HYDROACRIDINES AND RELATED COMPOUNDS

19.* ANGULAR HYDRIDE REDUCTIONS IN THE HYDROBENZ[c]ACRIDINE AND HYDROACRIDINE SERIES

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UDC 547.837.2:542.941

The hydride reduction of dihydro- and tetrahydropyridine derivatives and of angular nitriles in the hydrobenz[c]acridine and hydroacridine series, and also the reductive cleavage of the azoline and azine rings in 11a,12-benzoxazolino- and 11a,12-benzoxazinohydrobenz[c]acridines and 4a,10-benzoxazolinohydroacridines has been studied. The stereospecificity of all the reactions mentioned has been established.

The hydride reduction of decahydro- and dodecahydroacridines containing 1,4-dihydro- and 1,2,3,4-tetrahydropyridine structures has been studied previously [2] and so has the substitution by the hydride ion of angular cyano groups in the perhydroacridine series [3], and it has been shown that in the majority of cases the reactions take place stereospecifically.

Continuing an investigation of the properties of hydroacridines and related compounds, we have studied the behavior in relation to hydride reducing agents of analogous derivatives of the hydrobenz[c]acridine series and also, for the first time, of azolinohydroacridines, azolinohydrobenz[c]acridines, and oxazinohydrobenz[c]acridines and of α-enamino nitriles of the acridine and hydrobenz[c]acridine series. The reducing agents were complex hydrides, formic acid, and a mixture of DMFA with concentrated HCl [2].

In contrast to the analogous derivatives of the hydroacridine series [2], hydrobenz[c]-acridine derivatives containing a 1,4-dihydropyridine nucleus (shown with compound (Ia, b) as examples) are not reduced on treatment with formic acid acid or DMFA—HCl but are hydrolyzed with the formation of 1,5-diketones (IIa, b). On the other hand, the tetrahydropyridine derivative (III) with a nonconjugated double bond [4] is readily reduced by DMFA—HCl with the formation of the piperidine derivative (IV). The tetrahydropyridine derivative (V) containing a conjugated double bond is not reduced by DMFA—HCl but is reduced by 85% formic acid with the formation of the same compound (IV); in this case, the result is the opposite of the reduction of the dodecahydroacridines [2]. Finally, compound (X) is not reduced by either reducing agent, which is probably connected with the additional screening of the double bond by the phenyl radical. None of the compounds mentioned is reduced by complex hydrides.

The α-aminonitrile (VI) [obtained by the addition of HCN to compound (III)], like the cyanoperhydroacridines [3], on being heated with KBH_4 in DMFA readily exchanges the cyano group for a hydride ion with the formation of compound (IV). At the same time, α-enamino nitriles of both the hydroacridine series (XVIIa, b) and of the hydrobenz[c]acridine series (VIIa, b) exhibit no tendency to such a replacement. The reaction of the cyanododecahydroacridines (XVIIa, b) with KBH_4 even under severe conditions takes place with great difficulty and with the formation of complex mixtures of products from which it has been possible to isolate small amounts of perhydroacridines: (XIXa) in the form of the trans-syn-trans isomer and (XIXb) in the form of the trans-syn-trans and cis-syn-trans isomers, respectively. Since the same isomers of compound (XIXb) are formed in the tetrahydroborate reduction of the dicyanide (XVIIIb) [3], it may be assumed that under the given conditions there is a slow disproportionation of the enamino nitriles (XVII) in accordance with a scheme described previously [5], followed by the reduction of the dicyanides (XVIII) so formed.

*For communication 18, see [1].

Far-Eastern State University, Vladivostok. Translated from Khimiya Geterotsiklicheskikh Soedinenii, No. 4, pp. 508-513, April, 1980. Original article submitted April 2, 1979.

