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REACTIONS OF 2(3′-OXOALKYL)-1,3-CYCLOHEXANEDIONES WITH NITROGENOUS REAGENTS

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Condensed 1,4-dihydropyridines, which do not contain a substituent in position 4 and which are formed in the reaction of 2-(3′-oxoalkyl)-1,3-cycohexanediones with ammonium acetate in acetic acid, undergo disproportionation. Pyridine bases are formed as the result of two competing reactions: disproportionation and oxidation of 1,4-dihydropyridines, intermediates in the heterocyclization of oxo-1,3-diketones with participation of the nitrogen atom, by air oxygen.

The influence of the nature of nitrogenous reagents and of the reaction conditions on the conversion of 1′-3′-disubstituted (2-(3′-oxopropyl)-cyclohexane-1,3-diones has been studied in [1, 2]. It was found that in the reaction with ammonia in ethanol 2,4-disubstituted 5-oxo-1,4,5,6,7,8-hexahydroquinolines are formed, while 5-oxo-5,6,7,8-tetrahydroquinolines are obtained mainly with ammonium acetate in acetic acid [1]. The action of hydroxylamine hydrochloride leads to isomerization and the oximes of the 2,3-disubstituted 5-oxo-5,6,7,8-tetrahydroquinolines are obtained instead of the expected oximes of 2,4-disubstituted 5-oxo-5,6,7,8-tetrahydroquinolines [2].

By exploring the influence of the nature of the substituents in the side chain of the heptacyclic triketones we found that the latter, containing electron-donor substituents, undergo deeper conversions with ammonium acetate by forming 5-oxotetrahydroquinolines. The triketones, which contain electron-acceptor substituents, give 5-oxohexahydroquinolines with the same reagent. With hydroxylamine, the former isomerize easily and more completely, while the latter are not isomerized.

The results of the investigations suggest that the nature of the substituents in the molecules of the "heptacyclic" triketones has a significant influence on their conversions with nitrogenous reagents.

TABLE 1. Characteristics of Synthesized Compounds IIb-d, III, IV, Va-d

Compound	Empirical formula	mp, °C	IR spectrum, cm				
			$\nu_{C=O}$	ν_{N-H}	pyridine	$\nu_{C=C}$	ν_{OH}
IIb	$C_{17}H_{19}NO$	192...194	1665	3280	—	1580...1620	—
IIc	$C_{13}H_{17}NO$	167...171	1620	3285	—	1520...1585	—
IId	$C_{15}H_{21}NO$	206...208	1600	3240	—	1580...1620	—
IIIa	$C_{15}H_{13}NO$	128...128,5	1680	—	1560, 1240	—	—
IIIb	$C_{17}H_{13}NO$	71,5...73	1680	—	1560, 1240	—	—
IIIc	$C_{13}H_{15}NO$	92...93	1680	—	1560, 1240	—	—
IIId	$C_{15}H_{19}NO$	86...87	1680	—	1560, 1240	—	—
IVa	$C_{15}H_{17}NO$	258...259	1570	3220	—	1520	—
IVb	$C_{17}H_{21}NO$	240...241	1572	3220	—	1524	—
IVc	$C_{13}H_{19}NO$	189...191	1580...1600	—	—	1450...1530	—
IVd	$C_{15}H_{23}NO$	191...192	1600	3240	—	1515...1570	—
Va	$C_{15}H_{14}N_2O$	185...187	—	—	1550	—	3230
Vb	$C_{17}H_{18}N_2O$	215...217	—	—	1550	—	3220
Vc	$C_{13}H_{16}N_2O$	242...243	—	—	1550...1560	—	3150
Vd	$C_{15}H_{22}N_2O$	251...253	—	—	1550...1560	—	3170

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TABLE 2. Reaction of Triketones Ia-d with Ammonia in Ethanol

