STEREOCHEMISTRY OF DECAHYDROQUINOLINE AND DECAHYDRO-4-QUINOLONE (REVIEW)

G. V. Grishina and V. M. Potapov

UDC 547.831.7.8:541.634(07)

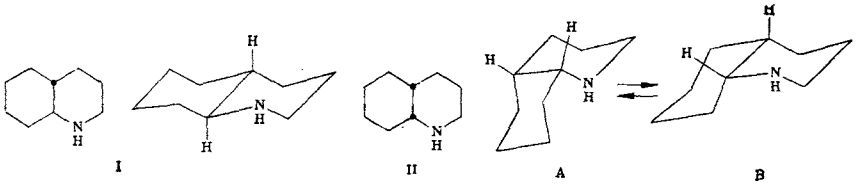
The configurational and conformational peculiarities of the cis and trans isomers of decahydroquinoline and decahydro-4-quinolone are discussed, and information on a new class of cis-decahydroquinoline alkaloid-neurotoxins and some data on the effect of the three-dimensional structures of decahydroquinoline derivatives on pharmacological activity are presented.

The great diversity and complexity of natural compounds that include a decahydroquinoline structure have stimulated numerous searches for the specific syntheses of derivatives of decahydroquinoline with certain three-dimensional structures. The systematic investigation of the pharmacological activity of decahydroquinoline derivatives has led to the synthesis of a number of new compounds that have a broad spectrum of biological activity.

In the present review we attempted to syntematize the large amount of available literature data on the stereochemical peculiarities of decahydroquinoline and decahydro-4-quinolone – key compounds for the synthesis and study of diverse derivatives of the decahydroquinoline series.

1. Configurations of Decahydroquinoline Derivatives

1.1. cis,trans Isomerism. The presence of two asymmetric nodal carbon atoms is responsible for the existence of decahydroquinoline in the form of two stable stereoisomeric forms with cis and trans fusion of the rings. trans-Decahydroquinoline (I) is a conformationally rigid system, while the conformationally labile cis-decahydroquinoline (II) can exist in the form of two interconvertible conformers A and B:



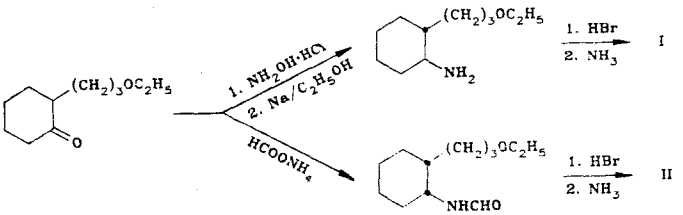
I II A B

The introduction of other chiral centers into the decahydroquinoline molecule significantly complicates the stereochemical composition of the compounds.

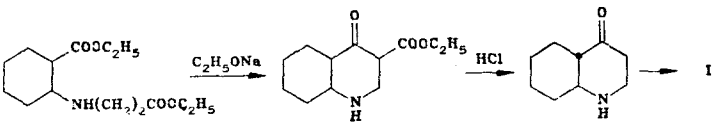
The existence of two racemic trans and cis isomers of decahydroquinoline was first observed in 1927 [1]. Solid and liquid forms of decahydroquinoline were isolated in the catalytic hydrogenation of quinoline over platinum. In conformity with the Auwers–Skita rule, a cis configuration was assigned to the liquid base, which has a higher boiling point, density, and refractive index, and a trans configuration was assigned to the solid base. Up until the last decade, the stereochemical assignments to cis and trans series of compounds of decahydroquinoline were made only in conformity with the data in [1]. The correctness of this assignment was confirmed by the chemically independent synthesis of cis- and trans-decahydroquinoline II and I from two stereoisomers of 2-(3-ethoxypropyl) cyclohexylamine [2]:

M. V. Lomonosov Moscow State University, Moscow 117234. Translated from Khimiya Geterotsiklicheskikh Soedinenii, No. 5, pp. 579-599, May, 1987. Original article submitted November 1, 1985.

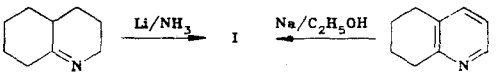
0009-3122/87/2305-0475$12.50



Individual trans-decahydroquinoline was synthesized by reduction of decahydro-4-quinolone via the Kishner method [3].

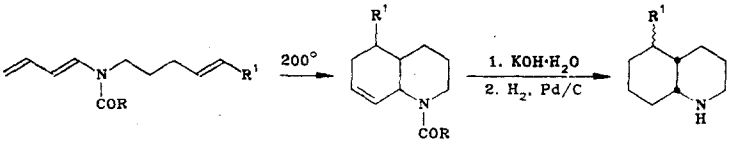


The catalytic hydrogenation of quinoline under various conditions usually leads to a mixture of isomers of decahydroquinoline with significant preponderance of the trans isomer [4-12]. The reduction of 2,3,4,5,6,7,8-octa-hydroquinoline with lithium in liquid ammonia [13, 14] or of 5,6,7,8-tetrahydroquinoline with sodium in alcohol [15] proceeds stereospecifically with the formation of only trans-decahydroquinoline.



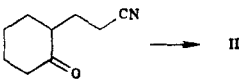
The introduction of a methyl group into the 2, 3, 6, or 8 position of $\Delta^{1,9}$-octahydroquinoline or 5,6,7,8-tetrahydroquinoline does not change the stereospecificity of reduction [16].

Pure cis-isomer II can be obtained conveniently by the successive catalytic hydrogenation of quinoline over Raney nickel and platinum black in concentrated hydrochloric acid [17]. cis-1-Acyl-$\Delta^{7,8}$-octahydroquinolines III, which are formed in the thermal cyclization of dieneamides, are readily hydrogenated to the corresponding cis-decahydroquinolines IV [18].

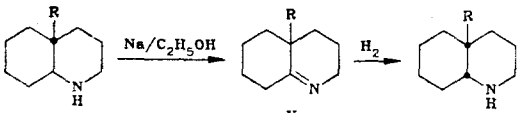


R=OCH$_3$, CH$_3$; R^1=H, CH$_3$

Virtually pure cis-decahydroquinoline is formed in the hydrogenation of 2-(2-cyanoethyl)cyclohexanone over Raney nickel [13, 19].

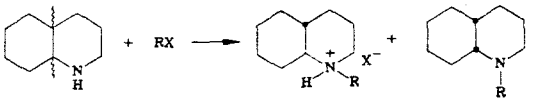


Depending on the conditions, the reduction of 10-substituted $\Delta^{1,9}$-octahydroquinolines V leads only to the cis or only to the trans isomers [20-23].



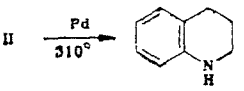
R=H, CH$_3$, C$_6$H$_5$

Stereoisomeric decahydroquinolines also differ with respect to their chemical properties. A mixture of N-alkyl-cis-decahydroquinoline and trans-decahydroquinolinium halide is formed in the quaternization of an equimolar mixture of the cis and trans isomers with one equivalent of alkyl halide at room temperature [23].

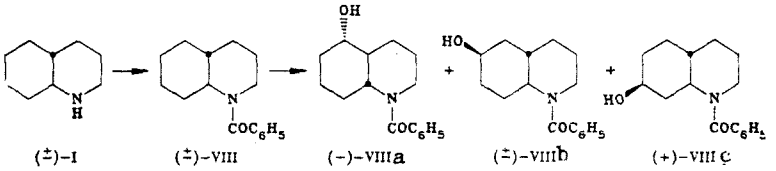


R=C_2H_5, $CH_2CH_2N(CH_3)_2$, $CH_2CH_2CH_2Cl$

Only the cis isomer undergoes catalytic dehydrogenation under identical conditions in the presence of palladium [24].



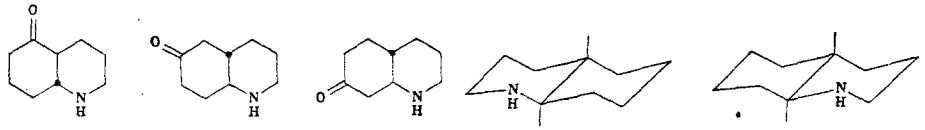
1.2. Optical Isomerism. Little information regarding optically active derivatives of decahydroquinoline is available. In 1915 (+)-trans-decahydroquinoline was isolated by fractional crystallization of the salt of trans-decahydroquinoline and D-bromocamphorsulfonic acid [25]; the (−)-form could not be obtained by the same method. The isolation of the (−)-enantiomer by means of repeated crystallization of the tartrate was later described [26]. The absolute configurations of the enantiomers of trans-isomer I were established in [27, 28]. A mixture of (−)-5-, (±)-6-, and (+)-7-hydroxy derivatives VIIIa-c in 80-90% overall yield is formed in the microbiological hydroxylation of racemic trans-1-benzoyldecahydroquinoline (VII). The hydroxylation of the (−)-enantiomer of VII gives a mixture of optically pure (5S,9R,10S)-trans-1-benzoyldecahydro-5-quinolol (VIIIa) and (6R,9R,10R)-1-benzoyl-trans-decahydro-6-quinolol (VIIIb) in a ratio of 87:13. A mixture of optically pure (7S,9R,10S)-1-benzoyl-trans-decahydro-7-quinolol (VIIIc) and (6S,9S,10S)-1-benzoyl-trans-decahydro-6-quinolol (VIIIb) in a ratio of 35:65 is formed in the similar oxidation of (+)-VII. It follows from the data obtained that the (−)-enantiomer is hydroxylated primarily in the 5 position, while the (+)-enantiomer is hydroxylated primarily in the 6 position. The oxidation of optically active quinolols VIIIa-c gave the corresponding chiral trans-quinolones IXa-c, the absolute configurations of which were established by means of application of the octant rule to their optical rotatory dispersion (ORD) curves. The absolute configurations of the enantiomers of trans-decahydroquinoline were also established on the basis of these results.