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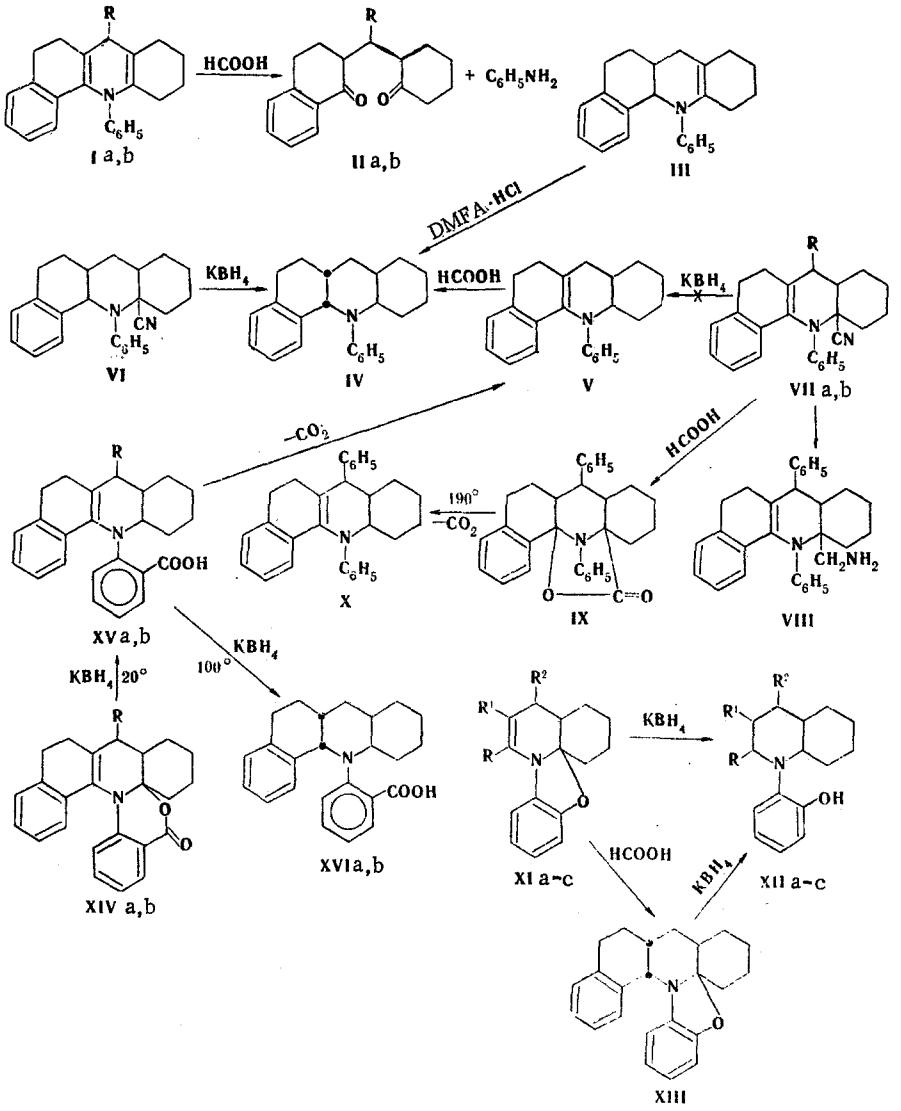
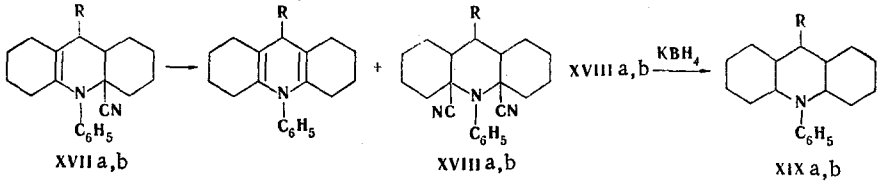


I, II, VII, XIV—XVI a R=H; b R=C_6H_5; XI, XII a R—R^1=$(CH_2)_4$, R^2=C_6H_5; b R—R^1= 1,2-benzotetramethylene, R^2=H; c R—R^1=1,2-benzotetramethylene, R_2=C_6H_5



XVII-XIX a R=H; b R=C_6H_5

The enamino nitriles of the hydrobenz[c]acridine series (VIIa, b) are incapable of such disproportionation; since the corresponding dicyanides cannot be formed [4], they do not change under the action of KBH_4 even in the most severe conditions.

