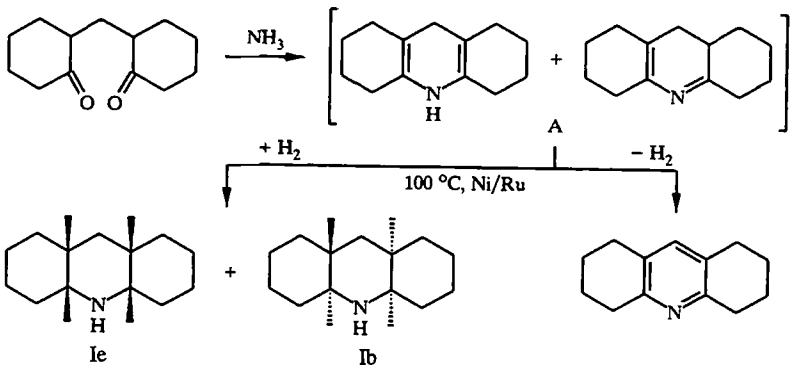
The stereoisomeric composition of the N-arylperhydroacridines is affected by the nature and position of the substituting groups in the aryl substituent. N-Phenylperhydroacridine is formed as a mixture of the *cis-syn-cis* and *cis-anti-cis* isomers (VIId, e) with a yield of 50% (in the presence both of aniline and of nitrobenzene). N-(*p*-Methoxyphenyl)perhydroacridine (XXId) has the *cis-anti-cis* configuration (yield 40%). The presence of a substituent at the *o* position of the aromatic ring leads to the appearance of the isomer with *trans* fusion of the rings, i.e., N-(*o*-aminophenyl)-*trans-syn-cis*-perhydroacridine (XXIIc).



XXIII Ar = C_6H_4OH-*o*, XXIV C_6H_4OH-*p*, XXV C_6H_4COOH-*m*, XXVI C_6H_4COOH-*p*

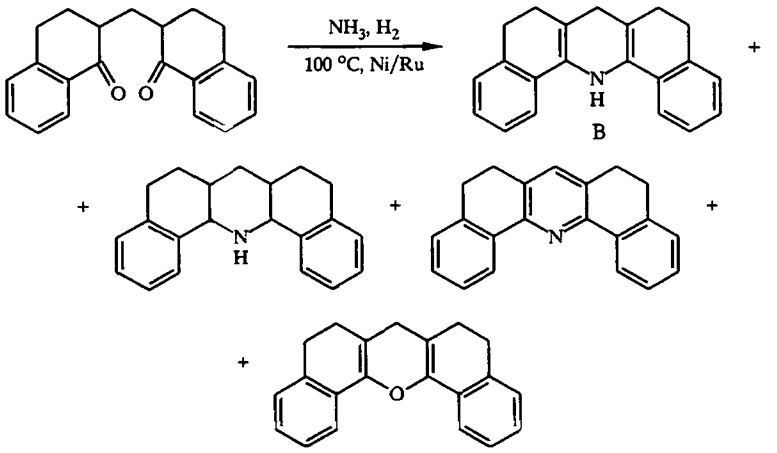
Hydroarylamination takes place most smoothly with *p*-amino- and *m*-nitrobenzoic acids. N-Carboxyphenyl-substituted perhydroacridines (XXV, XXVI) were isolated with quantitative yields as a result, clearly, of acid activation of the carbonyl groups in the substrate.

During the hydroamination of methylenecyclohexanone (with a 3-5% excess of ammonia) N-unsubstituted *cis-syn-cis*- and *trans-anti-cis*-perhydroacridines (Ib, e) with an overall yield of up to 20% and *sym*-octahydroacridine (60%) are formed [51, 56, 57].