(±)-I (±)-VIII (−)-VIIIa (±)-VIIIb (+)-VIIIc

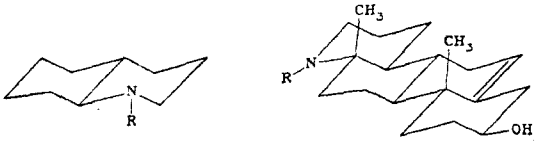
(+)-I → (−)-VII → (+)-VIIIa + (+)-VIII b

(−)-I → (+)-VII → (−)-VIIIb + (−)-VIII c



(9*R*,10*S*)-IXa (9*S*,10*R*)-IXb (9*S*,10*R*)-IXc (+)−(9*R*,10*S*)-trans-decahydroquinoline $[\alpha]_D^{20}+4.8°$ (−)−(9*S*,10*R*)-trans-decahydroquinoline $[\alpha]_D^{20}-4.6°$

A coordinate system for monitoring the active centers of hydroxylation in an investigated enzyme was established [28] in conformity with the data obtained on the absolute configuration and conformational rigidity of the trans-decahydroquinoline molecule. The absolute configurations of the enantiomers of trans-decahydroquinoline were confirmed by comparison of the chiroptical properties for pairs of N-chloro- and N-nitroso derivatives of (−)-trans-decahydroquinoline X and 17-α-aza-D-homoandrost-5-en-3β-ol (XI) with a known absolute configuration [29].



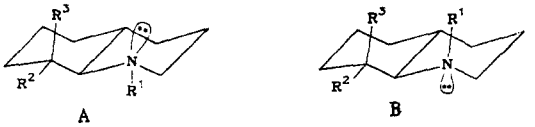
X XI

X, XI R=Cl, NO

Information regarding the enantiomers of cis-decahydroquinoline is not available. However, in the last 10 years data have been published regarding the isolation from the skin extracts of the South American tree frogs Dendrobates pumilio of several families of alkaloid-neurotoxins, the compositions of which include the cis-decahydroquinoline system, which has not previously been encountered in natural plant alkaloids; this will be discussed below.

2. Conformations of the cis and trans Isomers of Decahydroquinoline

2.1. trans-Decahydroquinoline and Its Derivatives. The structures of the cis and trans isomers of decahydroquinoline and the correctness of the assignment made by Huckel [1] were rigorously confirmed relatively recently [30, 31]. The conformational homogeneity and rigidity of the trans-decahydroquinoline molecule were established from the absence in the ^1H and ^{13}C NMR spectra of changes when the temperature was lowered to −80°C [30-36]. Only one dynamic process, viz., inversion of the nitrogen atom, which determines the chemical and biological reactivity of the amino function in donor-acceptor reactions, can be realized for trans-decahydroquinoline. Despite numerous studies [36-38] carried out by various physicochemical methods, it proved to be impossible to evaluate the position of the axial-equatorial inversion equilibrium. More definite conclusions were drawn for N-methyl derivative XII, for which the constant of the $N-CH_3(a) \rightleftarrows N-CH_3(e)$ equilibrium was calculated with the use of additional data from the ^1H and ^{13}C NMR spectra for model trans-decahydroquinolines XIIIa-h [37, 39].



I, XII, XIII a-h

I $R^1=R^2=R^3=H$; XII $R^1=CH_3$, $R^2=R^3=H$; XIII a-d $R^1=H$, e-h $R^1=CH_3$; a, e $R^2=CH_3$, b, d, f, h $R^2=H$, c, g $R^2=t\text{-}C_4H_9$; a, c, e, g $R^3=H$, b, f $R^3=CH_3$, d, h $R^3=t\text{-}C_4H_9$

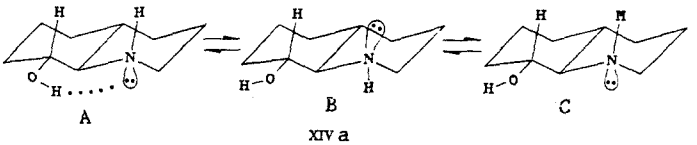
The calculated free conformational energy of the N-methyl group in XII is 7.5 kJ/mole, which constitutes evidence for the existence by a factor of greater than 95% of trans-1-methyldecahydroquinoline (XII) in conformation A with an equatorial $N-CH_3$ group [35, 36]. Two diastereomeric hydrochlorides are formed in the quaterization of methyldecahydroquinoline XII [36]:

92 : 8

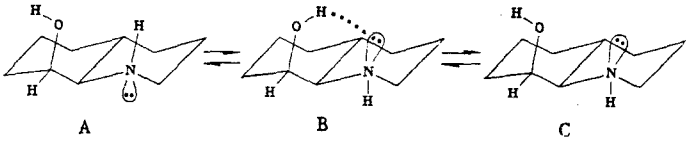
The N-equatorial conformer (ΔG^0 = 8.8 kJ/mole) also predominates for 1-ethyl-trans-decahydroquinoline. A study of a series of C- and N-substituted trans-decahydroquinolines showed that the introduction of an axial methyl group in the 3, 8, and 10 positions secures the $N-CH_3$ group primarily in an equatorial orientation (conformation A); the presence of an equatorial substituent attached to $C_{(8)}$ leads to a virtually complete shift of the equilibrium toward conformation B with an axial $N-CH_3$ group [36, 40].

Data on model trans isomers of 8α-(XIIIc) and 8β-tert-butyldecahydroquinoline (XIIId) and their methyl derivatives XIIIg, h, in which the equilibrium is shifted to different sides because of the presence of a tert-butyl group in the 8 position, have been used for the qualitative evaluation of the position of the $NH(e) \rightleftarrows NH(a)$ equilibrium in trans-decahydroquinoline [40]. A surprisingly slight deviation from the ideal double-chair form in the presence of an axial tert-butyl group was established from data from x-ray diffraction analysis of the picrate and $^{1,3}C$ NMR spectrosocpy of base XIIId [41]. For tertiary bases XIIIe-h on the basis of the IR spectra in the region of Boltzmann bands it was established that strong bands of almost constant intensity at 2815-2820 cm^{-1} are observed for XIIIf, h with a completely equatorial orientation of the N-methyl group [39]. Relatively strong bands at 2790-2800 cm^{-1} are characteristic for XIIIe, g. On the basis of a similar examination of the spectral data for trans-decahydroquinolines XIIIa-d the percentages of the equatorial NH conformer are ∿70% (I), 65% (XIIIa), 75% (XIIIb), 20% (XIIIc), and 80% (XIIId). The results obtained with respect to the inversion of nitrogen in trans-decahydroquinoline coincide with the previously known data extrapolated for it from spectral (IR) investigations of the conformational equilibria of epimers of trans-8α- and 8β-decahydro-7-quinolol (IVa,b) [42]. The mole

fractions and differences in the free energies of conformers A-C were calculated from the results of a comparative analysis of the conformational equilibrium of the free OH group and the associated form (OH...N) for dilute solutions of epimers XIVa, b. On the basis of these data the difference in the free energies of the NH(a) and NH(e) conformers for trans-decahydroquinoline is 2 ± 0.1 kJ/mole, which corresponds to preponderance of the NH-equatorial form also by a factor of 70%.

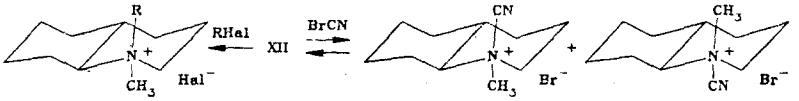


XIV a



XIV b

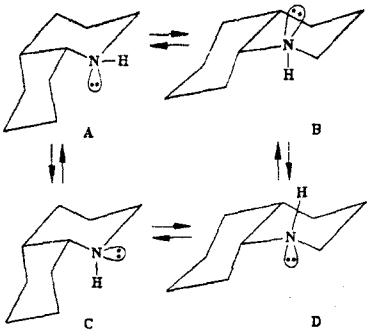
The stereoselectivity of the quaternization of N-methyl-trans-decahydroquinoline by alkyl halides at room temperature was investigated by PMR spectroscopy [43-46]. Axial attack was chiefly observed for all cases; to a certain extent, this may constitute evidence for a primarily equatorial orientation of the N-methyl group in the starting base. A different pathway of attack is realized in the quaternization of 1-methyl-trans-decahydroquinoline (XII) with cyanogen bromide at low temperature. According to the results of PMR spectroscopy and x-ray diffraction analysis, a mixture of CH_3(a) and CH_3(e) invertomers of N-cyano-N-methyl-trans-decahydroquinolinium bromide in a ratio of 9:1 is formed [46, 47].



R=CH_3, C_2H_5, C_3H_7; *i*-C_3H_7; $CH_2C_6H_5$

Similar results were also obtained in the case of quaternization with methyl iodoacetate; the ratio of CH_3(a) and CH_3(e) invertomers with respect to the nitrogen atom for trans-1-methyldecahydroquinoline is 3:2 [48].

