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TRANSFORMATIONS OF *sym*-OCTAHYDROXANTHENE-1,8-DIONES AND 1,8-DIOXO-*sym*-OCTAHYDROXANTHYLIUM SALTS IN RECYCLIZATION UNDER THE INFLUENCE OF AMINES

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The chemical behavior of 9-R-sym-octahydroxanthene-1,8-diones and salts based on them in recyclization reactions under the influence of amines was studied. The effect of the basicity of the amines on the direction of recyclization was established. A method is proposed for the single-stage synthesis of sym-octahydroacridine-1.8-dione oximes based on 1,8-dioxo-sym-octahydroxanthenes. Conditions were worked out for the oxidation of sym-octahydroxanthene-1,8-diones and N-R-decahydroacridinediones to the corresponding salts.

Keywords: decahydroacridine-1,8-diones, *sym*-octahydroacridine-1,8-dione oximes, 1,8-dioxo-*sym*-octahydroacridinium perchlorates, *sym*-octahydroxanthene-1,8-diones, 1,8-dioxo-*sym*-octahydroxanthylium salts, amination, oxidation, recyclization.

9-R-1,8-Dioxo-*sym*-octahydroxanthenes are well known and are easily formed when α-R-methylene-bis-2,2'-cyclohexane-1,3-diones are heated in acidic media [1, 2]. However, in spite of the presence of several reaction centers, their chemical transformations have been studied relatively little. There are isolated examples of the recyclization of 1,8-dioxo-*sym*-octahydroxanthenes to decahydroacridine-1,8-diones unsubstituted at the nitrogen atom during the action of ammonia in alcohol at 110-130°C [3, 4], ammonium acetate with boiling in an alcohol–acetic acid medium [5, 7], and urea with heating at 120°C in DMSO [8].

In order to establish the possibility of synthesizing decahydroacridine-1,8-diones with various structures from 1,8-dioxo-*sym*-octahydroxanthenes we studied the chemical behavior of the latter during recyclization in the presence of amines with various basicities (ammonia, benzylamine, aniline with heat in formic acid, or hydroxylamine hydrochloride boiled in solution in isopropyl alcohol).

The reaction of the octahydroxanthenes **1a-d** with formamide in formic acid was conducted at 100°C. Under these conditions the ammonia formed as a result of decarbonylation of the formamide reacts with the initial compounds **1a-d** with the formation of decahydroacridine-1,8-diones **2a-d** with yields of 71-82%. The process takes place smoothly in 4-6 h.

When benzylamine was used in the reaction 3-(benzylamino)-5,5-dimethyl-2-cyclohexen-1-one (**3**) (yields 28-42%) and N-benzylformamide were isolated as final products.

Octahydroxanthene-1,8-diones **1a-d** do not enter into reaction with aniline even after prolonged boiling (10-12 h) in formic acid. This agrees well with data in [6], where analogous reactions were carried out with aromatic amines in acetic acid.

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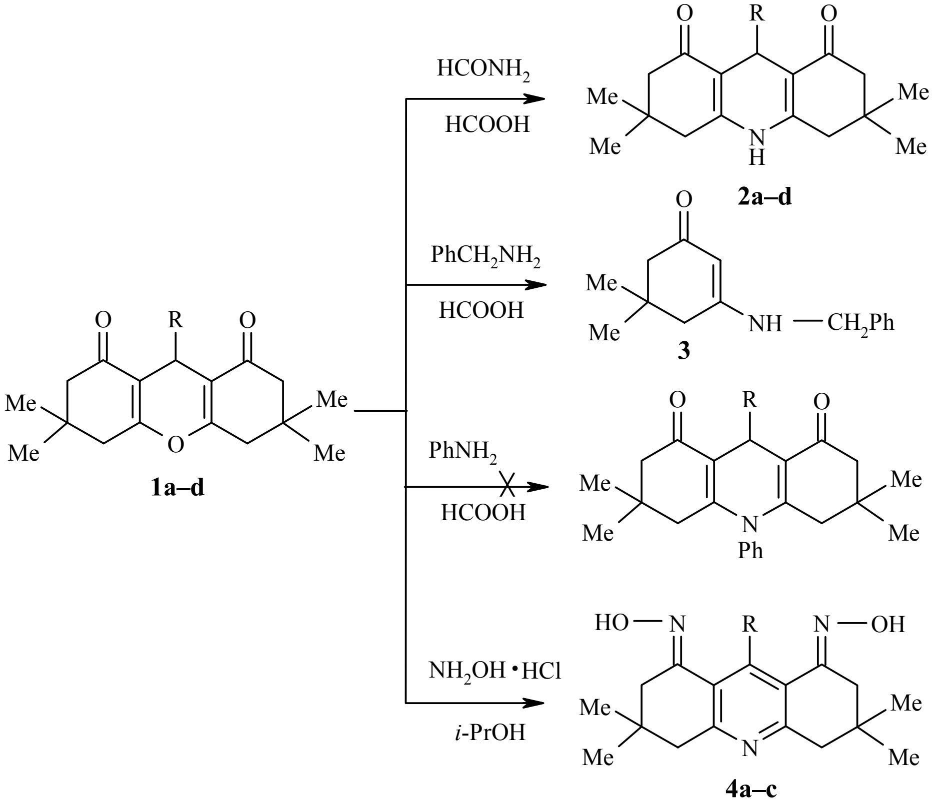
As a result of the recyclization of 1,8-dioxo-*sym*-octahydroxanthenes **1a-c** by the action of hydroxylamine hydrochloride in isopropyl alcohol the dioximes of *sym*-octahydroacridine-1,8-diones **4a-c** were isolated with yields of 79-82%. The process probably takes place through the formation of the corresponding decahydroacridinediones, the subsequent oxidation and oximation of which lead to the octahydro derivatives **4a-c** [9].