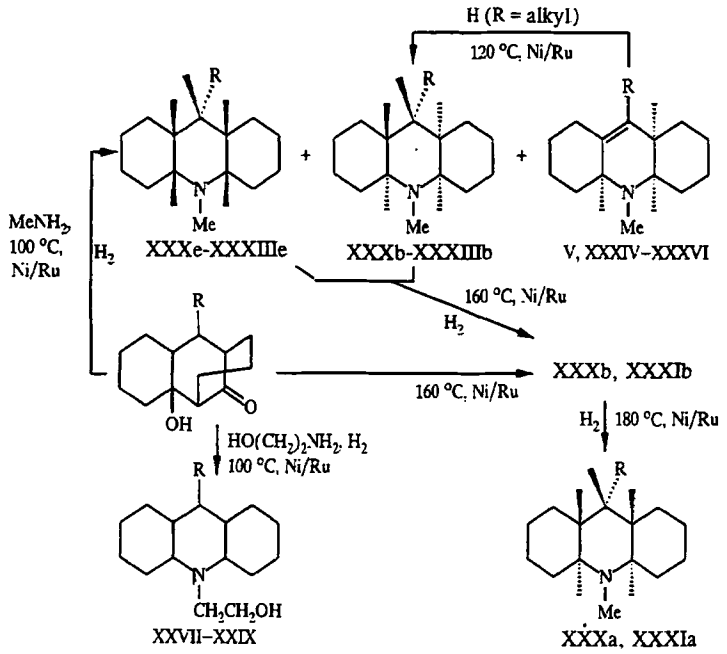
It was supposed that the formation of the latter results from dehydrogenation of the intermediately formed decahydroacridines A. If methylamine, ethanolamine, and aromatic amines are used aromatization is hindered, since dealkyl(aryl)ation is required, and hydrogenation of the intermediate A becomes more favorable [48, 49].

This suggestion is favored by the results from the hydroamination of methylenebis-α-tetralone in the presence of a 20-fold excess of ammonia [58]. 3,4,5,6-Dibenzo-1,2,7,8,9,10-hexahydroacridine B was obtained as one of the reaction products with a yield of 38%. Isolation of the latter became possible as a result of the presence of the annellated benzene rings, which stabilize the dihydroacridine fragment, and also the considerable excess of ammonia, which prevents hydrogenation of the C=C bonds of the heterocycle.



Change of the diketone–ammonia molar ratio (1:15) increases the yield of the piperazine base to 35%; dibenzohexahydroacridine B was detected by chromatography.

The transition to 9,10-substituted perhydroacridines (with yields of 70-95%) can be realized by the hydroamination of the products from intramolecular aldolization of α-R-methylenedicyclohexanones (β-cycloketols) with strong nucleophiles such as ethanolamine [50, 59, 60] and methylamine [61]. The stereochemical structure of the bases (XXVII, XXVIII) was not studied; 9-(2-furyl)-N-(β-hydroxyethyl)perhydroacridine (XXIX) was isolated in the form of the *trans-anti-cis* isomer [60]. The β-cycloketols are converted by the action of methylamine into *cis-syn-cis*- and *trans-anti-cis*-9-R-10-methylperhydroacridines (XXXe-XXXIIIe) and (XXXb-XXXIIIb) [61]. In addition, the partly unsaturated azaheterocycles 9-R-10-methyl-$\Delta^{8,9a}$-dodecahydroacridines (V, XXXIV-XXXVI) were found among the hydrogenation products (with yields of 17-20%, according to GLC).

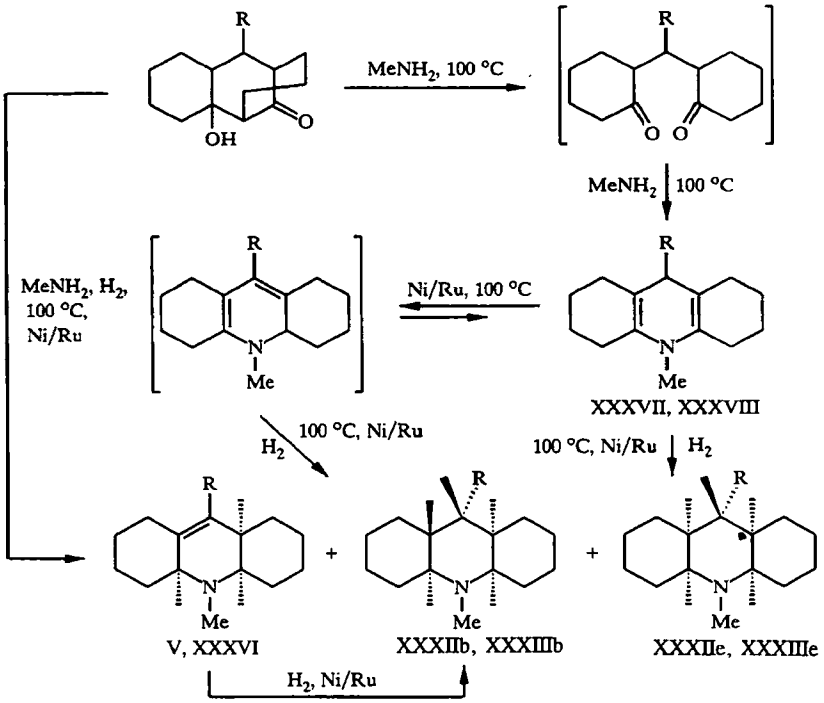


XXVII, XXXa,b,e, XXXIV R = CH_3, XXVIII, XXXIa,b,e, XXV R = C_2H_5, XXXIIb,e R = C_6H_5, XXIX, XXXIII B,e, XXXVI R = 2-furyl