2.2. cis-Decahydroquinoline and Its Derivatives. The simultaneous occurrence of two dynamic processes, viz., conversion of the rings and inversion of the nitrogen atom, is possible for the conformationally labile cis-decahydroquinoline (II):

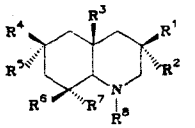


The barrier to ring conversion is evidently close to 42-50 kJ/mole, which is characteristic for decalin derivatives [49]. Inversion of the nitrogen atom with a barrier on the order of 39.8 kJ/mole mole may also occur for each conformer [50]. A conformational study of a large series of cis-decahydroquinolines was made independently by two groups of researchers. In [17, 51] it was shown by ^1H, ^{13}C, and ^{19}F NMR spectroscopy that cis-decahydroquinoline exists primarily in double chair conformation A. When the temperature is lowered to −74°C, the ring-inversion process becomes slow, and one observes "freezing" of conformers A and B, the ratio of which is 93.5:6.5. Inversion of the nitrogen atom still remains a rapid process. Virtually the same ratio of conformers A and B (90:10) was later found at −68°C [52]. The high preferableness for cis-decahydroquinoline of conformation A,

TABLE 1. Relative Percentages and Differences in the Free Energies of Conformers A and B in 1-Alkyl-cis-decahydroquinolines

R	%		T, °C	ΔG^0_{-68}, kJ/mole (A → B)
	A	B		
H	93,5	6,5	—74	—4,4
CH_3	70	30	—50	—1,6
CD_2CH_3	14	86	—55	+3,3
CH_2CF_3	17	83	—60	+2,8

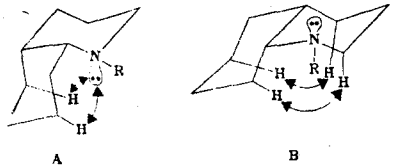
TABLE 2. Conformational Equilibria in cis-Decahydroquinolines II and XV-XVII in $CDCl_3$ at —68°C



XV $R^3=CH_3$; XVI $R^4=CH_3$; XVII unindicated $R^5=H$, $R^6=CH_3$

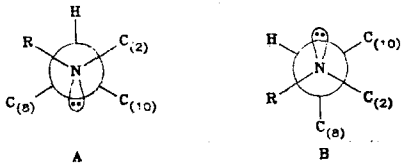
Compound	$R^5=H$			$R^5=CH_3$		
	A, %	B, %	ΔG^0_{-68}, kJ/mole	A, %	B, %	ΔG^0_{-68}, kJ/mole
II	90 ±1	10 ±1	3,76±0,05	71 ±2	29 ±2	1,50±0,04
XV	94,5±1	5,5±1	4,85±0,08	77 ±1	23 ±1	2,05±0,03
XVI	11 ±1	89 ±1	—3,56±0,4	5	95	—5,02
XVII	41 ±2	59 ±2	—0,62±0,04	89,5±1,5	10,5±1,5	3,44±0,07

in which the n pair of the nitrogen atom is located in a hindered internal position of the molecule, constitutes evidence for the substantially smaller steric requirements of the free n pair of the nitrogen atom as compared with the hydrogen atom. Two pairs of 1,4-hydrogen—n pair interactions that are typical only for cis-decahydroquinoline develop in conformation A; these interactions can thus be considered to be weaker than the two pairs of 1,4-hydrogen—hydrogen interactions in minor conformation B.



A B

Qualitatively, from examination of Newman projections along the $N-C_{(9)}$ bond for conformations A and B it follows that a repulsive $C_{(2)}/C_{(8)}$ interaction, which is minimal in conformation A, predominates for R = H, CH_3. With an increase in the size of R the dominant process becomes the $R(N)/C_{(8)}$ interaction, for a decrease in which the conformational equilibrium is shifted toward conformation B [52-55].



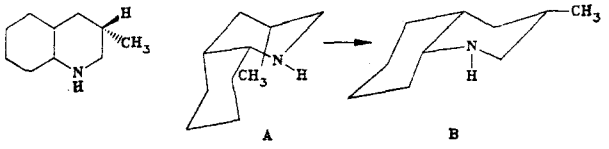
A B

Thus for 1-methyl-cis-decahydroquinoline the percentage of conformation A decreases to 71%; this is explained by an increase in the $C_{(8)}H_2/CH_3(N)$ interaction [52]. The introduction of other substituents at the nitrogen atom (ethyl, 2,2,2-trifluoroethyl, nitroso, phenylsulfonyl) leads to significant preponderance of conformation B. According to data from the low-temperature ^{19}F NMR spectrum, the energy of activation of the A → B transition for 1-(2,2,2-trifluoroethyl)-cis-decahydroquinoline is 68 kJ/mole [51, 53], which is very

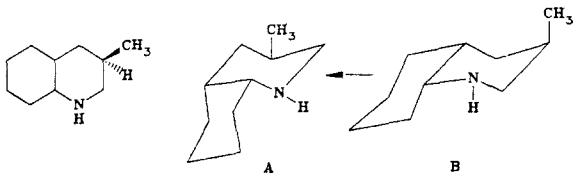
close to the barrier to ring inversion in cis-decalin [49]. Thus the nature of the substituent attached to the nitrogen atom has a pronounced effect on the conformational equilibria of cis-decahydroquinoline derivatives: conformer A predominates only for R = H, CH_3 (Table 1) [52, 53].

High sensitivity of the conformational composition to slight changes in the structure was established on the basis of the results of conformational analysis carried out on a large series of cis-decahydroquinolines. It is apparent from the data in Table 2 that the conformational composition changes markedly even when one methyl group is introduced into the cis-decahydroquinoline system.

The spatial orientation of the substituents also has a pronounced effect on the conformational composition. For epimeric 3α- and 3β-methyl-cis-decahydroquinolines (XVIIIa,b) at 20°C and −68°C one observes the complete preponderance of different conformers B and A, respectively, with an equatorially oriented methyl group [52].

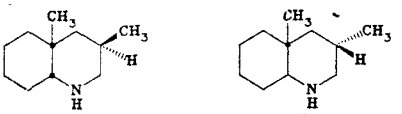


XVIIIa



XVIIIb

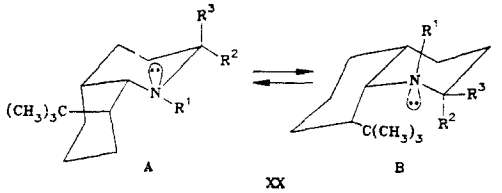
A similar principle was also noted for epimers of 3,10-dimethyl-cis-decahydroquinoline (XIXa, b), for which opposite conformational homogeneity was also observed.



XIXa XIXb

The facile change in the conformational compositions of C- and N-substituted cis-decahydroquinolines is a consequence of the presence of a shorter C—N bond as compared with the C—C bond, which leads to great steric compression of the region around the nitrogen atom of the piperidine ring and to a change in the torsion angles ($\tau \approx 60°$). Drawing together of the e,e- rather than the e,a-vicinal groups, as observed in cyclohexanones (where $\tau_{e,e} \approx 65° > \tau_{e,a} \approx 55°$) [52, 53], arises as a result of greater packing around the nitrogen atom. In this connection the 1,4-syn-axial interactions already mentioned become characteristic for cis-decahydroquinoline derivatives.

The unexpected fact of the existence of 8β-tert-butyl-cis-decahydroquinoline (XXa) in conformation A with an axial tert-butyl group was observed in [56]. The tert-butyl group does not usually take on an axial orientation and serves as a "retaining group" that hinders ring inversion [39].



XX

In the A⇄B conformational equilibrium conformation B therefore should have been assumed to be more favorable. This assumption was based on a comparison of the differences in the free energies of the conformers of cis-decahydroquinoline II (conformer A is more favorable than B by 4 kJ/mole) and tert-butylcyclohexane, for which the conformer with an equatorial

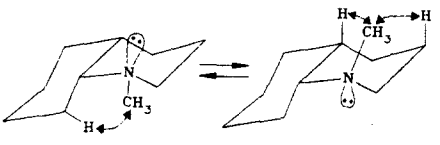
TABLE 3. Conformational Compositions of cis-Decahydroquinolines XXa-d [56]

Compound	R^1	R^2	R^3	A/B	T, °C	ΔG^0, kJ/mole
XXa	H	H	H	97/3	−75	−5,7
XXb	CH_3	H	H	62/38	−80	−0,8
XXc	H	CH_3	H	99/1	−70	−7,8
XXd	H	H	CH_3	2/98	−65	6,8

tert-butyl group is preferred to that with an axial tert-butyl group by 22 kJ/mole. However, according to ^{13}C NMR data at 27°C and −75°C, XXa exists virtually completely in the form of conformer A with an axial tert-butyl grup. This result was obtained on the basis of the ^{13}C NMR spectra for cis-decahydroquinolines XXb-d, which, because of the steric requirements of the methyl group attached to $C_{(2)}$, model conformers A and B (Table 3).

The repulsive trans-gauche interaction of the equatorial tert-butyl group and the n pair of the nitrogen atom should most likely be considered to be the factor that destabilizes conformation B. The calculated value of this interaction in the absence of appreciable distortions of the geometry of the molecule reaches 22 kJ/mole, which exceeds the value (20-4 kJ/mole) previously derived indirectly for conformer B.

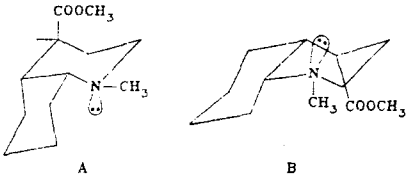
The existence of an $N{-}CH_3(a) \rightleftarrows N{-}CH_3(e)$ equilibrium was recorded for 1-methyl-cis-decahydroquinoline; the experimentally observed percentage of the N-axial conformer at 30°C was 11.5%, as compared with 6% at −68°C. In fact, for conformers A and C, because of the strong syn-axial $C_{(5)}$, $C_{(7)}/CH_3(N)$ interaction, an axial orientation of the methyl group at the nitrogen atom cannot be realized. However, the contribution of the N-axial conformer becomes fully appreciable in conformations B and D; there are two N(Me)/H interactions in conformer D and one such interaction in conformer B.