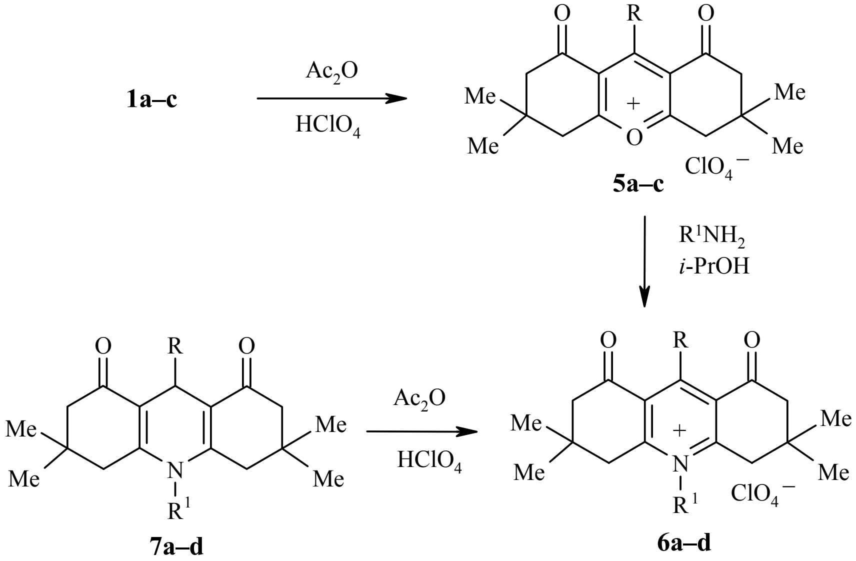


1, 2, 4 a R = H, **b** R = Me, **c** R = Ph; **1, 2 d** R = 4-MeOC$_6$H$_4$

The obtained results and the data from [3-8] make it possible to conclude that the nature of the reaction medium (ethyl alcohol, isopropyl alcohol, acetic acid, formic acid, alcohol–acid medium, DMSO) does not affect the direction of recyclization and that the determining factor is the basicity of the amines. The transformation of the 1,8-dioxo-*sym*-octahydroxanthenes into hydroacridine-1,8-diones only takes place smoothly under the influence of ammonia and amines whose basicity is comparable with the basicity of ammonia and hydroxylamine. Weakly basic aromatic amines do not enter into reaction with 1,8-dioxo-*sym*-octahydroxanthenes at all, while strong bases such as benzylamine promote their destructive cleavage with the formation of 3-N-R-5,5-dimethylcyclohex-2-enones.

In contrast to the *sym*-octahydroxanthene-1,8-diones, the recyclization of their salts in the presence of amines should take place in a more well-defined manner.

Since the oxidation of *sym*-octahydroxanthene-1,8-diones to the respective salts had not been realized before, we proposed a method for the production of the latter by the oxidation of compounds **1a-c** with acetic anhydride in the presence of perchloric acid. The 1,8-dioxo-*sym*-octahydroxanthylium perchlorates **5a-c** were isolated with yields of 48-64% by boiling the initial reagents for 6-8 h.