Lithium tetrahydroaluminate reduces the cyano group of an enamino nitrile [for example (VIIb)] to a primary amino group with the formation of compound (VIII). The action of formic acid on the nitrile (VIIb) does not lead to reduction of the double bond but to the hydrolysis of the cyano group with the formation of the oxazolidone (IX), which is readily decarboxylated by heating to 190°C with the formation of compound (X).

Compounds (XIa-c), containing the structure of a hydrogenated benzoaxazolo[3,2-a]pyridine are reduced by potassium tetrahydroborate in boiling butanol to compounds (XIIa-c), the hydroacridine derivative (XIa) being reduced an order of magnitude faster than the hydrobenz-

TABLE 1. Characteristics of the IR, PMR, and Mass Spectra of Hydrobenz[c]acridine Derivatives

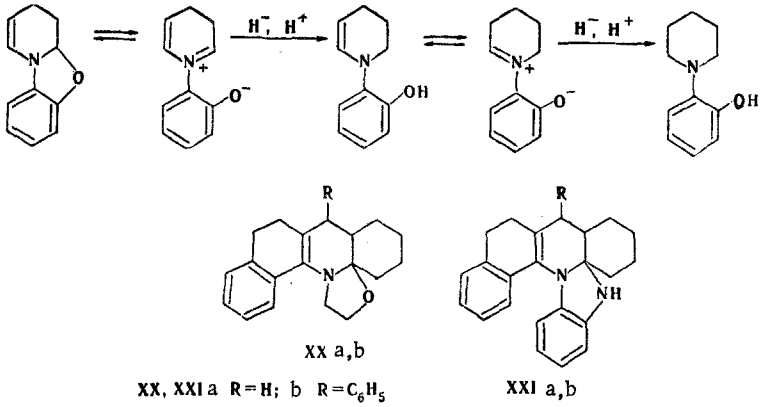
Compound	IR spectrum, cm^{-1}	PMR spectrum, ppm	Mass spectrum, m/e
IV	1600—1700 absent	4,20 br.s, 12a-H)	3,17, 274 $(M-C_3H_7)$[a]
V	1640	3,03—2,76 (m, 5-H, 11a-H)	315
VI	1600—1700 absent 2240	—	—
VIII	1635, 3400 (w)	—	420, 390 $(M-CH_2NH_2)$
IX	1760	—	435
X	1640	—	391, 314 $(M-C_6H_5)$
XIIb	1600—1700 absent 3350	3,82 (d,12a-H, J=2,6 Hz)	333, 290 $(M-C_3H_7)$
XIIc	1600—1700 absent 3350	4,00 (br. s, 12a-H)	409, 366 $(M-C_3H_7)$
XIII	No absorption in the 1600-1700 and 3199-3600 regions	4,77 (d,12a-H, J=5,6 Hz)	331
XVa	1640, 1670, 3370	—	359, 315 $(M-CO_2)$
XVb	1640, 1720	3,42 (d, 7-H, J=9,8 Hz)	435, 391 $(M-CO_2)$
XVIa	1680, 3380	4,55 (s, 12a-H)	361, 317 $(M-CO_2)$
XVIb	1720	4,29 (s, 12a-H)	437

[a] $M - C_3H_7$ is a fragmentary rearrangement ion characteristic for the fragmentation of perhydroquinolines [8].

[c]acridine derivative (XIb, c). The action of formic acid on compounds (XIb, c) leads mainly to hydrolysis to the diketones (IIa, b); however, in the case of (XIb) it was possible to isolate in small yield the product of the reduction of the double bond — compound (XIII). On being boiled with KBH_4 in butanol, it was reduced to compound (XIIb) twice as fast as compound (XIb). The reductive opening of the oxazolidine ring in 7-oxa-1-azabicyclo-[4,3,0]nonane derivatives has been described in the literature [6].

Compounds (XIVa, b) were reduced by KBH_4 considerably more easily than compounds (XI) and (XIII). At room temperature, the conjugated enamine bond was not affected, and compounds (XVa, b) were formed, the decarboxylation of compound (XVa) giving compound (V). Under somewhat more severe conditions compounds (XVa, b) were converted by the action of KBH_4 into the completely saturated products (XVIa, b). Attempts to decarboxylate these compounds did not lead to the isolation of individual products.