B D

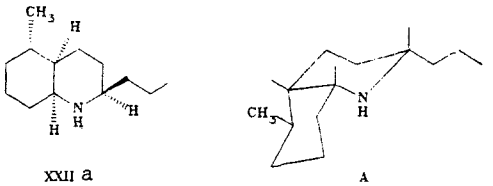
The value of the N(Me)/H interaction previously calculated for piperidine ranges from 3.8 kJ/mole [35] to 6.3 kJ/mole [57]. A quantitative evaluation of the composition of the N conformers of 1-methyl-cis-decahydroquinoline with the use of the first value indicates the presence of 18% conformer D at 30°C and 10% at −68°C, while on the basis of the second value we obtain 7.5% conformer D at 38°C and 2.5% at −68°C. The amounts of conformer D calculated in this way are in good agreement with the experimentally found percentage of the N(Me)-axial conformer [52]. The ratio of N conformers A:B for cis-decahydroquinoline XXb (Table 2) is 7:3 [56]. It seems rather unexpected as compared with unsubstituted XXa, since it is difficult to explain the increase in the percentage of conformer B, in which, for elimination of unbonded interactions with the tert-butyl group, the N-methyl group occupies an unfavorable axial orientation. For example, for 1-methylpiperidine the $N{-}CH_3(e)$ conformer is more preferable by 10 kJ/mole ($CHCl_3$) [50]. It is completely possible that this result is due to the presence of a tert-butyl group, which seriously changes the geometry of the cis-decahydroquinoline XXb molecule, in connection with which x-ray diffraction analysis is necessary.

A chemical evaluation of the relative steric requirements of the free electron pair of the nitrogen atom and of the hydrogen atom was made in a study of the equilibrium that develops under the influence of the methoxide ion in cis,cis- and trans,cis-3-(methoxycarbonyl)decalins and cis- and trans-4-methoxycarbonyl-1-methyl-cis-decahydroquinolines XXI. It was concluded that the two conformers have comparable stabilities in protic solvents, whereas conformer A, with the electron pair "within," is more stable in aprotic solvents [58, 59].



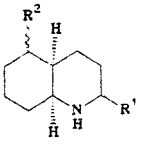
A B

2.3. cis-Decahydroquinoline Alkaloid-Neurotoxins. In 1969 there was a report regarding the isolation from the skin secretions of the Panamanian frogs Dendrobates pumilio and D. auratus of several alkaloid-toxins that have, according to preliminary data, a selective effect on the diverse functions of the membranes of nerve cells [60-62]. Chromatographic separation of the multicomponent mixture into microquantities yielded an alkaloid, which was called pumiliotoxin C (PTX-C), to which the 2-propyl-5-methyl-cis-decahydroquinoline structure (XXIIa) was assigned on the basis of mass-spectrometric and PMR spectroscopic data. According to the results of x-ray diffraction analysis, the PTX-C molecule exists in double-chain conformation A and has an R configuration at $C_{(2)}$ [63].



XXII a A

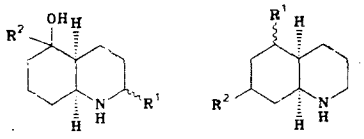
Several more alkaloids were found to be structurally related to PTX-C according to the PMR and mass-spectrometric data and their behavior with respect to catalytic hydrogenation and were united in one pumiliotoxin C family. Thus far, 26 new alkaloids have been isolated; the complete structures of these alkaloids have yet to be established, but, on the basis of the characteristic scheme of mass-spectral fragmentation, they have also been assigned to the PTX-C family. The presence of a cis-decahydroquinoline system containing saturated and unsaturated groupings in the 2 and (or) 5 positions, which has not been previously encountered in natural compounds, is characteristic for this entire class [61].



XXII b-e

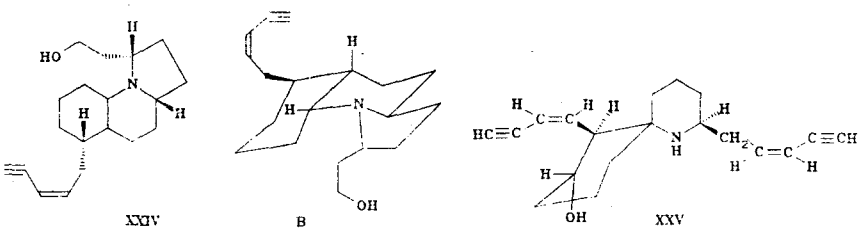
XXII b $R^1=C_4H_9$, c $R^1=C_3H_7$; d $R^1=(CH_2)_3—CH=C=CH_2$, e $R^1=CH_2—CH=CH—C\equiv CH$; b,d,e $R^2=H$, c $R^2=C_3H_7$

Sixteen alkaloids, which were isolated in trace amounts and were combined in the hydroxypumiliotoxin C (HPTX-C) family, were classified as the closest functional analogs of the PTX-C class. According to the preliminary results of chemical and spectral analysis, a cis-decahydroquinoline system containing a hydroxy group in the carbocycle (XXIIIa) or in side chain R^2 (XXIIIb) is also present in the HPTX-C alkaloids [61].



XXIII a XXIII b

Six alkaloids isolated from another species of frogs Dendrobates histrionicus, which were combined in the gephyrotoxin family, proved to be structurally related to alkaloids of the PTX-C family. The complete structure and absolute configuration of the first representative of this family, viz., the alkaloid gephyrotoxin (XXIV), were established [64].



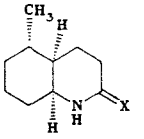
XXIV B XXV

It is interesting to note that the cis-decahydroquinoline system of pumiliotoxin C and gephyrotoxin, despite the identical absolute configuration of the nodal centers, exists in different conformations.

We should also mention alkaloids of the histrionicotoxin class (XXV), which contain a spiropiperidine system and are regarded as genetic precursors in the biosynthesis of the alkaloids PTX-C and gephyrotoxin [61].

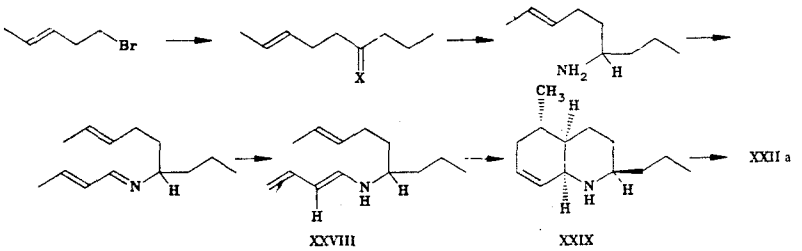
Thus far, more than 100 different alkaloids have been detected and isolated from the skin extracts of 18 species of Dendrobates; their structures are being established, and their pharmacological properties are under intensive investigation [61, 62]. These alkaloids have been separated into five classes with respect to their structural features. The most toxic of the known poisons batrachotoxin, tetrodotoxin, and their analogs, which are not examined here, were assigned to the first class [62]. The alkaloids PTX-C, HPTX-C, and gephyrotoxin, which contain a cis-decahydroquinoline system, were assigned to the next three classes. A group of 26 alkaloids, which were previously erroneously combined with the PTX-C family, were later isolated into a separate fifth class called PTX-A. The chief cyclic system of the alkaloids of this family was unknown for a long time, although the presence of a piperidine ring in virtually all of the alkaloids was demonstrated. In 1980 there was a report regarding the establishment of the structure and absolute configuration of the first member of the PTX-A class, which contains a perhydroindolizine system [65]. The establishment of the structures, stereochemistry, and the most important feature, viz., the biological activity of alkaloids of these classes, was markedly hindered by their limited availability, since multicomponent mixtures in trace amounts are isolated from natural sources. In this connection the efforts of chemists are presently being directed to searching for methods for their total synthesis.

A large number of reports of various variants for the construction of the cis-decahydroquinoline system and the partial and total syntheses of racemic PTX-C appeared in 1975. The focal point in the total synthesis of PTX-C [66] is the production of 5-methyl-$\Delta^{6,7}$-cis-tetrahydro-2-quinolone (XXVI) and amide cis-vinylog XXVII, subsequent chemical transformations of which gave (±)-PTX-C, which was identical to a natural sample with respect to spectral properties and the results of x-ray diffraction analysis.



XXVI X=O, XXVII X=CHCOCH$_3$

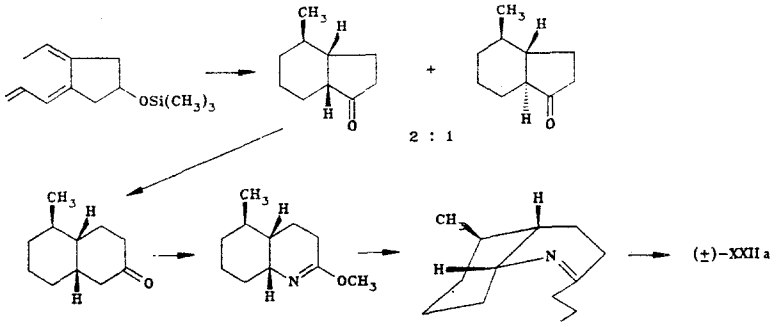
In the Oppolzer method [67] PTX-C is formed in a process involving the kinetically controlled intramolecular cycloaddition of acyclic trans-dienamide XXVIII.



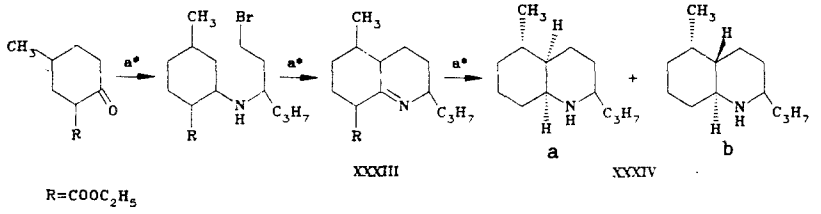
XXVIII XXIX XXIIa

The configuration of the simultaneously developing three chiral centers in the XXIX molecule is controlled by the chiral carbon atom present in dienamide XXVIII; this ensures definite stereoselectivity of the cycloaddition process. The hydrochloride of racemic XXIIa,

which is identical to natural PTX-C with respect to its spectral characteristics, is formed in the hydrogenation of cis-octahydroquinoline XXIX. Another variant of the total synthesis of pumiliotoxin C was later proposed; the focal point of this variant is the development of the necessary orientation of the propyl group in the 2 position of cis-quinoline XXIIa, which is dictated by the chirality of the available three centers in precursors XXX-XXXII [68].

