HYDROACRIDINES AND RELATED COMPOUNDS.

XV.* STEREOCHEMISTRY OF THE REDUCTION OF 4a,10a-SUBSTITUTED PERHYDROACRIDINES

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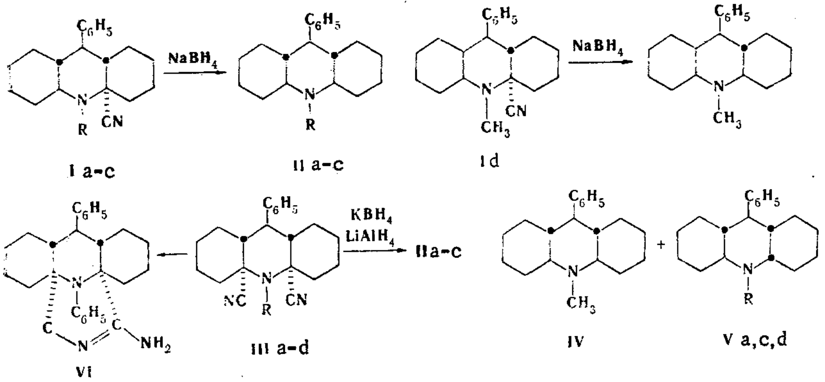
The stereochemistry of the hydride reduction of N-substituted 4a-cyano-, 4a,10a-dicyano-, and 4a,10a-peroxy-9-phenylperhydroacridines was studied. The configuration of a series of isomeric N-substituted 9-phenylperhydroacridines was established.

It has been previously shown [2] that the stereospecific formation of trans-syn-trans isomers occurs in the reduction of 9-phenyldecahydro and -dodecahydroacridines. The study of the stereochemistry and stereospecificity of the reactions of some 9-phenylperhydroacridine derivatives that have substituents in the 4a and 10a positions was the subject of further research. The hydride reduction of 4a-cyanoperhydroacridines Ia-d [2], 4a,10a-dicyanoperhydroacridines IIIa-d [3], and 4a,10a-peroxyperhydroacridines VIa-g was investigated.

It was established that, in contrast to decahydro- and dodecahydroacridines [2], Ia-d and IIIa-d are reduced in high yields by complex metal hydrides. trans-syn-trans-Perhydroacridines IIa-c are formed in the reduction of trans-syn-trans-mononitriles Ia-c [2] with sodium and potassium borohydrides in dimethylformamide (DMF). In contrast to Ia-c, Id has a cis-anti-trans configuration and gives cis-anti-trans-perhydroacridine IId on reduction. The fact that 9-phenyldodecahydroacridines are not reduced under similar conditions provides a basis for the assumption that the reduction does not proceed with prior splitting out of HCN but rather by nucleophilic substitution of the cyano group by a hydride ion with retention of the configuration.

A mixture of trans-syn-trans (IIa-c, IV) and cis-syn-trans isomer (Va,c,d) of perhydroacridine in approximately equal amounts is formed in the reduction of trans-syn-trans-dicyano derivatives IIIa-d; only the first stereoisomer is formed in the case of IIIb. As in the case of the reduction with borohydride, a mixture of perhydroacridine isomers is formed in the reduction of IIIa-c in excess $LiAlH_4$ in tetrahydrofuran (THF). If a smaller amount of $LiAlH_4$ is used in the reduction, only four-ring derivative VI is formed. This compound has a trans-syn-trans configuration, and its formation provides evidence for a cis-diaxial orientation of the cyano groups and the most probable trans-syn-trans configuration of IIIa.



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*See [1] for communication XIV.

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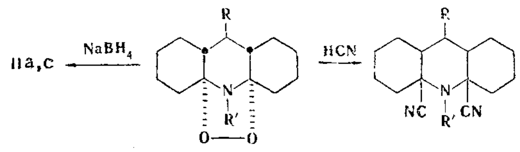

VIIa-g VIIIa-e IIIa,c

I—III, V a $R=C_6H_5$; b $R=o\text{-}C_6H_4OH$; c $R=CH_2C_6H_5$; d $R=CH_3$; VII, VIII a $R=H$, $R'=p\text{-}C_6H_4COOH$; b $R=CH_3$, $R'=H$; c $R=CH_3$, $R'=C_6H_5$; d $R=CH_3$, $R'=CH_2C_6H_5$; e $R=C_6H_5$, $R'=H$; f $R=R'=C_6H_5$; g $R=C_6H_5$, $R'=CH_2CH_5$