5 a R = H, **b** R = Me, **c** R = Ph; **6, 7 a,b** R = H, **c** R = Me, **d** R = 4-MeOC$_6$H$_4$,
a,c,d R^1 = Me, **b** R^1 = Ph

It was established that heating of the salts **5a**,**b** (7 h) in isopropyl alcohol, saturated with a fivefold molar excess of methylamine or containing an equimolar amount of aniline, leads irrespective of the basicity of the amine to their recyclization to the N-R^1-1,8-dioxo-*sym*-octahydroacridinium perchlorates **6a-c**, which were isolated with yields of 32-87%.

In the literature the synthesis of 1,8-dioxo-*sym*-octahydroacridinium salts is represented by a single publication [10], in which the oxidation of N-aryldecahydroacridine-1,8-diones unsubstituted at position 9 with nitrobenzene in the presence of perchloric acid was used for their production. The reaction was carried out at 130°C for 28 h, and the yields of the respective salts did not exceed 6-26%. For comparison we realized the oxidation of 9-R-N-R^1-decahydroacridine-1,8-diones **7a-d** under the conditions used for the synthesis of the 1,8-dioxo-*sym*-octahydroxanthylium salts. It was shown that the method can be used successfully not only for the oxidation of a pyran ring but also a 1,4-dihydropyridine ring. The transformation of the compounds **7a-d** into the salts **6a-d** takes 6-8 h, and the yields of the latter amount to 63-71%.

The structure of all the synthesized substances was established on the basis of data from IR and ^{1}H NMR spectroscopy and also, for the known compounds **2a-d**, **3**, **4a**,**c**, and **6b**, by comparison of their melting points with published data.

The IR spectra of the decahydroacridinediones **2a-d** are characterized by the presence of two strong absorption bands in the regions of 1585-1620 and 1640-1660 cm^{-1}, corresponding to the stretching vibrations of the conjugated system of bonds C=C–C=O. In the spectra of these compounds the enamine NH group is characterized by absorption at 3250-3300 cm^{-1}. The spectra of the dioximes **4a-c** contain a strong broad absorption band in the region of 3150-3400 cm^{-1}, confirming the presence of an associated hydroxyl group. In the spectra of the salts **5** and **6** the stretching vibrations of the carbonyl group appear at 1700-1720 cm^{-1}, and the vibrations of the ClO_4^- ion at 1090-1110 cm^{-1}.

The ^{1}H NMR spectra of the decahydroacridinediones **2a-d**, the dioximes **4a-c**, and the salts **5a-c** and **6a-d** correspond fully to their structure (Table 1).

The most characteristic for compounds **2a-d** are the signals for the proton of the amino group, which appear in the form of a broad singlet in the region of 8.12-9.09 ppm, and the chemical shifts of the hydrogen atoms at position 9, which appear at 3.24 (compound **2a**) or 4.12-5.24 ppm. For the dioxime **4a** and the salts **6a**,**b** the signal of the proton at the $C_{(9)}$ atom is shifted downfield – 7.63-9.83 ppm. In the spectra of the dioximes the chemical shifts of the protons of the hydroxyl groups are in the region of 11.54-11.64 ppm.

TABLE 1. The ^{1}H NMR Spectra of Decahydroacridine-1,8-diones **2a-d**, Octahydroacridine-1,8-dione Oximes **4a-c**, and Salts **5a-c** and **6a-d**

Compound	Chemical shifts, δ, ppm (SSCC, *J*, Hz)				
	H_2-2,2, H_2-7,7, s	H_2-4,4, H_2-5,5, 4H, s	H_2-9,9 /H-9	$C(CH_3)_2$, s	other signals
2a	2.32 (4H)	2.18	3.24 (2H, s)	1.06 (12H)	9.09 (1H, br. s, NH)
2b	2.35 (4H)	2.23	4.12 (1H, m)	1.02 (6H), 1.06 (6H)	0.88 (3H, d, *J* = 6.4, 9-CH_3); 8.12 (1H, br. s, NH)
2c	2.32 (2H), 2.40 (2H)	2.20	5.24 (1H, s)	0.98 (6H), 1.08 (6H)	7.18-7.26 (5H, m, H_{Ph}); 8.24 (1H, br. s, NH)
2d	2.36 (2H), 2.44 (2H)	2.24	5.12 (1H, s)	1.00 (6H), 1.10 (6H)	3.72 (3H, s, OCH_3); 6.78 (2H, d, *J* = 8.5, H_{Ar}-2',6'); 7.22 (2H, d, *J* = 8.5, H_{Ar}-3',5'); 8.18 (1H, br. s, NH)
4a	2.38 (2H)	2.24	7.63 (1H, s)	1.12 (12H)	11.58 (2H, br. s, OH)
4b	2.40 (2H)	2.26	—	1.12 (12H)	1.06 (3H, s, 9-CH_3); 11.64 (2H, br. s, OH)
4c	2.42 (2H)	2.26	—	1.06 (6H), 1.12 (6H)	7.28-7.63 (5H, m, H_{Ph}); 11.54 (2H, br. s, OH)
5a	2.94 (2H)	2.77	9.83	1.20 (12H)	–
5b	2.91 (2H)	2.80	—	1.19 (12H)	1.16 (3H, s, 9-CH_3)
5c	2.99 (2H)	2.81	—	1.09 (6H), 1.18 (6H)	7.41-7.72 (5H, m, H_{Ph})
6a	2.92 (2H)	2.80	9.73 (1H, s)	1.20 (12H)	4.12 (3H, s, NCH_3)
6b	2.90 (2H)	2.76	9.74 (1H, s)	1.20 (12H)	7.63-7.72 (5H, m, H_{Ph})
6c	3.02 (2H)	2.74	—	1.16 (12H)	1.12 (3H, s, 9-CH_3); 3.66 (3H, s, NCH_3)
6d	2.98 (2H)	2.76	—	1.08 (6H), 1.18 (6H)	3.58 (3H, s, NCH_3); 4.01 (3H, s, OCH_3); 7.08 (2H, d, *J* = 8.6, H_{Ar}-2',6'); 7.56 (2H, d, *J* = 8.6, H_{Ar}-3',5')