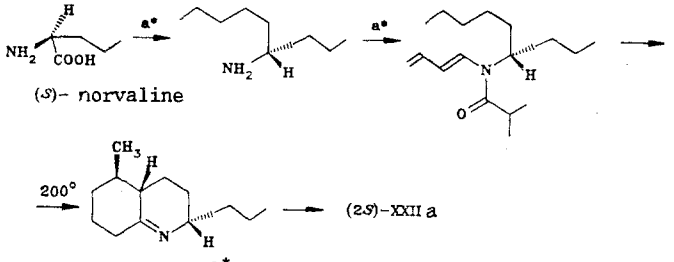


Alkylation with 1-(2-bromoethyl)butylamine of an enamine, viz., a derivative of 5-methyl-2-(ethoxycarbonyl)cyclohexanone, which leads to the formation of key two-ring imine XXXIII, was used in a third variant of the synthesis of (±)-PTX-C [69]. A mixture of cis- and trans-decahydroquinolines XXXIV, which were separated by crystallization of the hydrochlorides, is formed in the hydrogenation of imine XXXIII. According to the IR and PMR data, the isolated cis-isomer XXXIVa was identical to natural PTX-C.



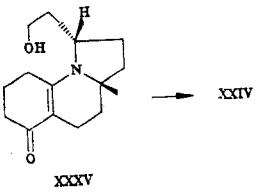
a* — several steps

Although they are not distinguished by high stereospecificity, all of the total syntheses of (±)-PTX-C nevertheless completely confirm the correctness of the determination of the structure and relative configuration of the alkaloid PTX-C [60, 70]. However, the (2R)-PTX-C obtained via the scheme presented above by alkylation of the enamine with (R)-1-(2-bromoethyl)butylamine had an opposite sign of the specific rotation as compared with the natural alkaloid; this necessitated refinement of earlier configurational assignments. A synthetic alkaloid obtained from (S)-norvaline proved to be completely identical to natural PTX-C with respect to its physical and chiroptical properties; this made it possible to correct previous conclusions and establish the 2S configuration of natural PTX-C [71].

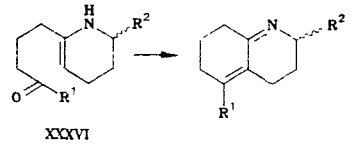


a* — several steps

Active searches for stereospecific methods for the synthesis of cis-decahydroquinoline alkaloids continue. There have been reports of the total synthesis of racemic perhydrogephyrotoxin [72], the construction of the cyclic system of gephyrotoxin [73], and, finally, the first stereoselective total synthesis of gephyrotoxin [74], the focal point of which is the stereocontrolling effect of the side hydroxy group in the hydrogenation of key amide vinylog XXXV. All five chiral centers of the (±)-gephyrotoxin molecule with the necessary configuration are created in the hydrogenation process.



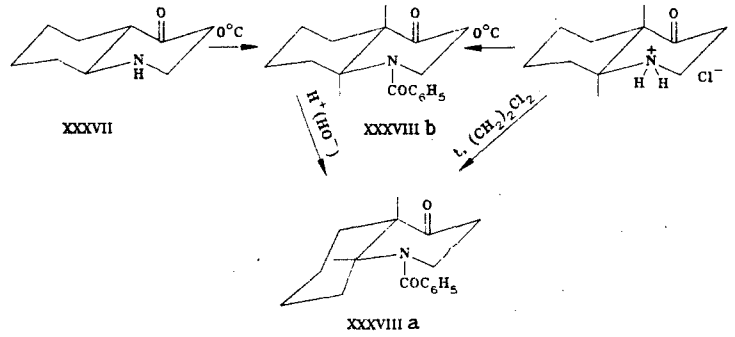
Information regarding the asymmetric synthesis of cis-decahydro-4-quinolols, which are key compounds for obtaining derivatives of cis-decahydroquinoline alkaloids, has been published [75]. Of interest is a report [76] regarding the possibility of a biomimetic approach to the synthesis of racemic PTX-C and gephyrotoxin with the use of enamine XXXVI, which is regarded as the most likely intermediate in their biosynthesis, as the synthone.



Research on new types of cis-decahydroquinoline alkaloids is stimulated to a significant extent by the necessity of their practical use as molecular instrumentsfor the study of functionally important components of biological membranes [62].

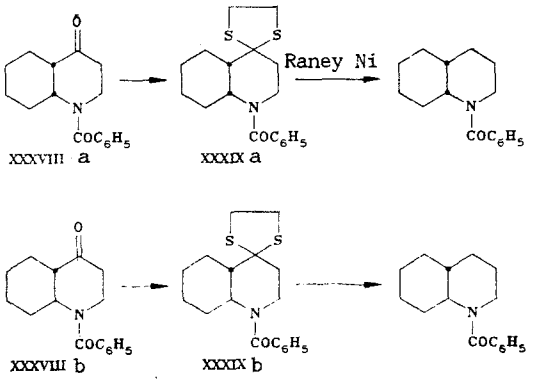
3. Stereochemical Peculiarities of Decahydro-4-quinolone

The introduction of a carbonyl group into the 4 position of decahydroquinoline leads to a significant change in the thermodynamic stabilities of the cis and trans isomers. Decahydro-4-quinolone (XXXVII) and its hydrochloride were isolated in the form of only one isomer, to which, in analogy with the greater thermodynamic stabilities of trans-decahydroquinoline and trans-1-decalone, a trans configuration was also assigned [77-81]. Depending on the conditions, cis- and trans-benzoyl derivatives XXXVIIIa, b are formed in the benzoylation of trans-decahydro-4-quinolone. Benzoyl derivative XXXVIIIb, which is formed from trans-decahydro-4-quinolone and its hydrochloride under mild conditions, was assigned to the trans series [3, 77].

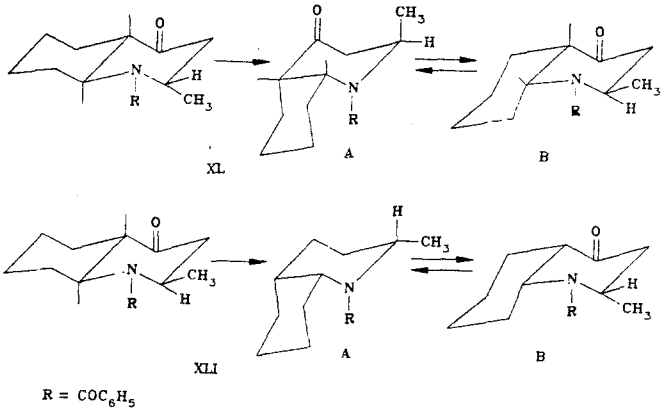


cis-1-Benzoyldecahydro-4-quinolone (XXXVIIIa) was obtained in the benzoylation of trans-decahydro-4-quinolone in refluxing dichloroethane [82]. The formation of the cis-benzoyl derivative was also observed in the acidic or alkaline isomerization of trans-benzoyldecahydro-4-quinolone [77]. Only trans-decahydro-4-quinolone is formed again in the acidic hydrolysis of both benzoyl derivatives. Consequently, the stability of the type of ring fusion changes on passing from trans-base XXXVII or its salt to benzoyl derivatives XXXVIIIa, b [78, 82]. The structures of cis- and trans-benzoyl derivatives XXXVIIIa, b were confirmed by their conversion to the known cis- and trans-1-benzoyldecahydroquinolines by reductive desulfuration of the corresponding thioketals XXXIXa, b and by the formation of oxazine derivatives [77, 78].

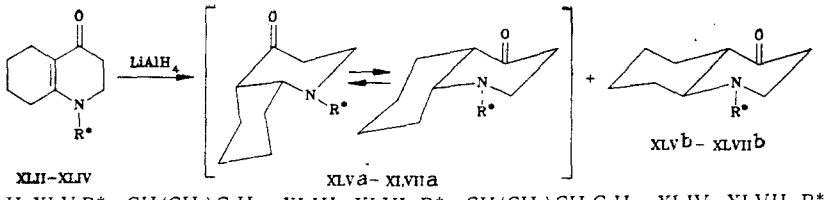
Similar principles were observed in the stereochemical investigation of isomers of 2-methyldecahydro-4-quinolone XL — high stabilities of the trans isomers in the bases and salts and of the cis isomers in the benzoyl derivatives. The reason for the facile trans-cis isomerization of N-benzoyl derivatives of the trans isomers of decahydro-4-quinolones was unclear for a long time despite numerous hypotheses [77-81, 83-88]. The most likely explana-



tion consists in the possibility of weakening in the cis isomers of the unbonded interactions of the equatorial α substituents of the piperidine ring and the n pair of the nitrogen atom, which are markedly intensified when a benzoyl group is introduced into the trans isomers. Precisely moving of the equatorial α substituents of the piperidine ring into an axial orientation via ring inversion, which becomes possible for decahydro-4-quinolones only in the case of cis fusion, leads to weakening of the repulsive interactions. The correctness of this point of view is confirmed by data from PMR spectroscopy and x-ray diffraction analysis for the most hindered N-benzoyl-2-methyl-cis-decahydro-4-quinolone (XLI). This isomer exists in conformation B with two axial substituents with respect to the piperidine ring – methyl [attached to $C_{(2)}$] and methylene [attached to $C_{(9)}$] groups [88].



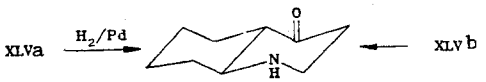
Not only the degree of hybridization of the nitrogen atom but also the nature of the substituent attached to this atom affect the relative stability of the ring fusion in decahydro-4-quinolone. Only cis-1-(S-α-phenylethyl)-(9R,10S)-decahydro-4-quinolone (XLVa) is formed in high chemical and optical yields in the kinetically controlled asymmetric reduction of 1-(S-α-phenylethyl)-$\Delta^{9,10}$-octahydro-4-quinolone (XLII) with $LiAlH_4$; XLVa is then converted to a mixture of cis- and trans-isomers XLVa, b in a ratio of 3:1 as a result of enolization [89-91].



