INVESTIGATIONS OF POLYHYDROACRIDINES AND RELATED COMPOUNDS

VII.* CARBINOLS OF THE sym-OCTAHYDROACRIDINE AND 1,2,3,4-TETRAHYDROACRIDINE SERIES

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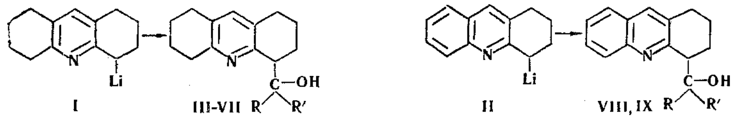
UDC 547.835.2.5.07:542.957

A method is proposed for the synthesis of polyhydroacridines with a hydroxyl group in the side chain by condensation of 4-lithio-sym-octahydroacridine and 4-lithio-1,2,3,4-tetrahydroacridine with aldehydes and ketones. The dehydration of the compounds obtained was studied. 4,5-Diarylidineoctahydroacridines are formed by heating 4-α-hydroxybenzyl-sym-octahydroacridine in acetic anhydride in the presence of aromatic aldehydes.

We have previously briefly reported the synthesis of carbinols III-V by the addition of 4-lithio-sym-octahydroacridine (I) to aldehydes and ketones [2]. In this paper we give a complete description of these syntheses as well as the syntheses of carbinols VI-IX.



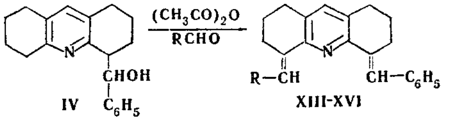
I III-VII II VIII, IX

III R=R'=H; IV R=H, R'=C_6H_5; V R+R'=—$(CH_2)_5$—; VI R=CH_3, R'=C_6H_5; VII R=R'=C_6H_5;
VIII R=H, R'=C_6H_5; IX R=R'=C_6H_5

Metallation of 1,2,3,4-tetrahydroacridine at room temperature is complete after stirring of equimolar amounts of the hydroacridine and phenyllithium for about 1 h; the metallation of sym-octahydroacridine proceeds more slowly. The high reactivity of 1,2,3,4-tetrahydroacridine in the reaction with phenyllithium can be explained by its great tendency for deprotonation, which is determined not only by electron migration but also by the stability of the carbanion formed [3].

The reactions of I and II with carbonyl compounds proceeds smoothly to give carbinols III-IX (Table 1).

The next step in this investigation was a study of the ratio of the carbinols obtained to acetic anhydride. Primary carbinol III forms acetate X in this process.† Secondary carbinols IV and VIII are dehydrated to form 4-benzal-sym-octahydroacridine (XI) and 4-benzal-1,2,3,4-tetrahydroacridine (XII), respectively. If the dehydration of alcohol IV is carried out in the presence of aromatic aldehydes, the reaction products are 5-arylidene-4-benzal-sym-octahydroacridines (XIII-XVI) (Table 2).



IV XIII-XVI

XIII R=C_6H_5; XIV R=p-$NO_2C_6H_5$; XV R=m-$NO_2C_6H_5$;
XVI R=$C_6H_5CH{=}CH$—

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*See [1] for Communication VI.

†As shown by L. N. Donchak.

Far-Eastern State University, Vladivostok. Translated from Khimiya Geterotsiklicheskikh Soedinenii, No. 11, pp. 1542-1545, November, 1970. Original article submitted December 23, 1968.

