5-OXOHEXAHYDROQUINOLINES, CONDENSED ANALOGS OF 1,4-DIHYDROPYRIDINES. PREPARATION AND PROPERTIES

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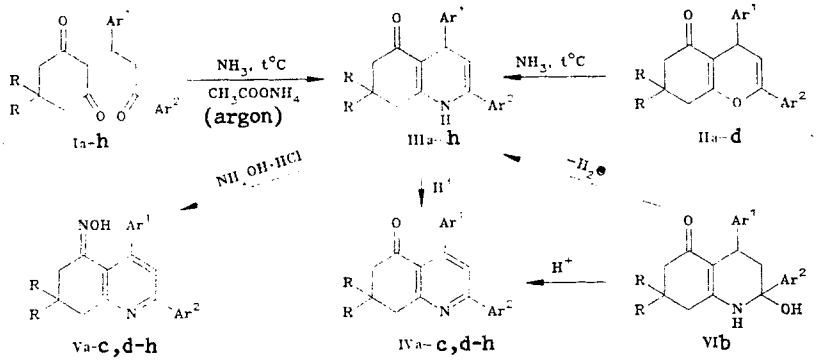
The optimum conditions for the preparation of 5-oxohexahydroquinolines have been established, and a probable reaction mechanism for their formation is proposed. Some reactions of these compounds have been examined.

1,5-Diketones react with ammonia to give compounds containing the 1,4-dihydropyridine ring [1]. There have, however, been no reports of this reaction with triketones such as 2-(3-oxypropyl)cyclohexane-1,3-dione.

In view of the considerable interest in compounds containing the 1,4-dihydropyridine moiety, which possess potential high biological activity and which are structurally similar to naturally occurring compounds [2], we have attempted to convert such triketones into condensed analogs of 1,4-dihydropyridine.

The reactions of triketones (Ia-h) with ammonia in ethanol and with ammonium acetate in glacial acetic acid have been examined. It was found that on treatment of the 2-(3-oxopropyl)cyclohexane-1,3-diones (Ia-h) with ammonia in ethanol, cyclization occurred to give the 1,4-dihydropyridines (IIIa-h) in high yields.



a—e R=H; f—h R=CH_3; a,f $Ar^1=Ar^2=C_6H_5$; b,g $Ar^1=C_6H_4$—OCH_3-4, $Ar^2=C_6H_5$; c, h $Ar^1=Ar^2=C_6H_4$—OCH_3-4; d $Ar^1=C_6H_4$—NO_2-4, $Ar^2=C_6H_5$; e $Ar^1=C_6H_5$, $Ar^2=C_6H_4$—OCH_3-4

We have shown previously [3] that triketones of this type containing electron-donor substituents undergo cyclization on boiling with ammonium acetate in glacial acetic acid, to give 5-oxotetrahydroquinolines.

We have sought to establish the factors responsible for the acid-catalyzed formation of 1,4-dihydropyridines in the reaction of ammonia with 2-(3-oxopropyl)cyclohexane-1,3-diones (Ia-h).

The mode of reaction of the triketones (Ia-h) with ammonium acetate in glacial acetic acid has been found to depend on the reaction temperature and the substituents present in the starting compound. Reducing the reaction temperature to 50-80°C in the case of triketones (Ia, f, g) resulted in the preferential formation of the 5-oxohexahydroquinolines (IIIa, f, g).

Introduction of an electron-acceptor group into the phenyl group (triketone (Id), resulted in a quantitative yield of the 5-oxohexahydroquinoline (IIId), irrespective of tem-

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TABLE 1. Properties of Products (IIIa-h) and (VIb)

Compound	Empirical formula	mp, °C	IR spectrum, cm^{-1}		Yield, %
			$\nu_{C=O}$	ν_{N-H}	
IIIa	$C_{21}H_{19}NO$	250...251	1670	3280	85, 90*, 83**
IIIb	$C_{22}H_{21}NO_2$	205...207	1665	3280	65, 84*
IIIc	$C_{23}H_{23}NO_3$	192...193	1665	3280	78, 92*
IIId	$C_{21}H_{18}N_2O_3$	184...186	1680	3225	97, 70**
IIIe	$C_{22}H_{21}NO_2$	195...196	1650	3280	70
IIIf	$C_{23}H_{23}NO$	193...195	1660	3290	57, 90*, 92***, 79**
IIIg	$C_{24}H_{25}NO_2$	203...204	1665	3290	55, 66*, 10**
IIIh	$C_{25}H_{27}NO_3$	200...201	1665	3300	24***
VIb	$C_{22}H_{23}NO_3$	184...185	1665	3280	50