XLII, XLV $R^* = CH(CH_3)C_6H_5$; XLIII, XLVI $R^* = CH(CH_3)CH_2C_6H_5$; XLIV, XLVII $R^* = CH(CH_3)C_2H_5$

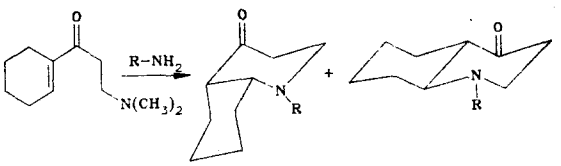
In contrast to this, the asymmetric reduction of enamino ketones XLIII and XLIV, which also have chiral substituents attached to the nitrogen atom, leads to the primary formation in high optical yields of only the trans isomers of decahydro-4-quinolones XLVIa and XLVIIa [92]. The occurrence of asymmetric synthesis in 1,4-hydride addition to enamino ketone XLII was confirmed by obtaining optically active decahydro-4-quinolone in the case of removal of the chiral α-phenylethyl substituent in each of cis- and trans-isomers XLVa, b;

the same thermodynamically stable trans-(9S,10S)-decahydro-4-quinolone was isolated from both isomers XLVa, b [91, 93].



(9S,10S)-XXXVII

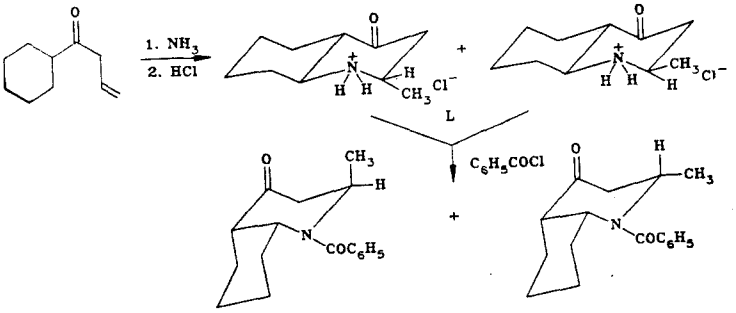
1-Benzyl- and 1-(2-phenylethyl)decahydro-4-quinolones are formed primarily in the form of cis-isomers XLVIIIa and XLIXa [94].



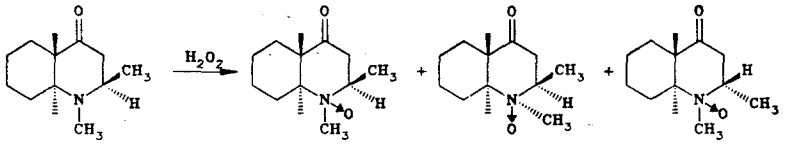
XLVIIIa, XLIX a XLVIIIb, XLIX b

XLVIII R=$CH_2C_6H_5$, XLIX R=$CH_2CH_2C_6H_5$

Significant stability of the trans isomers with an axial or equatorial methyl group attached to $C_{(2)}$ was noted in a study of the stereochemistry of isomers of 2-methyldecahydro-4-quinolone (L), andmild conditions for the virtually quantitative conversion of N-benzoyl derivatives of ketones of the trans series to cis isomers were found [86-88].

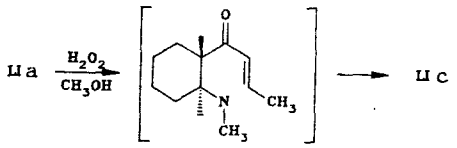


A study of the dependence of the basicities of the compounds on the character and spatial orientation of the substituents in the 2 and (or) 4 positions of the decahydroquinoline system showed that a decrease in the basicity by four orders of magnitude is observed in the series trans-decahydroquinoline, 2-methyl-trans-decahydro-4-quinolol, and trans-2-methyldecahydro-4-quinolone [95]. For comparison, the basicities of N-methylpiperidine and N-methyl-4-piperidone differ by two orders of magnitude [96]. Interesting results were obtained in a stereochemical study of the oxidation of epimers (LIa, b) of 1,2-dimethyl-trans-decahydro-4-quinolone with hydrogen peroxide. In addition to the formation of the expected N-oxides LIIa and LIIb, N-oxide LIIc with a diffferent orientation of the methyl group in the 2 position was isolated. The oxidation of epimer LIb also proceeds similarly. In the opinion of the authors, interconversion of the epimers in the oxidation process is associated with participation of the carbonyl group, since the spatial orientation of the 2-methyl group is unchanged in the oxidation of the corresponding ketals [97].

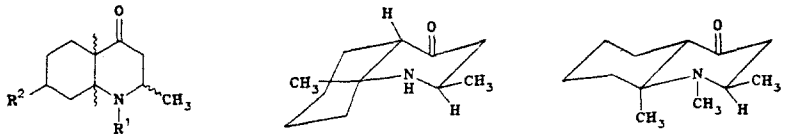


LI a LII a LII b LII c

However, epimerization with respect to $C_{(2)}$ is most likely the result of opening of the decahydroquinoline system with the formation of the open form of an α,β-unsaturated amino ketone, in the subsequent recyclization of which the orientation of the methyl group attached to $C_{(2)}$ changes [98, 99].



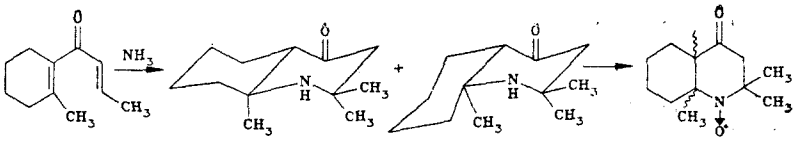
The stereochemistry of 2,7-dialkyl- and 1,2,7-trialkyldecahydroquinolines LIII, which are key compounds for the synthesis of substances that have cholinolytic, ganglion-blocking, and antiarrhythmic activity, was investigated in detail [100-105]. The trans isomers with an axial orientation of the methyl groups in the 2 and 7 positions are the most stable [100]. The trans isomer of 1,2-dimethyl-7-tert-butyldecahydro-4-quinolone (LIIId) exists in a double-chair conformation with an equatorial orientation of all of the alkyl groups [101]. The most stable isomer of 2,9-dimethyldecahydro-4-quinolone has cis-fused rings and an equatorial methyl group attached to $C_{(9)}$, whereas 1,2,9-trimethyldecahydro-4-quinolone exists in the form of the stable trans isomer with an axial methyl group attached to $C_{(9)}$ [106].



LIII a-d LIV

LIIIa,c R^1=H, b,d R^1=CH_3; a,b R^2=CH_3, c,d R^2=$C(CH_3)_3$

The recently very popular, stable, and optically active iminoxyl radicals LVI were obtained on the basis of the cis and trans isomers of 2,2,9-trimethyldecahydro-4-quinolone (LV) and are being used extensively [107]. A study of the chiroptical properties of the iminoxyl radicals showed that the iminoxyl group can be regarded as an analog of a carbonyl chromophore and that the sign of the Cotton effect (CE) of the iminoxyl chromophore can be predicted from the octant rule.



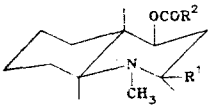
LV LVI

Thus the stereochemistry of decahydroquinoline and decahydro-4-quinolone is determined to a significant degree by the nature and character of the substitution in the decahydroquinoline system.

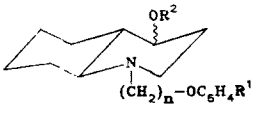
4. Synthetic Physiologically Active Derivatives of Decahydroquinoline

The synthesis and study of the biological activity of a large number of derivatives of decahydroquinoline have made it possible to obtain new pharmacological preparations. Despite the numerous successful results obtained in the pharmacological investigation of decahydroquinoline derivatives, virtually all attempts to establish a relationship between the structure and the activity have only retrospective character. An empirical relationship between the structure, three-dimensional structure, and biological activity of this series of compounds has been uncovered in some cases. In the search for new analgesics a significant difference in the activities of compounds of the piperidine and decahydroquinoline series was noted. As compared with isomers of promedol (1,2,5-trimethyl-4-phenyl-4-piperidol propionate hydrochloride), which are two to six times more active than morphine, a marked decrease in activity was noted for derivatives of trans-decahydroquinoline VLII; 1-methyl-4-cyclohexyl-4-acetoxy-trans-decahydroquinoline, in which the "4-phenyl-4-propionyloxy" fragment that is responsible for the analgesic activity in promedol and morphine is absent, has the greatest analgesic activity among the derivatives with structures similar to that of promedol [108-110]. Consequently, the appearance of a second ring significantly changes the pharmacological properties of piperidine derivatives. A certain difference in the neurotropic activity was observed for the cis and trans isomers of 2-(2-furyl)decahydro-4-quinolone. The trans isomer has a depressive effect on the central nervous system: it lowers the body temperature and interferes with motor coordination. The use of the cis isomer leads only to a decrease in the body temperature [111]. An attempt was made to uncover

a relationship between the structure and the activity in order to search for compounds with high antiarrhythmic activity in a large series of trans-decahydroquinoline derivatives LVIIIa-d. However, the results obtained do not give a clear idea of the relationship between the structure and the activity and cannot be used to predict the structures of compounds with high antiarrhythmic activity [109].



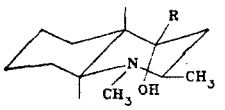
LVII



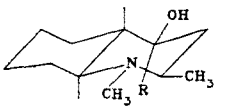
LVIII a-d

LVII $R^1=C_6H_5$, C_6H_{13}, $CH_2C_6H_5$; $R^2=CH_3$, C_2H_5, C_3H_7; LVIII a $R^1=H$; b-d $R^1=4$-F; a,b $R^2=H$; c $R^2=CONHCH_3$; d $R^2=CONHC_6H_3Cl(3')CH_3(4')$

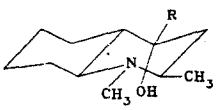
Among the stereoisomers of 4-substituted trans-decahydro-4-quinolols LIX, the stereoisomer with an axial methyl group attached to $C_{(4)}$ has the maximum antinicotine activity [112]. The greatest ganglion-blocking and antinicotine activity is observed for stereoisomer LIXb with an axial vinylethynyl group attached to $C_{(4)}$.