In contrast to nitriles I and III, as well as unsubstituted peroxyperhydroacridine [4], the reduction of peroxyperhydroacridines VIIa-g (which we obtained from alicyclic 1,5-diketones, hydrogenperoxide, and primary amines or ammonia, as described in [4]) proceeds with great difficulty. We were able to reduce VIIf,g to trans-syn-trans-perhydroacridines only by refluxing them for 40 h with $NaBH_4$ in an aqueous alcohol medium. In the remaining cases a considerable amount of the starting materials remained even after refluxing for 70 h. It was established that amino peroxides VIIe-g most likely have a trans-syn-trans configuration, whereas it is difficult to make any kind of assignment for the remaining compounds. As previously described in [4], amono peroxides VIIa-g undergo exchange of the peroxide bridge by two cyano groups to give dinitriles VIIIa-e and IIIa,c. The structures of the newly synthesized compounds are confirmed by the IR, PMR, and mass spectral data. The IR spectra of Id and VIIIa-e contain an absorption band at 2230 cm^{-1}, which is characteristic for the $C \equiv N$ group. The IR spectra of IVa,c do not contain the "Bohlman" absorption bands that develop when there are no less than two axial protons adjacent to a nitrogen atom [5]. The methyl group attached to the nitrogen atom is responsible for the presence of this absorption band in the spectra of Id, IId, and IVd at 2785, 2810, and 2790 cm^{-1}, respectively. The IR spectrum of VI contains absorption bands of a $C = N$ bond at 1660 cm^{-1} and of an NH_2 group at 3400 and 3520 cm^{-1}.

In a previous paper [2] we established that Ia-c and IIa-c have a trans-syn-trans configuration on the basis of PMR spectral data. The presence in the spectra of Id and IId of a broad 10a-H singlet at 2.86 and 2.26 ppm and a 9a-H quartet at 2.85 and 2.52 ppm, respectively, makes it possible to conclude that they have a cis-anti-trans configuration [6]. We examined the spectra of Id and IId in the presence of $Eu(DPM)_3$ and $Eu(FOD)_3$ shift reagents. The character of the change in the chemical shifts of the protons is similar in both cases and demonstrates that the shift reagent forms a complex with the axially directed unshared electron pair of the nitrogen atom. The signal of the 10a-H proton of IId is shifted to stronger field as compared with 10-unsubstituted cis-anti-trans-perhydroacridine, in the same way as the 10a-H signal in the spectrum of N-methyl-substituted derivative of this isomer [6]. The contribution of the cyano group to the 10a-H chemical shift corresponds to their 1,3-diaxial orientation in Id [7].

A peculiarity of the spectra of IIIa-c and VIIIe is the fact that there is a broad doublet (J = 7 Hz, 6H) at 1.16-1.20 ppm, whereas the 9-H, 8a-H, and 9a-H axial protons absorb at weaker field and can be considered to be the ABC portion of an ABCXY system. The latter is confirmed by calculation of the theoretical spectra of these protons. The absence of spin–spin coupling of the nodal methylidyne protons with the adjacent equatorial protons shows that the dihedral angle between these vicinal protons is close to 90°. This becomes possible as a result of contraction of the molecules of the dinitrile because of repulsion of the cis-diaxial cyano groups (the minimum intramolecular distance between the unbounded carbon atoms is 2.9 Å [8], and the $C_{4a}-C_{10a}$ distance is 2.52 Å).

In IIId the difference in the chemical shifts between the 9a and 8a protons is 0.39-0.47 ppm less than in IIIa,c and VIIIe. The shift of the signals of the nodal protons to weak field is most likely associated with an axial orientation of the methyl group [6]. The use of a shift reagent showed that the chemical shift of the methylidyne protons does not change. Only a certain degree of change in the intensity in the center of the overall signal of the remaining protons was observed. This indicates that the shift reagent does not form a complex with the axial unshared electron pair of the ring nitrogen atom.

The PMR spectrum of Va contains a multiplet of the 10a-H proton at 3.96 ppm and a $9\text{-}H_a$ triplet at 3.16 ppm (J = 11.8 Hz). In conjuction with the absence of a "Bohlman" absorption band in the IR spectrum of this compound, this indicates the cis-syn-trans configuration of Va [5, 6]. In contrast to the spectrum of cis-anti-trans-N-benzylperhydroacridine [9], the spectrum of Vc contains a quartet of methylene protons of a benzyl group at 3.71 ppm (Δ = 0.27 ppm, J = 14.5 Hz). From a comparison with the corresponding signal of Ic one should assume an axial orientation of the $C_{10a}-C_5$ bound. A theoretical calculation of the multiplets at 2.05-2.35 ppm (1H) and 2.40-2.85 ppm (3H) by means of a program that simulates the spectra showed that they con-