TABLE 1. Carbinols III-IX

Compound	Mp, °C	Empirical formula	Found %			Calc. %			IR spectrum, ν_{OH}, cm^{-1}	Yield, %	Picrate			
											Mp, °C	empirical formula	N, %	
			C	H	N	C	H	N					found	calc.
III	92—93[a]	$C_{14}H_{19}NO$	77,2	9,1	6,6	77,4	8,8	6,4	3350	50	132—133[b]	$C_{14}H_{19}NO \cdot C_6H_3N_3O_7$	12,9	12,5
IV	147—148[c]	$C_{20}H_{23}NO$	81,4	7,8	5,1	81,8	7,9	4,8	3340	49	161—162[d]	$C_{20}H_{23}NO \cdot C_6H_3N_3O_7$	10,8	10,7
V	89—90[e]	$C_{19}H_{27}NO$	79,9	9,6	5,1	80,0	9,2	4,9	3350	62	151—152[f]	$C_{19}H_{27}NO \cdot C_6H_3N_3O_7$	10,8	10,9
VI	134—135[d]	$C_{21}H_{25}NO$	82,1	8,8	5,0	82,0	8,2	4,6	3250	30	161[d]	$C_{21}H_{25}NO \cdot C_6H_3N_3O_7$	10,8	10,6
VII	159—160[g]	$C_{26}H_{27}NO$	84,7	7,1	4,0	84,5	7,4	3,8	3250	41	—	—	—	—
VIII	134—135[a]	$C_{20}H_{19}NO$	82,6	6,7	5,1	83,0	6,6	4,8	3270	72	136—138[d]	$C_{20}H_{19}NO \cdot C_6H_3N_3O_7$	10,7	10,8
IX	132—133[h]	$C_{26}H_{23}NO$	85,1	6,4	4,2	85,4	6,3	3,8	3270	54	—	—	—	—

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a) From pentane. b) From xylene. c) From petroleum ether. d) From alcohol. e) From acetone. f) From isobutyl alcohol. g) From hexane. h) From ethyl acetate.

TABLE 2. 5-Arylidene-4-benzal-sym-octahydroacridines (XIII-XVI)

Compound	Mp, °C	Empirical formula	N, %		Yield, %	Picrate			
						Mp, °C	empirical formula	N, %	
			found	calc.				found	calc.
XIII	182—184*	$C_{27}H_{25}$	—	—	33	194—196*	$C_{27}H_{25}N \cdot C_6H_3N_3O_7$	—	—
XIV	160—162	$C_{27}H_{24}N_2O_2$	6,9	6,8	81	210—212	$C_{27}H_{24}N_2O_2 \cdot C_6H_3N_3O_7$	10,8	10,9
XV	158—159	$C_{27}H_{24}N_2O_2$	6,8	6,8	63	206—208	$C_{27}H_{24}N_2O_2 \cdot C_6H_3N_3O_7$	10,6	10,9
XVI	160—161	$C_{29}H_{27}$	3,5	3,6	30	210—212	$C_{29}H_{27}N \cdot C_6H_3N_3O_7$	9,3	9,0

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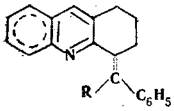
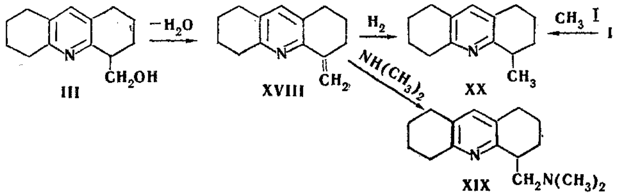
*mp 184°, picrate mp 195° [7].

Treatment of tertiary carbinols VI, VII, and IX with acetic anhydride leads to cleavage of these compounds to the corresponding ketones and hydroacridines. This sort of cleavage is sometimes observed for branched aldols and carbinols related to them. A similar cleavage was recently noted [4] for one of the branched pyridine alcohols. The difficulties in the dehydration of alcohols VI, VII, and IX are apparently explained by the fact that cleavage of water leads to rotation of the substituents in the plane of the hydroacridine ring; models indicate that the electron clouds of substituent R and the nitrogen atom overlap if R is something other than H.

4-(1-Hydroxycyclohexyl)-sym-octahydroacridine (V) gives a dehydration product under both the action of acetic anhydride and thionyl chloride, and the sterically unhindered 4-(1-cyclohexenyl)-sym-octahydroacridine (XVII) is formed; the structure of XVII is confirmed by the presence in the PMR spectrum of a signal for a proton on a double bond at 5.1 ppm, the presence in the IR spectrum of a characteristic band for the =C−H bond (3010 cm^{-1}), and by the absence in the UV spectrum of an absorption at 303 nm, characteristic for 4-methylene-sym-octahydroacridine (XVIII) and 1,2,3,4,7,8-hexahydroacridine [5]. The latter indicates that XVII does not have a double bond conjugated with the pyridine ring.