LIX a



LIX b



LIX c

LIX $R=CH_3$, C_2H_5, $CH=CH-C\equiv CH$, $COCH_3$, $C\equiv C-CH=CH_2$

The possibility of predicting the activities of newly synthesized compounds of the decahydroquinoline series with the use of information regarding the relationship between the structure and the activity is currently under investigation [113-115]. Such information can be obtained as a result of statistical treatment of a group of biologically active decahydroquinoline derivatives by means of the ORACL system for predicting biologically active chemical compounds.

LITERATURE CITED

1. W. Huckel and F. Stepf, Annalen., 453, 163.
2. P. E. King, T. Henshall, and H. L. Whitenead, J. Chem. Soc., No. 9, 1373 (1948).
3. G. R. Clemo, J. G. Cook, and H. Raper, J. Chem. Soc., No. 8, 1183 (1938).
4. E. Bamberger and F. Lengfeld, Berichte, 23, 1138 (1890).
5. E. Bamberger and S. Williamson, Berichte, 27, 1458 (1894).
6. W. Ipatiev, Berichte, 41, 991 (1908).
7. A. Skita and W. A. Meyer, Berichte, 45, 3589 (1912).
8. J. Braun, A. Petsold, and I. Seeman, Berichte, 55, 3779 (1922).
9. P. Sabatier and M. Murat, C. R. Acad. Sci., 158, 309 (1914).
10. C. F. Bailley and S. M. McElvain, J. Am. Chem. Soc., 52 4013 (1930).
11. F. L. Pickard and H. L. Lochte, J. Am. Chem. Soc., 69, 14 (1947).
12. A. Burger and L. R. Modlin, J. Am. Chem. Soc., 62, 1079 (1940).
13. É. A. Mistryukov, Izv. Akad. Nauk SSSR, Otd. Khim. Nauk, No. 11, 2001 (1965).
14. É. A. Mistryukov, Izv. Akad. Nauk SSSR, Otd. Khim. Nauk, No. 5, 929 (1963).
15. V. Prelog and S. Szpilfogel, Helv. Chim. Acta, 28, 1684 (1945).
16. F. W. Vierhapper and E. L. Eliel, J. Org. Chem., 40, 2734 (1975).
17. H. Booth and A. H. Bostock, J. Chem. Soc., Perkin 2, No. 5, 615 (1972).
18. W. Oppolzer and W. Frostl, Helv. Chim. Acta, 58, 590 (1975).
19. I. N. Nazarov, G. A. Shvekhgeimer, and V. A. Rudenko, Zh. Obshch. Khim., 24, 3191 (1954).
20. C. F. Koelsch and D. L. Ostercamp, J. Org. Chem., 26, 1104 (1961).
21. T. Henshall and E. W. Parnell, J. Chem. Soc., No. 2, 661 (1962).
22. N. J. Leonard, L. A. Miller and P. D. Thomas, J. Am. Chem. Soc., 78, 3463 (1956).
23. A. P. Gray, D. E. Heitmeier, and C. J. Cavallito, J. Am. Chem. Soc., 81, 728 (1959).
24. M. Ehrenstein and W. Bunge, Berichte, 67, 1715 (1934).
25. L. Mascarelli and F. Nigrisoli, Gazz. Chim. Ital., 45, 106 (1915).
26. A. Popovici, C. F. Geschickter, E. L. May, and E. Mosettig, J. Org. Chem., 21, 1283 (1956).

27. R. A. Johnson, H. G. Murray, L. M. Reinike, and G. S. Fonken, J. Org. Chem., 33, 3207 (1968).
28. R. A. Johnson, M. E. Herr, and H. C. Murray, J. Org. Chem., 33, 3217 (1968).
29. H. Ripperger and K. Schreiber, Tetrahedron, 25, 737 (1969).
30. W. L. F. Armarego, J. Chem. Soc., C, No. 5, 377 (1967).
31. H. Booth and D. V. Griffiths, J. Chem. Soc., Perkin 2, No. 15, 2361 (1972).
32. H. Booth, Tetrahedron, 22, 615 (1966).
33. H. Booth and A. H. Bostock, Chem. Commun., No. 4, 177 (1967).
34. H. Booth and D. V. Griffiths, J. Chem. Soc., Perkin 2, No. 6, 842 (1973).
35. E. L. Eliel and F. W. Vierhapper, J. Am. Chem. Soc., 96, 2257 (1974).
36. E. L. Eliel and F. W. Vierhapper, J. Am. Chem. Soc., 97, 2424 (1975).
37. E. L. Eliel and F. W. Vierhapper, J. Org. Chem., 41, 199 (1976).
38. G. T. Furst, R. L. Lichter, and F. W. Vierhapper, J. Org. Chem., 45, 1521 (1980).
39. F. W. Vierhapper and E. L. Eliel, J. Org. Chem., 44, 1081 (1979).
40. F. W. Vierhapper, G. T. Furst, R. L. Lichter, S. N. Y. Fauso-Free, and E. L. Eliel, J. Am. Chem. Soc., 103, 5029 (1981).
41. K. D. Hargrave and E. L. Eliel, Tetrahedron Lett., No. 22, 1987 (1979).
42. H. S. Aaron and C. P. Ferguson, J. Am. Chem. Soc., 98, 7013 (1976).
43. D. R. Brown, R. Lygo, I. McKenna, I. M. McKenna, and B. G. Hutley, J. Chem. Soc., B, No. 11, 1184 (1967).
44. I. McKenna, I. M. McKenna, and A. Tulley, J. Chem. Soc., No. 10, 5439 (1965).
45. I. McKenna, I. M. McKenna, and J. White, J. Chem. Soc., No. 3, 1733 (1965).
46. G. Fodor, S. Abidi, and T. C. Carpenter, J. Org. Chem., 39, 1507 (1974).
47. G. Fodor and S. Abidi, Tetrahedron Lett., No. 18, 1369 (1971).
48. S. Abidi, G. Fodor, C. S. Huber, I. Miura, and K. Nakanishi, Tetrahedron Lett., No. 5, 355 (1972).
49. F. R. Jensen and B. H. Beck, Tetrahedron Lett., No. 37, 4523 (1966).
50. P. J. Crowley, M. J. T. Robinson, and M. G. Ward, Tetrahedron, 33, 915 (1977).
51. H. Booth and D. V. Griffiths, Chem. Commun., No. 18, 666 (1973).
52. F. W. Vierhapper and E. L. Eliel, J. Org. Chem., 42, 51 (1977).
53. H. Booth and D. V. Griffiths, J. Chem. Soc., Perkin 2, No. 2, 111 (1975).
54. H. Booth and A. H. Bostock, Chem. Commun., No. 1, 179 (1967).
55. H. Booth and A. H. Bostock, J. Chem. Soc., Perkin 2, No. 5, 616 (1972).
56. F. W. Vierhapper, Tetrahedron Lett., No. 51, 5161 (1981).
57. M. J. T. Robinson, Chem. Commun., No. 20, 844 (1975).
58. K. Brown, A. R. Katritzky, and A. J. Waring, Proc. Chem. Soc., No. 8, 25 (1964).
59. K. Brown, A. R. Katritzky, and A. J. Waring, J. Chem. Soc., B, No. 5, 487 (1967).
60. J. W. Daly, T. Tokuyama, G. Habermehl, I. L. Karle, and B. Witkop, Annalen, 729, 198 (1969).
61. J. W. Daly, G. B. Brown, M. Mensch-Dwumah, and C. W. Meyrs, Toxicon, 16, 163 (1978).
62. J. W. Daly, J. Toxicol.-Toxin Rev., 1, 33 (1982).
63. G. Habermehl, H. Andres, K. Miyahara, B. Witcop, and J. W. Daly, Annalen, 736, 1577 (1976).
64. J. W. Daly, B. Witcop, T. Tokuyama, T. Nishikava, and I. L. Karle, Hevl. Chim. Acta, 60, 1128 (1977).
65. J. W. Daly, T. Tokuyama, t. Fujiwara, R. J. Highest, and I. L. Karle, J. Am. Chem. Soc., 102, 830 (1980).
66. T. I. Ibuke, Y. Mori, Y. Inubushi, I. Saji, K. Tanaka, and N. Masaki, Tetrahedron Lett., No. 5, 323 (1975).
67. W. Oppolzer, W. Frostl, and H. P. Weber, Helv. Chim. Acta, 58, 593 (1975).
68. W. Oppolzer, C. Fehr, and J. Warneke, Helv. Chim. Acta, 60, 48 (1977).
69. G. Habermehl and H. Andres, Naturwissenschaften, 62, 345 (1975).
70. K. Hattori, Y. Matsumura, T. Miyazani, K. Maruoko, and H. Yamamoto, J. Am. Chem. Soc., 103, 7368 (1981).
71. W. Oppolzer and E. Flaskamp, Helv. Chim. Acta, 60, 204 (1977).
72. L. E. Overman and C. Fukuya, J. Am. Chem. Soc., 102, 1454 (1980).
73. D. Hart, J. Am. Chem. Soc., 102, 397 (1980).
74. R. Fuyimoto, Y. Lischi, and Y. F. Blount, J. Am. Chem. Soc., 102, 7154 (1980).
75. G. V. Grishina, V. M. Potapov, and T. A. Gudasheva, Khim. Geterotsikl. Soedin., No. 1, 101 (1980).
76. M. Bonin, R. Besslievre, D. S. Grierson, and H. P. Husson, Tetrahedron Lett., No. 14, 1493 (1983).