It may be assumed that the reduction of the cyanides and of compounds (XI, XIII, and XIV) takes place through the formation of imonium salts — imonium cyanides and imonium betains, respectively [shown for the case of the reduction of compound (XI)]:



XX a,b

XX, XXI a R=H; b R=C_6H_5 XXI a,b

In the case of the reduction of the cyanides and of compounds (XI) and (XIII), the slowest stage is probably the splitting of a cyanide anion and the opening of the oxazoline ring, respectively. The presence of an enaminic double bond in each of compounds (VII), (XI), and (XVII) interferes with the occurrence of this stage, since in this case the iminium salt will be less stable than in the case of compound (VI) and (XIII). The influence of the double bond should have a greater effect in the case of the nitriles, since the dissociation of the

TABLE 2. Hydrobenz[c]acridine and Hydroacridine Derivatives

Compound	mp, °C	Found, %			Empirical formula	Calculated, %			Yield, %
		C	H	N		C	H	N	
IV	112—114	86,5	8,6	4,7	$C_{23}H_{27}N$	87,1	8,5	4,4	83[a]
V	166—167	87,2	7,7	4,9	$C_{23}H_{25}N$	87,6	7,9	4,4	40
VI	156—158	84,3	8,0	8,3	$C_{24}H_{26}N_2$	84,5	7,6	8,2	40
VIII	178—180	85,6	7,2	6,8	$C_{30}H_{32}N_2$	85,7	7,6	6,7	60
IX	168—170	82,2	6,8	3,3	$C_{30}H_{29}NO_2$	82,7	6,7	3,2	35
X	152—153	89,0	7,6	4,0	$C_{29}H_{29}N$	89,0	7,4	3,6	50
XIIb	148—150	82,5	8,4	4,5	$C_{23}H_{27}NO$	82,8	8,2	4,2	34
XIIc	187—190	85,1	7,6	3,9	$C_{29}H_{31}NO$	85,5	7,1	3,5	54
XIII	162—163	83,2	7,9	4,4	$C_{23}H_{25}NO$	83,4	7,6	4,2	10
XVa	140—142	79,5	7,2	3,9	$C_{24}H_{25}NO_2$	80,2	7,0	3,9	86
XVb	217—219	82,3	6,8	3,2	$C_{30}H_{29}NO_2$	82,8	6,7	3,2	82
XVIa	109—110[b]	79,8	7,7	4,1	$C_{24}H_{27}NO_2$	79,8	7,5	3,9	95
XVIb	267—268	82,0	7,3	3,3	$C_{30}H_{31}NO_2$	82,4	7,1	3,2	40
XVIIb	159—160	85,2	8,0	7,9	$C_{26}H_{28}N_2$	84,8	7,6	7,6	39

[a]By method A. [b]From heptane. The other compounds from ethanol.

C=C bond in nitriles should take place with greater difficulty than the opening of the oxazoline ring in compounds (XI) and (XIII); in harmony with this is the fact that compounds (XI) are reduced by KBH_4, while the enamino nitriles are not reduced. The fact that the nitrile (VI) is reduced faster than compound (XIII) is possibly explained by the higher equilibrium concentration of iminium salt in the case of the nitrile (VI), since in the case of compound (XIII) [and compound (XI)] the spatial propinquity of the OH group and the iminium bond facilitates the occurrence of the back-reaction — intramolecular cyclization. Compound (XX) and, particularly (XXI), to a smaller extent than compounds (XI) and (XIII), have a tendency to form intermediate iminium betains; they have proved stable to the action of KBH_4. In this sense, compounds (XXI) differ from the hydrogenated imidazo[1,2-a]pyridines with a C=N bond, which readily opened in the imidazoline ring under the action of $NaBH_4$ [7]. The lactone ring of compound (XIV) opens very readily, which also explains the ease of their reduction. The structures of the compounds obtained are confirmed by their IR, PMR, and mass spectra (Table 1).

The structures of compounds (XVa and b) and (XVIa and b) are also confirmed by the fact that they titrate as monobasic acids, while the initial substances (XIVa and b) do not titrate and neutralize alkali only on boiling on ethanolic solution. The shift of the carboxyl absorption in the direction of higher frequencies and the absence of absorption in the region above 3100 cm^{-1} in the IR spectra of compounds (XVb) and (XVIb) is probably explained by a strong hydrogen bond between the COOH group and the nitrogen atom, because of which this acid does not form dimers.