We obtained 4-methylene-sym-octahydroacridine (XVIII) by dehydration of carbinol III with potassium hydroxide. The exocyclic position of the double bond is confirmed by the PMR spectrum [5]. We obtained the known [6] 4-(dimethylaminomethyl)-sym-octahydroacridine (XIX) by addition of dimethylamine to the double bond of XVIII; hydrogenation of XVIII gives 4-methyl-sym-octahydroacridine (XX) [5], which we also obtained from I and methyl iodide.



The authors thank A. K. Dzizenko and co-workers for obtaining the IR and PMR spectra.

EXPERIMENTAL

Carbinols III-IX. A solution of 0.1 mole of the hydroacridine in 50 ml of absolute ether was placed in a flask equipped with a stirrer, a dropping funnel, a reflux condenser, and a tube for introduction of argon, and a solution of 0.1 mole of phenyllithium in ether was added in the course of 1 h under argon. The mixture was allowed to stand overnight. A solution of 0.1 mole of the aldehyde or ketone in absolute ether was added dropwise to the suspension in the course of 15 min; to obtain carbinol III, a stream of formaldehyde was bubbled into the suspension, and the mixture was stirred for another 45 min.

A. Carbinols III, V, and VII. The alkoxide precipitate was removed, washed with absolute ether, and dissolved in 20% hydrochloric acid. The solution was filtered, washed with ether, and made alkaline with 20% KOH.

B. Carbinols IV and VIII. Hydrochloric acid [100 ml (20%)] was added, and the hydrochloride was filtered and washed with water and ether. The methanol solution of the hydrochloride was made alkaline with 20% aqueous KOH.

C. Carbinol VI. Hydrochloric acid [100 ml (20%)] was added, and the hydrochloride solution was filtered, washed with ether, and made alkaline with 20% KOH. The base was treated with 75 ml of ether, and the carbinol was filtered.

D. Carbinol IX. Water (50 ml) was added, the mixture was stirred for 15 min, and the carbinol was separated and washed with water and ether.

Ratio of Carbinols III-IX to Acetic Anhydride. A 10% solution of the carbinol in acetic anhydride was refluxed for 3 h.

A. Carbinols IV and VI-IX. The acetic anhydride was evaporated, and the residue was treated with 20% hydrochloric acid. The neutral substances were extracted with ether, and the hydrochloride was decomposed with aqueous alkali. Sym-octahydroacridine, obtained from carbinols VI and VII, and 1,2,3,4-tetrahydroacridine, obtained from carbinol IX, were identified by means of a mixed melting-point determination; acetophenone (carbinol VI) or benzophenone (carbinols VII and IX) were detected in the neutral reaction products by chromatography and identified in the form of their phenylhydrazones.

4-Benzal-sym-octahydroacridine (XI). This was obtained in 80% yield from carbinol IV and had mp 80-81° (from alcohol). A mixture of it with a known sample [7] melted without depression.

4-Benzal-1,2,3,4-tetrahydroacridine (XII). This was obtained in 89% yield from carbinol VIII and had mp 102-103° (from aqueous alcohol). It was identified by a mixed melting-point determination with a known sample [8].

B. Carbinols III and V. The reaction mixture was diluted with water, stirred for 30 min, and treated with saturated potassium carbonate solution to isolate the reaction product.

4-Acetoxymethyl-sym-octahydroacridine (X). This was obtained in the form of a viscous oil with n_D^{18} 1.5441. Found %: C 75.5, 74.4; H 8.3, 8.2; CH_3CO 16.3, 16.4. $C_{16}H_{21}NO_2$. Calculated %: C 74.1; H 8.2; CH_3CO 16.6.