TABLE 2. The Characteristics of the Synthesized Compounds

Compound	Empirical formula	Found, % / Calculated, %			mp, °C	Yield, %
		C	H	N		
4b	$C_{18}H_{25}N_3O_2$	68.74 68.57	7.99 7.94	13.21 13.33	267-269	80
5a	$C_{17}H_{27}ClO_7$	54.27 53.90	7.00 7.13	—	217-219	48
5b	$C_{18}H_{29}ClO_7$	54.83 55.03	7.52 7.39	—	189-191	53
5c	$C_{23}H_{25}ClO_7$	61.17 61.54	5.89 5.57	—	201-202	64
6a	$C_{18}H_{24}ClNO_6$	56.49 56.03	6.35 6.23	3.91 3.63	235-237	48 (67*)
6b	$C_{23}H_{26}ClNO_6$	61.79 61.68	5.99 5.85	3.42 3.13	283-285	32 (71*)
6c	$C_{19}H_{26}ClNO_6$	57.38 57.07	6.92 6.51	3.31 3.50	182-184	87 (63*)
6d	$C_{25}H_{30}ClNO_7$	60.85 61.04	6.41 6.10	3.13 2.85	236-237	65*

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* The yields of the products obtained from compounds **7a-d**.

Thus, by studying the transformations of 9-R-*sym*-octahydroxanthene-1,8-diones in amination and oxidation reactions it was possible to develop conditions for the production of decahydroacridine-1,8-diones, 9-R-*sym*-octahydroacridinedione dioximes, and 9-R-1,8-dioxooctahydroxanthylium and 9-R-10-R^1-1,8-dioxo-*sym*-octahydroacridinium salts from them.

EXPERIMENTAL

The IR spectra were recorded on a Specord M-80 instrument (suspensions in vaseline oil and hexachlorobutadiene). The ^{1}H NMR spectra were obtained on a Bruker AC-300 spectrometer (300 Hz) in deuterochloroform (compounds **2a-d**), DMSO-d$_6$ (compounds **4a-c**), and CF_3COOD (compounds **5a-c** and **6a-d**) with TMS as internal standard.

The reactions and the individuality of the compounds were monitored by TLC on Silufol UV-254 plates with 3:1:1 hexane–acetone–chloroform as eluant and iodine vapor as developer.

The 1,8-dioxo-*sym*-octahydroxanthenes **1a-d** were synthesized by familiar methods [1, 12], and the decahydroacridine-1,8-diones **7a-d** were obtained by the method in [9].

3,3,6,6-Tetramethyl-9-phenyl-1,2,3,4,5,6,7,8,9,10-decahydroacridine-1,8-dione (2c). A mixture of the xanthenedione **1c** (7.00 g, 20 mmol), formamide (2.70 g, 60 mmol), and formic acid (15 ml) was boiled with a reflux condenser for 6 h and was then poured into cold water (300 ml). After 12 h the precipitate was filtered off, washed with water, and recrystallized from isopropyl alcohol.

Decahydroacridinediones 2a,b,d. These compounds were obtained similarly.