TABLE 1. Perhydroacridine Derivatives

Compound	mp, °C	m/e	Found, %			Emperical formula	Calc. %			Yield, %
			C	H	N		C	H	N	
Id	133—134[a]	—	82,2	9,5	9,3	$C_{21}H_{28}N_2$	81,8	9,1	9,1	35
IId	108[b]	283	84,8	10,5	5,4	$C_{20}H_{29}N$	84,8	10,3	4,9	95
IV	104—106[c]	283	84,9	10,1	4,7	$C_{20}H_{25}N$	84,8	10,3	4,9	37
Va	165—167[b]	345	86,3	9,3	3,8	$C_{25}H_{31}N$	87,0	9,0	4,1	52
Vc	145—147[b]	359	86,6	9,4	4,0	$C_{26}H_{33}N$	86,9	9,2	3,9	40
Vd	77—78[c]	283	85,3	10,7	5,1	$C_{20}H_{29}N$	84,8	10,3	4,9	40
VI	221,5—222[d]	401	80,8	8,9	10,2	$C_{27}H_{33}N_3$	81,2	8,3	10,5	95
VIIa	145[b]	—	68,8	7,3	4,0	$C_{20}H_{25}NO_4$	70,0	7,3	4,1	98
VIIb	106—108[b]	—	76,3	9,0	4,7	$C_{20}H_{27}NO_2$	76,7	8,6	4,5	37
VIIe	120—121[b]	—	76,1	8,5	4,7	$C_{19}H_{25}NO_2$	76,2	8,4	4,7	95
VIIf	140[b]	—	80,1	8,2	3,9	$C_{25}H_{29}NO_2$	80,0	7,7	3,7	40
VIIg	146—147[b]	—	79,6	8,1	3,4	$C_{26}H_{31}NO_2$	80,2	8,0	3,6	54
VIIIa	213—215[b]	—	72,5	7,1	11,5	$C_{22}H_{25}N_3O_2$	72,2	7,2	12,0	95
VIIIb	156—158[b]	—	74,2	8,7	16,4	$C_{16}H_{23}N_3$	74,7	9,0	16,3	46
VIIIc	203—205[c]	—	78,8	8,2	12,4	$C_{22}H_{27}N_3$	79,3	8,4	12,6	48
VIIId	206[b]	—	79,4	8,0	12,3	$C_{23}H_{29}N_3$	79,5	8,4	12,1	70
VIIIe	173—175[b]	—	79,2	8,1	13,0	$C_{21}H_{25}N_3$	79,6	7,8	13,2	72
IX	280[f]	—	64,1	5,7	4,0	$C_{26}H_{24}ClNO_4$	63,5	6,6	3,7	61

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[a] From propanol. [b] From ethanol. [c] From hexane. [d] From ethyl acetate. [e] From propanol–dioxane (2:1). [f] With decomposition.

sist of signals of 10a-H_e, 4a-H_a, 9-H_a, and 8a-H_a protons at 2.75, 2.70, 2.57, and 2.65 ppm, respectively. This indicates that perhydroacridine Vc has a cis-syn-trans configuration.

The chemical shift of the signal of the methyl group (2.32 ppm) of 9-phenyl-10-methylperhydroacridine (IV), the character of the signals of the methylene protons at 0.7-2.0 ppm, which is similar to the character of the signals of the same protons in the same region of the spectra of perhydroacridines with a trans-syn-trans configuration [2, 6], and the form of the signals and the chemical shift of the signals of the 4a-H, 10a-H, and 9-H_a protons (1.95-2.35 ppm) make it possible to assume that this compound has a trans-syn-trans configuration. The PMR spectrum of Vd is similar to the spectra of Va,c; specifically, there is a broad 10a-H multiplet at 2.93 ppm. In addition, the signal of the methyl group is shifted to weaker field (2.42 ppm) as compared with the methyl group of IV. This makes it possible to assign a cis-syn-trans configuration to Vd.

The PMR spectrum of VI contains a 9-H_a triplet at 2.52 ppm ($J = 11.5$ Hz), from which it follows that 9a-H and 8a-H are syn-oriented; VI probably has a trans-syn-trans configuration, since the alternative cis-syn-cis configuration is energically unfavorable. The signal of the NH_2 group of this compound gives a singlet at 4.82 ppm, and the protons of the CH_2 group of the pyrazine ring give a quartet at 3.57 ppm ($\Delta = 0.54$ ppm, $J = -17$ Hz).

The PMR spectra of VIIe-g contain a triplet at 2.63, 2.54, and 2.50 ppm, respectively, with $J = 10$ Hz; in addition, the spectrum of VIIg contains a singlet of the α protons of a benzyl group at 4.16 ppm, and the spectrum of VIIe contains a broad singlet of an NH group at 3.13 ppm. Since, in analogy with VI, the formation of a fourth ring is possible only in the case of diaxial orientation of the C—O bonds, the presence of a triplet with $J = 10$ Hz indicates the trans-syn-trans configuration of VIIe-g.