4-(1-Cyclohexenyl)-sym-octahydroacridine (XVII). This was obtained in 50% yield from carbinol V and had mp 109.5-110.5°. Found %: C 84.5, 84.7; H 10.1, 9.9; N 5.2, 5.3. $C_{19}H_{25}N$. Calculated %: C 84.7; H 10.1; N 5.2. IR spectrum (UR-20, in CCl_4): 3010; 3060; 1610 cm^{-1} (all weak), no OH group absorption. PMR spectrum (ZKR-60, $CDCl_3$): 1.75 (multiplet), 2.85 (multiplet), 5.10 (triplet with J = 10 Hz), 6.67 ppm (multiplet). Picrate, mp 188-189° (from ethanol). Found %: N 11.4, 11.4. $C_{19}H_{25}N \cdot C_6H_3N_3O_7$. Calculated %: N 11.4.

5-Arylidene-4-benzal-sym-octahydroacridines (XIII-XVI). Alcohol IV (1 g) was refluxed for 8 h with an equimolar amount of aromatic aldehyde in 10 ml of acetic anhydride. The 5-arylideneoctahydroacridines precipitated on cooling and were recrystallized from alcohol (Table 2).

4-Methylene-sym-octahydroacridine (XVIII). A mixture of 21.7 g (0.1 mole) of alcohol III and 3 g of powdered KOH was heated at 140° for 2 h. The mixture was then distilled in vacuo, and the fraction with bp 139-145° (0.9 mm) was collected; a second distillation gave 10.25 g (45%) of XVIII with n_D^{20} 1.5850. Found %: C 84.8, 84.9; H 8.7, 8.7; N 7.1, 6.9. $C_{14}H_{17}N$. Calculated %: C 84.4; H 8.6; N 7.0. Picrate, mp 157-159° (from acetone). Found %: N 13.0, 12.8. $C_{14}H_{17}N \cdot C_6H_3N_3O_7$. Calculated %: N 13.1.

4-(Dimethylaminomethyl)-sym-octahydroacridine (XIX). Compound XVIII [3 g (0.01 mole)] was refluxed with 2.43 g (0.03 mole) of dimethylamine hydrochloride in 15 ml of methanol for 24 h. The methanol was removed, and the residue was treated with saturated potassium carbonate solution. The base was extracted with ether, and the extract was evaporated and chromatographed on 100 g of activity-II Al_2O_3. The unchanged XVIII was eluted with CCl_4, while amine XIX was eluted with chloroform to give 1.2 g (27%) of product. Its identity with the previously obtained compound [6] was established by thin-layer chromatography and mixed melting-point determinations with the picrates. Dipicrate, mp 164-165°. Found %: N 15.8, 15.8. $C_{16}H_{24}N_2 \cdot 2C_6H_3N_3O_7$. Calculated %: N 15.9.

4-Methyl-sym-octahydroacridine (XX). A. Methyleneacridine XVIII [3 g (0.01 mole)] was hydrogenated on 0.04 g of Adams catalyst in 50 ml of absolute ethanol. A total of 300 ml of hydrogen was absorbed (calc. 327 ml). The catalyst was filtered off, the solution was evaporated, and the residue of methylacridine XX [2.53 g (84%)] was purified by vacuum sublimation to give a product with mp 28-30°. Found %: C 83.6, 83.7; H 9.4, 9.6; N 6.8, 6.6. $C_{14}H_{19}N$. Calculated %: C 83.5; H 9.4; N 6.9. Picrate, mp 144-145° (alcohol). Found %: N 13.0, 13.0. $C_{14}H_{19}N \cdot C_6H_3N_3O_7$. Calculated %: N 13.0.

B. A solution of 1.42 g (0.01 mole) of methyl iodide in 10 ml of absolute ether was added to a suspension of I, obtained from 1.87 g (0.01 mole) of sym-octahydroacridine and 8 ml of 1.3-M solution of phenyllithium in ether, as described above. The mixture was stirred for 1 h and treated with 100 ml of 20% hydrochloric acid. The hydrochloric acid solution was separated, washed with ether, and made alkaline with 20% KOH. The base was extracted with ether, the extract was evaporated, and the residue was separated by preparative chromatography on plates in a thin layer of activity-II Al_2O_3 in CCl_4. The yield of XX was 0.62 g (30%).

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