Unlike the N-methylperhydroacridines (IVd, e), the 9-alkyl-N-methylperhydroacridines (XXXb, e, XXXIb, e) are capable of isomerization transformations when the temperature is increased to 160-180°C [61]. At 120°C the double bond in dodecahydroacridines (XXXIV, XXXV) is hydrogenated with the formation of the isomers (XXXb, XXXIb); after heating at 160°C for 7-12 h the reaction mixture contains only the *trans-anti-cis* isomers (XXXb, XXXIb), and at 180°C it contains the thermodynamically more stable *trans-syn-trans* forms (XXXa, XXXIa). Thus, it is possible by varying the temperature regime to realize the synthesis of 9,10-substituted perhydroacridines with a specific configuration, as was confirmed in the case of the hydromethylamination of ethyl-substituted β-cycloketol at 160°C; 9-ethyl-10-methyl-*trans-anti-cis*-perhydroacridine (XXXIb) was isolated with a yield of 90%.

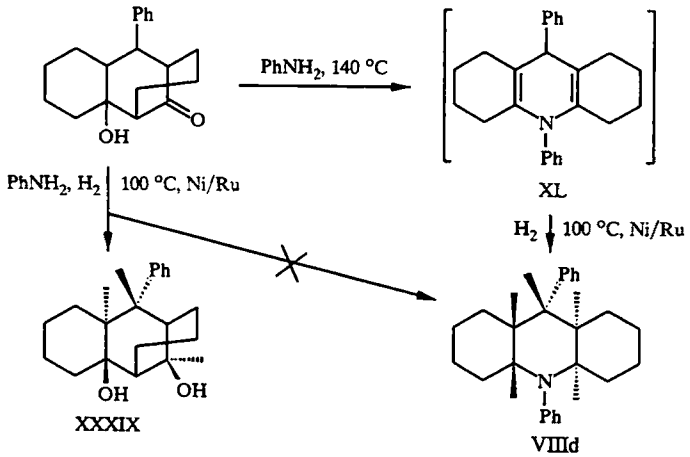
The intermediates in the hydroamination of β-cycloketols are $\Delta^{4a,8a,9a,10a}$-decahydroacridines [62]. In order to obtain evidence for the participation of the latter in the formation of the perhydroacridines 9-phenyl- and 9-(2-furyl)-10-methyl-decahydroacridines (XXXVII, XXXVIII) were synthesized from the corresponding β-cycloketols under the conditions of hydroamination (a fivefold excess of methylamine in methanol at 100°C and 10 MPa) but in the absence of a catalyst, and they were hydrogenated over Ni/Ru (100°C, 10 MPa). As during the direct hydromethylamination of β-cycloketols [61], the final products were *cis-syn-cis-* and *trans-anti-cis*-perhydroacridines (XXXIIb, e, XXXIIIb, e) with a small amount of the dodecahydroacridines (V, XXXVI) as impurity. The formation of the isomers (XXXIIe, XXXIIIe) can be regarded as the result of *cis*-addition of hydrogen to the intermediates (XXXVII, XXXVIII) after one adsorption event. The *trans-anti-cis* isomers (XXXIIb, XXXIII) are clearly formed during the isomerization of the intermediate dicyclohexa-1,4-dihydropyridines (XXXVII, XXXVIII) to the corresponding 1,2-dihydropyridines followed by *cis*-addition of hydrogen by the edge doublet scheme through the formation of the dodecahydroacridines (V, XXXVI). The double bond in the latter is stabilized by conjugation and is screened by the substituent at the $C_{(9)}$ atom. This reduces its hydrogenation rate and makes it possible to detect the formation of compounds (V, XXXVI).