EXPERIMENTAL

The IR spectra of chloroform solutions of the compounds were recorded with a UR-20 spectrometer. The PMR spectra of $CDCl_3$ solutions were recorded with a Bruker HX-90E spectrometer. The course of the reactions and the individuality of the substances were monitored by TLC on activity II Al_2O_3 and Silufol.

9-Phenyl-10-methyl-4a-cyanoperhydroacridine (Id). A mixture of 0.04 mole of 9-hydroxy-4-phenyl-2,3-tetramethylenebicyclo[3.3.1]nonan-2-one, 0.1 mole of methylamine hydrochloride, and 0.1 mole of sodium acetate was refluxed in 100 ml of acetic acid for 3 h, after which it was cooled, diluted with 200 ml of water, and made alkaline with ammonium hydroxide. The liberated oil was extracted with ether. A solution of ammonium perchlorate was added to the aqueous layer, and the precipitated 9-phenyl-10-methyl-syn-octahydroacridinium perchlorate (IX) was removed by filtration, washed with water, and dried (see Table 1). The uncrystallized residue that remained after the ether was removed from the dried extract by distillation was dissolved in 15 ml of acetic acid, and a mixture of 2 g of 50% potassium cyanide solution, 5 ml of water, and 15 ml of acetic acid were added with stirring to the resulting solution. The mixture was stirred for 5 h, after which it was diluted with 70 ml of water and made alkaline with ammonium hydroxide. After 24 h, Id was removed by filtration, washed with water, and dried.

Reduction of Ia-d. A 0.01-mole sample of I was mixed with 0.02-0.03 mole of KBH_4 in 50 ml of DMF, and the mixture was heated to 120-130° for 2-3 h. It was then cooled and diluted to 200 ml with water. At the end of the decomposition of the KBH_4, II was removed by filtration, washed with water, and dried.

Reduction of IIIa-d. A) The reduction was carried out as in the case of Ia-d in DMF by means of KBH_4. Compounds Va,c were much less soluble in acetic acid than IIa,c, and they were separated by treatment of the reduction products with hot acetic acid. Reduction products IV and Vd were separated by chromatography with a column filled with L 40/100 silica gel (elution with methanol). Only IIb was formed in the case of dinitrile IIIb.

B) A 0.0025-mole sample of dinitrile III was dissolved in 10-15 ml of absolute THF, a suspension of 0.005-0.01 mole of $LiAlH_4$ in 20 ml of THF was added, and the mixture was refluxed for 3-5 h. It was then cooled and treated with 1 ml of water, 1 ml of 30% NaOH solution, 2 ml of water, and 10 ml of THF, and the solution was filtered. The precipitate was washed with THF, and the filtrates were combined. The dried filtrate was evaporated, and the residual mixture of products was separated as in the case of method A.

2-Amino-7,9-diphenyl-1,8,5,6-bis(tetramethylene)-3,9-diazabicyclo[3.3.1]non-2-ene (VI). A mixture of 0.01 mole of dinitrile IIIa and 0.01 mole of $LiAlH_4$ in 40 ml of absolute THF was heated for 30 min, after which another 0.01 mole of $LiAlH_4$ was added, and the mixture was refluxed for 2 h. The product was isolated as in method B.

4a,10a-Peroxyperhydroacridines (VII). A 0.02-mole sample of the appropriate primary amine and 0.2 mole of a 30% solution of hydrogen peroxide were added to a solution of 0.02 mole of 2,2'-ethylidene- or 2,2'-benzylidenedicyclohexanone in 50 ml of alcohol. After 24 h, the precipitate was removed by filtration, washed with alcohol and water, and dried. In the case of peroxy derivative VIIf the precipitate formed only when 25 ml of a saturated sodium carbonate solution was added. All of the compounds obtained were chromatographically individual (although VIIc,d were obtained in the form of oils) and gave a positive reaction for a peroxy group.

Reaction of VII with HCl. A 0.02-mole sample of VII was added to a solution of 0.05 mole of KCN in 15 ml of acetic acid. After 24 h, the precipitated VIII or III was removed by filtration, washed with CH_3COOH and water, and dried. Compounds IIIa,c were identical to the previously obtained samples (60-70% yields). See Table 1 for data on VIII.

Reduction of VIIf,g. A 0.02-mole sample of VII was dissolved in the minimum volume of alcohol, and the solution was added to a solution of $NaBH_4$ in 70% alcohol. The reaction mixture was refluxed for 40 h, after which it was diluted with a threefold amount of water, and the precipitate (IIa or IIc, respectively) was removed by filtration and washed with water, alcohol, and ether. The products were obtained in 60-70% yields and were identical to genuine samples of IIa and IIc.

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