As follows from the results given, in all the cases considered angular hydride reduction takes place stereospecifically, the action of different reducing agents on a given substrate leading to one and the same stereosiomer. The SSCCs of the 12a-H signal in the PMR spectra of the hydrobenz[c]acridine derivatives obtained (0-3 Hz) show the cis-linkage of the rings at the 6a,12a positions. At the same time, the perhydroacridine derivative (XIIa) has the trans-syn-trans configuration [2]: thus, the reduction of a conjugated double bond in the hydrobenz[c]acridine series has a different stereochemistry from that of an unconjugated bond in the hydroacridine series. The nature of the linkage of the rings at the 7a,11a positions has not been determined, since it is not possible to isolate the 11a-H signal in the PMR spectra.

EXPERIMENTAL

The IR spectra were taken on a UR-20 instrument in paraffin oil and chloroform, the PMR spectra on a Brüker HE 90X instrument at room temperature in $CDCl_3$ with TMS as internal standard, and mass spectra on a MKh-1303 instrument with the direct introduction of the sample at an energy of the ionizing electrons of 30 eV. The course of the reaction was followed and the purity of the products obtained was checked by the TLC method on Solufol in petroleum ether–ethyl acetate (from 8 : 1 to 1 : 1) systems.

12-Phenyl-5,6,6a,7,7a,8,9,10,11,11a,12,12a-dodeca-hydrobenz[c]acridine (IV). A. A mixture of 1 mmole of compound (III), 1.5 ml of DMFA, and 0.5 ml of concentrated HCl was heated in the water bath for 2 h and was then diluted with water, and the substance (IV) was filtered off and was washed with water.

B. A solution of 0.024 mole of (V) in 5 ml of 85% formic acid was heated in the water bath for 10 h, diluted with water, and extracted with ether, the ether was evaporated, and the residue was chromatographed on Al_2O_3 of activity grade 2, compound (IV) being eluted with petroleum ether. Yield 40%.

C. A mixture of 0.015 mole of the cyanide (VI) and 0.003* mole of KBH_4 in 5 ml of dimethylformamide was heated with stirring at 130°C for 2 h and was then diluted with water, and the precipitate was filtered off and was triturated with ethanol to give 88% of product (IV). The samples obtained by method A, B, and C were identical according to mixed melting points and IR spectra.

11a-Cyano-12-phenyl-5,6,6a,7,7a,8,9,10,11,11a,12,12a-dodecahydrobenz[c]acridine (VI). A solution of 0.01 mole of the diketone (IIa) and 0.011 mole of aniline in 10 ml of acetic acid was heated in the water bath for 5 h and was then cooled, and a solution of 3 g of KCN in 5 ml of water was added (with stirring), and after 2 h substance (VI) was filtered off.

9,10-Diphenyldodecahydroacridine (XVIIb) was obtained by a method similar to that for the synthesis of compound (XVIIa) [5].

Reduction of the Enamino Nitriles (XVIIa,b). A mixture of 2 mmole of compound (XVIIa or b) and 8 mmole of KBH_4 in 5 ml of n-butanol was boiled for 30 h. In the case of (XVIIa), the solution was filtered, the butanol was distilled off from the filtrate with steam, the residue was treated with acetone, and 5% of compound (XIXa) was filtered off. The product was identified by a mixed melting point with a sample of 10-phenylperhydroacridine and by IR spectroscopy. In the case of (XVIIb), the mixture was cooled and the precipitate was filtered off and dried and was then boiled with a small amount of ethanol. The fraction not dissolving in the ethanol consisted of trans-syn-trans-(XIXb) (yield 8%); when the ethanolic solution was cooled it deposited trans-syn-cis-(XIXb) (yield 5%). The products were identical with authentic samples according to mixed melting points and IR spectra.