Thus, stage-by-stage hydroamination of β-cycloketols and study of the stereochemical structure of the final products made it possible to regard this reaction as a process taking through retroaldol cleavage of the β-cycloketols to the corresponding 1,5-diketones. This is followed by amination of the latter with the formation of 1,4-dihydropyridine systems, catalytic isomerization, and hydrogenation of the obtained deca- and dodecahydroacridine intermediates with the *cis*-addition of hydrogen characteristic of catalytic reactions.



V, XXXIIIb,e XXXVII R = Ph, XXXIIIb,e XXXVI, XXXVIII R = 2-furyl

During the hydroamination of the β-cycloketols (aniline, 100°C, Ni/Ru) the azacyclization process is fully suppressed by the concurrent hydrogenation of the oxo function and the formation of tricyclic diols of the (XXXIX) type [63], since aniline as a weak base does not catalyze the retrodissociation of the initial ketols under the selected conditions. In the case of the reaction of aniline and the phenyl-substituted β-cycloketol it was shown that decyclization of the latter occurs at 140°C, and 9,10-diphenyldecahydroacridine (XL) is consequently formed [62]. During the hydrogenation of decahydroacridine (XL) (methanol, 100°C, 10 MPa) over Ni/Ru 9,10-diphenyl-*cis-anti-cis*-perhydroacridine (VIIId) was obtained with a yield of 77%.



It is not advisable to conduct the hydroamination of β-cycloketols at 140°C on account of the ease of reduction of the aryl substituents under these conditions. The synthesis of 9-R-arylperhydroacridines must therefore be carried out by successive amination of the β-cycloketols and catalytic hydrogenation of the obtained 9-R-N-aryldecahydroacridines.

Thus, by catalytic reductive amination it is possible to obtain perhydroacridines in the form not only of the well-known *trans-syn-trans*, *trans-anti-cis*, and *cis-syn-trans* isomers but also of the little-investigated *cis-syn-cis* and *cis-anti-cis* isomers.

3. STRUCTURAL INVESTIGATIONS OF PERHYDROACRIDINES

IR and ^1H and ^{13}C NMR spectroscopy, x-ray crystallographic analysis, and in a number of cases chemical transformations to perhydroacridines of known structure, Hofmann degradation, etc., have been used to establish the stereochemical structure and conformational features of isomeric perhydroacridines. The assignment to the α isomers can be made on the basis of the presence of the "Bohlman" absorption band in the region of ~ 2800 cm^{-1}, which only appears if both hydrogen atoms at the bridgehead atoms $C_{(4a)}$ and $C_{(10a)}$, adjacent to the nitrogen atom, occupy the axial position [12, 64].

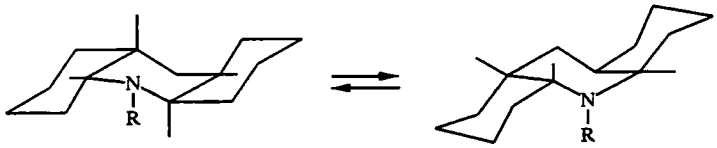
In the ^1H NMR spectra of the α, β, and γ isomers of the perhydroacridine (I) the signals of the hydrogen atoms at positions 4a and 10a are the most characteristic for each isomer [26, 37]. In the spectra of the α isomer these protons give a common signal at 2.05 ppm, which agrees with the symmetry of compound (Ia), leading to the magnetic equivalence of these protons. In the β isomer (Ib) these protons are nonequivalent and appear in the form of two signals at 2.05 ppm ($H_{(10a)}$) and 2.85 ppm ($H_{(4a)}$). The γ isomer (Ic) is characterized by signals in the region of 2.83 ppm ($H_{(10a)}$) and 2.15 ppm ($H_{(4a)}$). In addition to the chemical shifts of the protons it is also necessary to consider their spin–spin coupling, which leads to various multiplicities in the signals.

A detailed review of the ^1H NMR spectra of the α, β, and γ isomers of perhydroacridine and its N-substituted derivatives was given in [25, 26, 37, 40].

The most complete information on the stereochemical structure and conformational features of the isomeric perhydroacridines was given after analysis of the ^{13}C NMR spectra [11, 42, 51, 61].

The symmetrically constructed α isomers are characterized by a decrease in the number of carbon atoms in the perhydroacridine skeleton to seven and the absence of upfield signals in the region of ~ 20 ppm, which appear as a result of 1,3-diaxial coupling with *cis*-fusion of the heterocycles and alicycles [11, 65]. However, such a signal is observed in the spectra of the unsymmetrical β isomers, which have the *trans-anti-cis* configuration [51, 61], and of the γ isomer with the *cis-syn-trans* configuration [42].