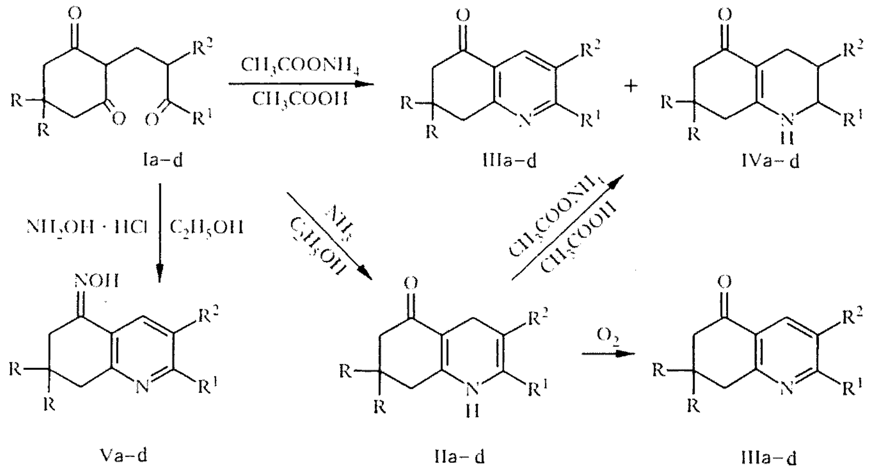
Initial triketone	End products	Yield, %
Ia	IIIa	93
Ib	IIb	80
	IIIb	12
Ic	IIc	57
	IIIc	30
Id	IId	72
	IIId	21

We have attempted to explain the influence of the degree of substitution on the relationship between the above triketones and the nitrogenous reagents. The present article investigates the reactions of 2-(3′-oxopropyl)-cyclohexane-1,3-diones Ia-d, unsubstituted in position 1′ of the side chain, with nitrogenous reagents.

In the presence of ammonia in boiling ethanol the triketones Ia-d undergo heterocyclization; a mixture of compounds is formed which includes the pyridine and the 1,4-di-hydropyridine rings (Tables 1 and 2), whereby the less substituted triketone undergoes the deeper conversion. Thus, the triketone Ia forms with the above reagent the 5-oxotetrahydroquinoline IIIa with a yield of 93%; on the other hand, the triketones Ib-d are converted with ammonia to the compounds IIb-d with yields of 70-80%, containing the 1,4-dihydropyridine ring.

Unexpected results were obtained in the reaction of the triketones Ia-d with ammonium acetate in acetic acid. It was found that besides the condensed pyridines IIIa-d the corresponding condensed tetrahydropyridines IVa-d are formed; according to our and literature data [3] they represent products of the disproportionation of condensed 1,4-dihydropyridines IIa-d.

The yields of the obtained bases IIIa-d and IVa-d are 41-43% (Table 3).



I—IV a $R = R^2 = H$, $R^1 = C_6H_5$; I—V b $R = CH_3$, $R^1 = C_6H_5$, $R^2 = H$; I—V c $R = H$, $R^1 + R^2 = (—CH_2—)_4$; I—V d $R = CH_3$, $R^1 + R^2 = (—CH_2—)_4$

A similar character of conversions has been described in [3] at different conditions: passage of ammonia through a boiling solution of 5,5-dimethyl-2-(3′-oxobutyl)-cyclohexane-1,3-dione in toluene.

We have studied the behavior of the triketones Ib, d at the conditions cited in [3]. It was found that by refluxing of the triketones Ib, d with ammonia in toluene disproportionation products IIIb, d and IVb, d are also formed.

The ratio of 5-oxohexahydroquinoline IIb to ammonium acetate in acetic acid also speaks in favor of the proposed mechanism. At these conditions the following disproportionation products are formed: 5-oxotetrahydroquinoline IIIb and 5-oxooctahydroquinoline IVb, with yields of 45 and 42% respectively (Table 3).