3-(Benzylamino)-5,5-dimethylcyclohexen-2-one (3). A mixture of the xanthenedione **1c** (7.00 g, 20 mmol), benzylamine (2.14 g, 20 mmol), and formic acid (15 ml) was boiled with a reflux condenser for 6 h. It was then cooled, made alkaline with a 1M solution of potassium hydroxide to pH 6, and extracted with ether (3 × 40 ml). The extract containing N-benzylformamide was separated. The aqueous layer was made alkaline with a 1M solution of potassium hydroxide to pH 8 and evaporated. The dry residue was dissolved in 10 ml of anhydrous acetone and filtered, and 40 ml of ether was added. The precipitate was separated, washed with ether, and dried. We obtained 3.48 g (38%) of the enamino ketone **3**; mp 128-130°C (ethanol) (mp 128-130°C [13]). ^{1}H NMR spectrum, δ, ppm, (*J*, Hz): 9.24 (1H, br. s, NH); 7.22 (5H, m, H_{Ph}); 5.12 (1H, s, CH); 4.42 (4H, d, $J = 6.2$, N–CH_2); 2.26 (2H, s, CH_2); 2.13 (2H, s, CH_2); 0.98 (6H, s, $2CH_3$).

The enamino ketone **3** is formed similarly from the xanthenediones **1a**,**b**,**d** with yields of 28, 36, and 42% respectively.

3,3,6,6-Tetramethyl-9-phenyl-1,2,3,4,5,6,7,8-octahydroacridine-1,8-dione Dioxime (4a). A mixture of the xanthenedione **1c** (7.00 g, 20 mmol), hydroxylamine hydrochloride (5.56 g, 80 mmol), and 2-propanol (50 ml) was boiled with a reflux condenser for 6 h. It was then cooled and poured into cold water (300 ml). After 12 h the precipitate that formed was filtered off, washed with water, and recrystallized from ethanol.

Dioximes 4a,b. These compounds were obtained similarly from the xanthenediones **1a**,**b**.

Compounds 2a-d and 4a,c. 2a, yield 71%; mp 300-302°C (mp 301-303°C [11]); **2b**, yield 78%; mp 255-257°C (mp 256-258°C [14]); **2c**, yield 82; mp 289-291°C (mp 290-291°C [11]); **2d**, yield 79%; mp 271-273°C (mp 270-272°C [15]); **4a**, yield 79%; mp 279-280°C (mp 280°C [11]); **4c**, yield 82%; mp 249-250°C (mp 250°C [16]). Compound **6b**, yield 6-25% (mp 284-285°C [10]).

1,8-Dioxo-3,3,6,6-tetramethyl-9-phenyl-1,2,3,4,5,6,7,8-octahydroxanthylium Perchlorate (5c). A mixture of xanthenedione **1c** (7.00 g, 20 mmol), acetic anhydride (30 ml), and perchloric acid (calculated on 100% $HClO_4$) (20 mmol) was boiled with a reflux condenser for 6 h. It was then cooled, and absolute ether (200 ml) was added. The oily precipitate was separated, isopropyl alcohol (20 ml) was added, and the mixture was heated to boiling and cooled. After 4 h the crystals that separated were filtered off, washed with isopropyl alcohol, and dried. The product was recrystallized from isopropyl alcohol.

Perchlorates 5a,b. These compounds were obtained similarly from the xanthenediones **1a**,**b**.

3,3,6,6,9,10-Hexamethyl-1,8-dioxo-1,2,3,4,5,6,7,8-octahydroacridinium Perchlorate (6c). A mixture of compound **5b** (3.77 g, 10 mmol) and 2-propanol (20 ml), containing methylamine (1.55 g, 50 mmol), was boiled with a reflux condenser for 7 h. It was then cooled, and 70% perchloric acid (2 ml) was carefully added. After 4 h absolute ether (100 ml) was added to the solution, and the precipitate was filtered off, washed with ether, and dried. The product was recrystallized from isopropyl alcohol.

Salt 6a. This salt was obtained similarly from the perchlorate **5a**. If the methylamine is replaced by an equivalent amount of aniline the salt **6b** is formed.

9-(4-Methoxyphenyl)-3,3,6,6,10-pentamethyl-1,8-dioxo-1,2,3,4,5,6,7,8-octahydroacridinium Perchlorate (6d). A mixture of acridinedione **7d** (4.01 g, 10 mmol), acetic anhydride (15 ml), and perchloric acid (calculated on 100% $HClO_4$) (10 mmol) was boiled with a reflux condenser for 6 h. It was then cooled, and absolute ether (100 ml) was added. The oily precipitate was separated, isopropyl alcohol (10 ml) was added, and the mixture was heated to boiling and cooled. The product was recrystallized from isopropyl alcohol.

Perchlorates 6a-c. These compounds were obtained similarly from the xanthenediones **7a-c**.

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