A feature of the perhydroacridines of the *cis-cis* type is the conformational mobility. The *cis-anti-cis* isomers exist in the form of energetically degenerate enantiomeric conformations, easily transformed from one to the other even at room temperature [42, 51]:



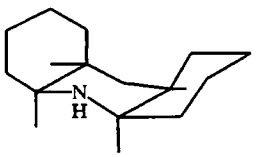
R = CH_3, C_6H_5, CH_2CH_2OH, $C_6H_4OCH_3$-*p*

The ease of the inversion of the *cis-anti-cis* isomers leads to a decrease in the number of signals in the ^{13}C NMR spectra and also to their broadening except for the signal of the $C_{(9)}$ atom and the signals of the atoms in the substituent [51].

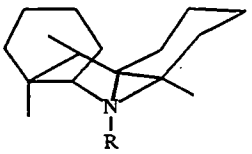
The structure of the N-phenyl-*cis-anti-cis*-perhydroacridine (VIId) was confirmed by x-ray crystallographic analysis [42]. It was established that the hetero- and carbocycles have the chair conformation, and the piperidine ring is more planar than the alicycles. The phenyl substituent occupies the equatorial position; the $C_{(5)}-C_{(10a)}$ and $C_{(1)}-C_{(9a)}$ bonds are axial, while the $C_{(4)}-C_{(4a)}$ and $C_{(8)}-C_{(8a)}$ bonds are equatorial in relation to the heterocycle, and this corresponds to the *cis-anti-cis* configuration.

The conformational behavior of the *cis-syn-cis*-perhydroacridines differs significantly from that of the *cis-anti-cis* isomers. For the *cis-syn-cis* isomer (Ie) the most stable is the conformer in which the axial C–C bonds are in the β position to the nitrogen atom [51], and by analogy with *cis*-decahydroquinoline it can be called the A conformer [65]. The reason for such stabilization is the decrease in the length of the C–N bonds compared with the C–C bonds, which leads to significant strengthening of the repulsion of the axially oriented substituents at the position to the nitrogen atom. Since the introduction of a substituent at the nitrogen atom destabilizes conformation A in the *cis*-decahydroquinolines [65], the same effect can also be expected in the N-substituted perhydroacridines. In actual fact, the conformational equilibrium in N-R-*cis-syn-cis*-perhydroacridines (IVe, VIIe, XXe) is displaced completely toward conformer B [51], due to the increase in the size of the N–R group. As a result its axial position in relation to the carbocycles in conformer A becomes unfavorable. The increase

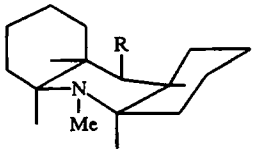
in the steric loading at position 9 again displaces the equilibrium toward conformation A; it is in such a conformation with the equatorial arrangement of the substituent at the $C_{(9)}$ atom that the 9-R-10-methyl-*cis-syn-cis*-perhydroacridines (XXXe-XXXIIe) are realized [61]:



A (Ie)



B (IVe, VIIe, XXe)



A (XXXe-XXXIIe)

A unique marker for the conformationally nonuniform *cis-syn-cis*-perhydroacridines can be the position and intensity of the signal of the $C_{(9)}$ atom. For the A conformers this signal is in the downfield region with an intensity approximately half that of the other signals [51].

X-ray crystallographic analysis of the *cis-syn-cis* isomer (XXe) showed [51] that the hetero- and carbocycles are in the chair form, and the latter are somewhat flattened. The $C_{(1)}-C_{(9a)}$ and $C_{(8)}-C_{(8a)}$ bonds are equatorial, and the $C_{(4)}-C_{(4a)}$ and $C_{(5)}-C_{(10a)}$ bonds are axial, which agrees with conformation B. The substituent at the N atom has the equatorial orientation.

The ^{13}C chemical shifts of the isomeric N-R-perhydroacridines are given in Table 1, and those of the 9-R-10-methylperhydroacridines are given in Table 2.

Thus, the presented material summarizes the data on the synthesis and stereochemical structure of perhydroacridines. It can be supposed that investigations in this region will continue, primarily, in the development of conditions for stereoselective synthesis, the reaction mechanisms, and the stereochemistry of this important group of compounds.

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