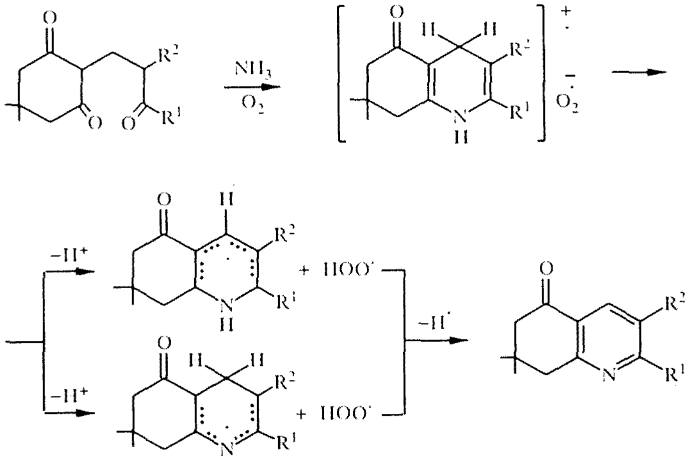
However, it was mentioned above that the action of ammonia in ethanol on the triketones Ia-d leads to heterocyclization to the pyridine bases IIIa-d or in mixture with the condensed 1,4-dihydropyridines IIa-d; no disproportionation products with the tetrahydropyridine IVa-d were detected in the reaction mixture. We assumed that at these conditions pyridinization was the result of the oxidation of 1,4-dihydropyridine bases IIa-d by air oxygen. In order to verify this assump-

TABLE 3. Reaction of Triketones Ia-d with Ammonium Acetate in Acetic Acid

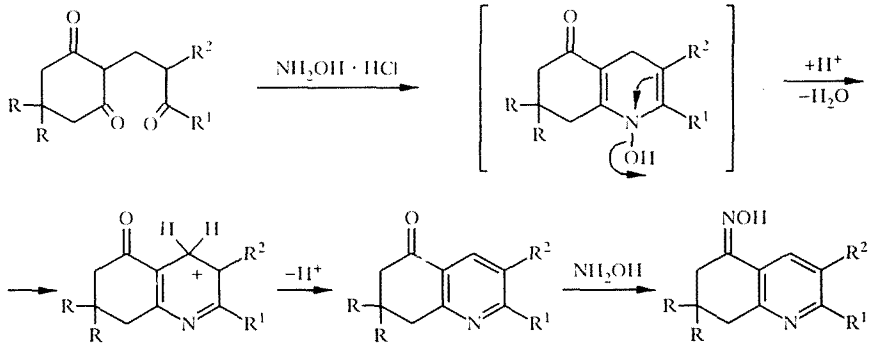
Initial triketone	End products	Yield, %		
		in air	in helium	in oxygen
Ia	IIIa	43	—	—
	IVa	42	—	—
Ib	IIIb	42	50	72
	IVb	40	48	27
Ic	IIIc	43	—	—
	IVc	42	—	—

tion, we reacted the triketones Ib, d with ammonium acetate in acetic acid in an atmosphere of argon and oxygen. It was found that the yields of the disproportionation products IIIb, d and IVb, d in argon were 46-47 and 43-45%, while in oxygen they were 66-72 and 18-27% respectively (Table 3).

The data presented lead to the conclusion that pyridinization of the 1,4-dihydropyridines IIa-d at normal conditions is the result of two competing processes: disproportionation and oxidation by air oxygen.



By examining the possibility of disproportionation of condensed 1,4-dihydropyridines IIa-d by the action of hydroxylamine hydrochloride in ethanol, it was established that at these conditions disproportionation does not occur: instead, quantitative pyridinization is taking place with the formation of 5-oxotetrahydroquinoline oximes Va-d (Table 1). The reaction mechanism is probably based on dehydration of the intermediate formed: the condensed 1-hydroxy-4H-dihydropyridine [2].



The composition and structure of the synthesized compounds was confirmed by spectroscopic investigations and elemental analysis.