77. É. A. Mistryukov and V. F. Kucherov, Izv. Akad. Nauk SSSR Otd. Khim. Nauk, No. 10, 1816 (1961).
78. É. A. Mistryukov and V. F. Kucherov, Izv. Akad. Nauk SSSR Otd. Khim. Nauk, No. 5, 925 (1963).
79. É. A. Mistryukov, N. I. Aronova, and V. F. Kucherov, Izv. Akad. Nauk SSSR, Otd. Khim. Nauk, No. 9, 1599 (1962).
80. É. A. Mistryukov and V. F. Kucherov, Izv. Akad. Nauk SSSR Otd. Khim. Nauk, No. 7, 1343 (1961).
81. É. A. Mistryukov and V. F. Kucherov, Izv. Akad. Nauk SSSR Otd. Khim. Nauk, No. 11, 2044 (1961).
82. I. N. Nazarov and É. A. Mistryukov, Izv. Akad. Nauk SSSR, Otd. Khim. Nauk, No. 5, 584 (1958).
83. D. V. Sokolov, G. S. Litvinenko, and K. I. Khludneva, Zh. Obshch. Khim., 29, 1112 (1959).
84. D. V. Sokolov, G. S. Litvinenko, and K. I. Khludneva, Zh. Obshch. Khim., 29, 3555 (1959).
85. D. V. Sokolov, G. S. Litvinenko, and K. I. Khludneva, Zh. Obshch. Khim., 29, 3204 (1959).
86. D. V. Sokolov, V. V. Sosnova, and G. S. Litvinenko, Izv. Akad. Nauk Kazakh. SSR, Ser. Khim., No. 3, 63 (1967).
87. D. V. Sokolov, G. S. Litvinenko, and M. N. Akimova, Izv. Akad. Nauk Kazakh. SSR, Ser. Khim., No. 1, 59 (1962).
88. G. S. Litvinenko, A. A. Espenbetov, and Yu. T. Struchkov, Izv. Akad. Nauk Kazakh. SSR, Ser. Khim., No. 5, 63 (1982).
89. V. M. Potapov, G. V. Kiryushkina, and G. P. Tokmakov, Khim. Geterotsikl. Soedin., No. 12, 1656 (1972).
90. V. M. Potapov, G. V. Grishina, E. A. Golov, P. B. Terent'ev, and R. Herzschu, Khim. Geterotsikl. Soedin., No. 7, 953 (1976).
91. I. F. Leshcheva, N. M. Sergeev, G. V. Grishina, and V. M. Potapov, Khim. Geterotsikl. Soedin., No. 2, 230 (1983).
92. G. V. Grishina, N. E. Agafonov, and V. M. Potapov, Khim. Geterotsikl. Soedin., No. 4, 519 (1983).
93. V. M. Potapov, G. V. Grishina, and E. A. Golov, Khim. Geterotsikl. Soedin., No. 8, 1093 (1976).
94. M. Prost, M. Urbain, A. Schumer, C. Houben, and C. Van Meerbeeck, Helv. Chim. Acta, 58, 40 (1975).
95. D. V. Sokolov, G. S. Litvinenko, V. I. Artyukhin, and A. A. Andrusenko, Izv. Akad. Nauk Kazakh. SSR, Ser. Khim., No. 11, 73 (1965).
96. P. Geneste, J. Hugon, C. Reminiac, G. Lamaty, and J. P. Rogue, Bull. Soc. Chim. France, Nos. 5-6, 845 (1976).
97. A. A. Akhrem, L. I. Ukhova, and N. F. Marchenko, Khim. Geterotsikl. Soedin., No. 3, 394 (1974).
98. É. A. Mistryukov and G. N. Smirnova, Tetrahedron, 27, 375 (1971).
99. G. V. Grishina, V. M. Potapov, S. A. Abdulganeeva, and E. Yu. Korchagina, Khim. Geterotsikl. Soedin., No. 12, 1648 (1985).
100. A. A. Akhrem, T. E. Prokof'ev, A. S. Fridman, L. I. Ukhova, and A. N. Sergeeva, Khim. Geterotsikl. Soedin., No. 5, 651 (1976).
101. A. A. Akhrem, L. I. Ukhova, and A. N. Sergeeva, Vestnik Akad. Nauk Belorussk. SSR. Ser. Khim., No. 4, 46 (1975).
102. A. A. Akhrem, L. I. Ukhova, T. E. Prokof'ev, A. S. Arsen'ev, and A. N. Sergeeva, Khim. Geterotsikl. Soedin., No. 11, 1569 (1977).
103. A. A. Akhrem, B. B. Kuz'mitskii, L. I. Ukhova, and N. F. Uskova, Dokl. Akad. Nauk SSSR, 169, 724 (1966).
104. B. B. Kuz'mitskii, A. A. Akhrem, and L. I. Ukhova, Izv. Akad. Nauk SSSR, Ser. Khim., No. 7, 1678 (1970).
105. I. N. Nazarov, L. I. Ukhova, and V. A. Rudenko, Izv. Akad. Nauk SSSR, Otd. Khim. Nauk, No. 3, 498 (1963).
106. A. A. Akhrem, L. I. Ukhova, N. F. Uskova, and T. E. Prokof'ev, Khim. Geterotsikl. Soedin., No. 6, 796 (1977).
107. J. S. Roberts and C. Thomson, J. Chem. Soc., Perkin 2, No. 14, 2129 (1972).
108. M. Prost, M. Urbain, A. Schumer, C. Houben, C. Van Meerbeeck, M. Colot, and R. Charlier, Eur. J. Med. Chem., 10, 231 (1975).
109. M. Prost, M. Urbain, A. Schumer, C. Houben, C. Van Meerbeeck, M. Colot, and R. Charlier, Eur. J. Med. Chem., 10, 236 (1975).

110. E. E. Smissman and M. Steinman, J. Med. Chem., 9, 455 (1966).
111. D. V. Sokolov, K. D. Praliev, P. T. Sydykov, B. I. Artyukhin, D. M. Manatadov, V. M. Kurilenko, Zh. N. Khlienko, and L. M. Moiseeva, in: Summaries of Papers Presented at the All-Union Conference on the Synthesis and Mechanism of the Action of Physiologically Active Substances [in Russian], Odessa (1976), p. 13.
112. M. Prost, M. Urbain, A. Schumer, V. Van Cromphaut, C. Houben, C. Van Meerbeeck, M. Colot, and R. Charlier, Eur. J. Med. Chem., 11, 337 (1976).
113. B. B. Kuz'mitskii, A. A. Akhrem, L. I. Ukhova, and N. F. Uskova, Izv. Akad. Nauk SSSR, Ser. Khim., No. 12, 2774 (1970).
114. V. V. Gavrilova, V. E. Golender, A. B. Rozenblit, N. M. Sukhova, M. Yu. Lidak, and É. Ya. Lukevits, Khim.-farm. Zh., 13, 45 (1979).
115. V. V. Drboglav, V. P. Golubovich, L. I. Ukhova, A. A. Akhrem, V. E. Golender, and A. B. Rozenblit, Khim.-farm. Zh., 6, 581 (1982).

METHOD FOR THE SYNTHESIS OF BISBENZO[c]PYRYLIUM SALTS

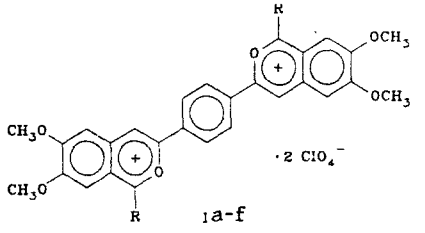
V. I. Dulenko and Yu. A. Nikolyukin

UDC 547.814.1.07

A new method for the synthesis of bisbenzo[c]pyrylium salts was developed. The new method is based on the acylation of 1,4-bis(3,4-dimethoxyphenylacetyl)benzene with carboxylic acid anhydrides in the presence of perchloric acid or with carboxylic acids in polyphosphoric acid.

Owing to their ability to undergo recyclization under the influence of nucleophilic reagents, benzo[c]pyrylium salts are of interest as intermediates for the synthesis of a large number of heterocyclic and aromatic compounds [1]. Benzo[c]pyrylium salts are obtained most readily via the reaction in [2], which consists in catalytic acylation with subsequent heterocyclization of ring-activated arylacetones and deoxybenzoins. The use of dibasic aliphatic acids with no less than three carbon atoms between the carboxy groups as the acylating agents in the indicated reaction made it possible to synthesize the previously unknown bisbenzo[c]pyrylium salts; some of them served as the basis for obtaining analogs of the natural alkaloid dauricine [3, 4].

We have developed a new variant of the synthesis of compounds, the molecules of which contain two pyrylium cations, viz., p-phenylenebis(1-R-6,7-dimethoxybenzo[c]-3-pyrylium) diperchlorates I.



Ia-f

I a R=H; b R=CH_3; c R=C_2H_5; d R=$CH_2C_6H_5$; e R=C_6H_5; f R=4-OCH_3—C_6H_4

The proposed method consists in acylation of 1,4-bis(3,4-dimethoxyphenylacetyl)benzene (II) with carboxylic acid anhydrides in the presence of perchloric acid or with carboxylic acids in polyphosphoric acid (PPA). The presence in starting substrate II of two aromatic rings that are activated to electrophilic attack makes it possible to avoid the limitations that are imposed in known methods [3, 4] on the structure of the acylating agents and to use a more extensive series of accessible monobasic aromatic and aliphatic acids and their anhydrides to obtain the bisbenzo[c]pyrylium salts.

Institute of Physical Organic Chemistry and Coal Chemistry, Academy of Sciences of the Ukrainian SSR, Donetsk 340114. Translated from Khimiya Geterotsiklicheskikh Soedinenii, No. 5, pp. 600-602, May, 1987. Original article submitted December 10, 1985; revision submitted March 26, 1986.

0009-3122/87/2305-0493$12.50