11a-Aminomethyl-5,6,7,7a,8,9,10,11,11a,12-decahydrobenz[c]acridine (VIII). A suspension of 1 g of the nitrile (VIIb) in 5 ml of absolute ether was added over 1 h 30 min to a suspension of 0.15 g of $LiAlH_4$ in 5 ml of absolute ether, and then the precipitate was filtered off and dissolved in chloroform, the solution was filtered, and the chloroform was evaporated off from the filtrate to give the unpurified product (VIII). The ethereal solution after the separation of the precipitate was evaporated and the residue was treated with 40% NaOH, and an additional amount of compound (VIII) was filtered off.

12a-Hydroxy-12-phenyl-5,6,6a,7,7a,8,9,10,11,11a,12,12a-dodecahydrobenz[c]acridine-11a-carboxylic acid Lactone (IX). A solution of 6 mmole of the nitrile (VIIb) in 15 ml of 85% formic acid was heated in the water bath for 7 h and cooled, and the precipitate was filtered off, washed with 50% formic acid and with water, and dried.

Decarboxylation of Compound (IX). Substance (IX) (0.7 g) was heated in an atmosphere of argon at 170-190°C for 30 min. The melt was treated with ethanol, and compound (X) was filtered off.

Reduction of Compound (XIa-c) and (XIII). A mixture of 3 mmole of a substance (XI) or substance (XIII), 6 mmole of KBH_4, and 5 ml of butanol was boiled until the spot of the initial compound had disappeared on TLC [in the case of compound (XIa) this required 3 h, for (XIb and c) 30 h, and for (XIII) 20 h]. In the case of (XIa), the mixture was cooled and substance (XIIa) was filtered off and crystallized from ethanol, and was shown to be identical with an authentic sample [2] by a mixed melting point and by IR spectroscopy. Yield 69%. In the case of compound (XIb and c), the reaction mixture was cooled and was diluted with 5 ml of ethanol, and then the compound (XIIb or c) was filtered off and it was washed with ether and dried. In the case of (XIII), the butanol was distilled off with steam, the residue was diluted with water and extracted with ether, the etheral extract was evaporated, the residue was treated with 3 ml of ethanol, and 43% of compound (XIIb) was filtered off.

Reduction of Compound (XIb) with Formic Acid. A mixture of 0.05 mole of compound (XIb) and 120 ml of 85% formic acid was heated in the water bath in a current of argon for 5 h and was then cooled, diluted with water, neutralized with Na_2CO_3, and extracted with ether, and the etheral extract was washed with sodium carbonate solution and with water, dried, and

*As in Russian original — Publisher.

evaporated. The residue was treated with ethanol. After three days, compound (XIII) was filtered off.

7-Substituted 12-(o-Carboxyphenyl)-5,6,7,7a,8,9,10,11,11a,12-decahydrobenz[c]acridines (XVa,b). With stirring, a solution of 3 mmole of KBH_4 in 10 ml of water was added over 2 h to a solution of 1 mmole of (XIVa) or (XIVb) in 30 ml of dioxane, and then the mixture was filtered, diluted twofold with water, and extracted with ether, and the aqueous layer was acidified with acetic acid. The oil that deposited rapidly crystallized; the reaction product (XVa) or (XVb) was filtered off, washed with water, and dried.

7-Substituted 12-(o-Carboxyphenyl)-5,6,6a,7,7a,8,9,10,11,11a,12,12a-dodecahydrobenz[c]-acridines (XVIa, b). In portions, 4 mmole of KBH_4 was added to a solution of 1 mmole of (XVa) or (XVb) in 20 ml of DMFA. In the case of (XVa) the mixture was heated in the water bath for 8 h, diluted with water threefold, and acidified with acetic acid, and the reaction product (XVIa) was filtered off. In the case of (XVb) the mixture was boiled for 1 h 30 min, cooled, diluted with water threefold, and extracted with 10 ml of ether, and the precipitate of (XVIb) that had formed at the phase-separation boundary was filtered off. Acidification of the aqueous layer yielded unchanged compound (XVb).

Decarboxylation of Compound (XVa). Compound (XVa) (0.01 mole) was heated in a current of argon. The evolution of CO_2 began at 140°C and was complete at 240°C. After cooling, the reaction products were chromatographed on Al_2O_3 of activity grade 2, and product (V) was eluted with ether.

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