The unambiguous assignment of the absorption bands in the longwave region of the IR spectra of compounds IIb-d and IVa-d is difficult due to the presence of a conjugated enamine system $HN_1{-}C_{8a}{=}C_{4a}{-}C_5{=}O$ [4]; this leads to a strong bathochromic shift of the absorption bands of the carbonyl group in the spectra of the compounds IIb-d at 1600-1665 cm^{-1} and of the C=C bond at 1580-1620 cm^{-1}, and for the compounds IVa-d at 1520-1570 and 1450-1515 cm^{-1} respectively. The conjugation affects also the absorption, corresponding to the vibrations of the NH group. It is shifted into the region of lower frequencies and appears in the region which is characteristic rather for the amides (3200-3300 cm^{-1}) than for amines.

In the IR spectra of 5-oxotetrahydroquinolines IIIa-d and of the corresponding oximes Va-d the absorption bands in the region 1240 and 1560 cm^{-1} correspond to the vibrations of the pyridine ring and at 1680 cm^{-1} to vibrations of the carbonyl group in position 5; the absorption bands at 3150-3280 cm^{-1} correspond to the stretching vibrations of the hydroxyl of the oxime group.

In the PMR spectra of 5-oxohexahydroquinolines IIb-d one can identify the proton at the N−H heteroatom in the region 5.18-5.44 ppm. A multiplet of the phenyl protons at 7.26-7.42, a singlet of the 3-H proton at 5.13, a doublet of the 4-H proton at 3.19-3.24, a multiplet of the cyclohexanone protons (CH × 2) at 2.21-2.26, and the protons of two methyl groups at 1.1 ppm are also observed for the compound IIb.

The spectra of compounds IVa, b contain signals of the protons of the N−H group at 5.08-6.17 ppm and singlets of the protons at the nodal atom $C_{(2)}$, besides the absorption bands of the aromatic protons in the region 7.19-7.28 and 7.40-7.96 ppm respectively. The remaining protons form a multiplet of the cyclohexane protons.

The character of the signals and the chemical shifts of the protons of compounds IVc, d are in good agreement with the data in [4] and confirm the structure of dodecahydroacridin-1-ones. In the spectra of the compounds IVc, d we have identified the signals of the protons of the N−H group at 4.4-4.65 and also at 3.42 and 1.68 ppm, which correspond to the protons at the nodal carbon atoms of the heterocycle $C_{(10a)}$ and $C_{(8a)}$.

EXPERIMENTAL

The IR spectra were taken on an UR-20 spectrometer in Vaseline oil and perchloro-1,3-butadiene. The PMR spectra were obtained on a Varian 80FTA spectrometer in $CDCl_3$ at a sample concentration of 0.1 M, with HMDS as the internal standard. The progress of the reaction was checked by TLC on sulufol UV-254 plates with hexane−ether−chloroform (2:1:1) as the mobile phase; the spots were revealed by exposure to iodine vapors. The elemental analysis data for C, H, and N corresponded to the theoretical values.

Reaction of Triketones Ia-d with Ammonia. Triketones Ia-d were exposed to ammonia in ethanol according to the procedure given in [1]. The yields and characteristics of the compounds formed are presented in Tables 1 and 2. Compound IIa has not been characterized because it is converted to compound IIa in recrystallization. PMR spectra; IIb: 7.42-7.26 (5H, m, C_6H_5), 5.18 (1H, s, N−H), 5.13 (1H, s, 3-H); 3.24-3.19 (2H, d, 4-H); 2.26-2.21 (4H, m, $2\times CH_2$); 1.05 (6H, s, $2\times CH_3$); IIc: 5.12 (1H, s, N−H); 3.67-1.1 (16H, m, $8\times CH_2$); IId: 5.44 (1H, s, N−H); 2.94-2.90 (4H, d, $2\times CH_2$); 2.50 (2H, s, CH_2-CO); 2.23-1.66 (8H, m, $4\times CH_2$); 1.06 ppm (6H, s, $2\times CH_3$).

Reaction of Triketones Ia-d Ammonium Acetate. A mixture of 10 mmole 2-(3′-oxopropyl)-1,3-cyclohexanedione Ia-d and 30 mmole ammonium acetate in 30 ml acetic acid was heated on a water bath for 48 h until the conversion of the initial triketone was complete. The mixture was poured into 200 ml water. The precipitate formed was subjected to fractional recrystallization, first from hexane and then from ethanol to separate 5-oxotetrahydroquinolines IIIa-d and 5-oxooctahydroquinolines IVa-d (Tables 1 and 3). PMR spectra; IIIa: 8.03-7.34 (5H, m, C_6H_5); 7.52 (1H, s, 3-H); 8.18 (14H, s, 4-H); 3.10 (2H, s, 6-H); 2.12 (2H, s, 7-H); 2.60 (2H, s, 8-H); IIIb: 8.6-7.42 (5H, m, C_6H_5); 7.51 (1H, s, 3-H); 8.25 (1H, s, 4-H); 3.09 (2H, s, 6-H); 2.08 (2H, s, 7-H); 2.53 (2H, s, 8-H); 1.13 (6H, s, $2\times CH_3$); IIIc: 7.94 (1H, s, 4-H); 2.15-3.14 (14H, m, $2\times CH_2$); IIId: 7.93 (1H, s, 4-H); 2.95-2.87 (6H, m, $3\times CH_2$); 2.50 (2H, s, CH_2—CO); 1.91-1.82 (4H, m, $2\times CH_2$); 1.07 (6H, s, $2\times CH_3$); IVa: 7.96-7.40 (5H, m, C_6H_5); 6.17 (1H, s, N−H); 3.60 (1H, s, 2H; 2.9 (2H, m, 4H); 2.08-2.0 (2H, d, 3H); 1.85-1.24 (6H, m, $3\times CH_2$); IVb: 7.28-7.19 (5H, m, C_6H_5); 5.08-4.45 (3H, m, NH and C_2—H); 2.32-2.16 (8H, m, $4\times CH_2$); 1.03 (6H, s, $2\times CH_3$); IVc: 4.65 (1H, s, N−H); 3.42 (1H, s, 2-H); 2.33-1.45 (10H, m, $5\times CH_2$); IVd: 4.40 (1H, s, N−H); 3.46 (1H, s, 2-H); 2.33-1.44 (8H, m, $4\times CH_2$); 1.02 (6H, s, $2\times CH_3$).

Reaction of Triketones Ib,d with Ammonia in Toluene. A sample of triketone Ib, d (1 mmole) in 20 ml toluene is refluxed for 3 h with a Dean-and-Stark attachment and continuous passage of ammonia through the solution. According to TLC data the compounds II, III, and IVb, d are present in the reaction mixture.

Disproportionation of 7,7-Dimethyl-5-oxo-2-phenyl-1,4,5,6,7,8-hexahydroquinoline (IIb). A sample of 2.84 g (11.2 mmole) IIb in 25 ml acetic acid is heated for 3 h on a water bath until the conversion of the initial material is complete.

The mixture is poured into 200 ml water, the precipitate formed is subjected to fractional recrystallization, first from hexane, then from ethanol; yield 1.3 g (45%) IIIb and 1.2 g (42%) IVb.

Reaction of Triketones Ia-d with Hydroxylamine Hydrochloride. The oximes Va-d were obtained from the triketones Ia-d by the procedure given in [2] with the yields of 72, 80, 90, and 96% respectively (Table 1). PMR spectra; Va: 8.97-7.39 (5H, s, C_6H_5); 8.24 (1H, s, 4-H)7.57 (1H, s, 3-H); 3.0 (2H, s, 6-H); 2.75 (2H, s, 8-H); 2.09 (2H, s, Hal—H); Vc: 7.85 (1H, s, 4-H); 2.80-1.86 (14H, m, 7×CH_2).

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