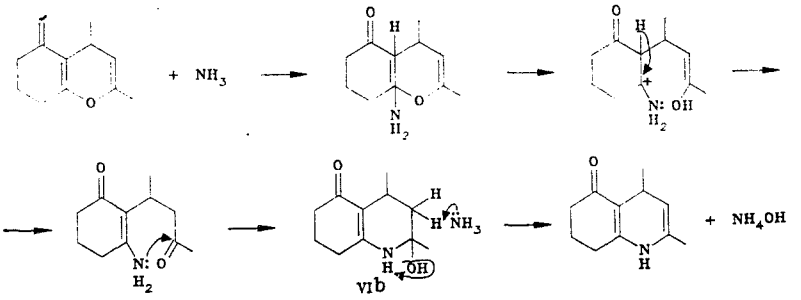
*Obtained in an autoclave or ampul.
**Obtained by reaction with ammonium acetate.
***Obtained by reaction with 25% aqueous ammonia.

perature. No pyridinization occurred in this instance even on boiling the acetic acid solution of the reaction mixture.

It was also found that the formation of 1,4-dihydropyridines was facilitated by exclusion of atmospheric oxygen. For example, heterocyclization of the triketones (Ia, f) with ammonium acetate in boiling acetic acid under argon afforded the 1,4-dihydropyridines (IIIa, f). The presence of the electron-donor methoxy substituent in the phenyl group of the triketone (Ig) facilitates the formation of the pyridine base from the initially formed 5-oxyhexahydroquinoline (IIIg), so that the yield of the latter in an argon atmosphere is low (Table 1).

In view of the accessibility of 5-oxotetrahydrochromenes (IIa-d) [4], we examined their recyclization on treatment with ammonia in ethanol. Under these conditions, the oxotetrahydrochromenes (IIa-d) were converted smoothly into the corresponding 5-oxohexahydroquinolines. The optimum conditions for the formation of condensed 1,4-dihydropyridines, either from triketones or from 5-oxotetrahydrochromenes are provided by carrying out the reaction in an ampul or an autoclave. Under these conditions a higher concentration of ammonia is present, and the absence of atmospheric oxygen prevents the oxidation of the 1,4-dihydropyridines formed. This is well shown by the heterocyclization of the triketones (Ia-c) and (If, g), and the recyclization of the oxochromenes (IIa-d) (Table 1).

A probable mechanism for the recyclization of the 5-oxotetrahydrochromenes (IIa-d) is as follows:



It appears that ammonia adds initially to the C=C double bond of the 5-oxotetrahydro-4H-chromene, followed by opening of the pyran ring. This reaction sequence is supported by the fact that in the case of the 5-oxotetrahydrochromene (IIb) the recyclization product is (VIb). The latter is readily dehydrated to the 5-oxohexahydroquinoline (IIIb), and on heating in acid is converted into the 5-oxo-tetrahydroquinoline (IVb).

The dihydropyridine ring in 5-oxohexahydroquinolines (IIIa-g), unlike that in oxoindenopyridines [5], is not cleaved by treatment with mineral acids. On heating in glacial acetic acid, however, they are readily oxidized (apart from IIId) to the 5-oxotetrahydroquinolines (IVa-c, e-g). Reaction of the 5-oxohexahydroquinolines (IIIa-c, e-g) with hydroxylamine hydrochloride gives the pyridine bases (Va-c, e-g), the carbonyl group being simultaneously oximated.

TABLE 2. PMR Spectra of 5-Oxo-1,4,5,6,7,8-hexahydroquinolines (IIIa-c, e, f)

Compound	Chemical shifts, δ, ppm						J, Hz	
	N—H, s	4-Ar[1], 2-Ar[2], m	3-H, d	4-H, d	—OCH$_3$, s	6-H, 7-R, 8-H	$^3J_{3,4}$	$^4J_{1,3}$
IIIa	5,74	7,37 ... 7,22	5,24	4,73	—	2,59 ... 1,90 m	5,3	1,9
IIIb	5,85	7,37 ... 6,71	5,22	4,68	3,72	2,54 ... 1,92 m	5,3	1,9
IIIc	5,78	7,37 ... 6,64	5,13	4,67	3,73, 3,79	2,56 ... 1,94 m	5,4	1,9
IIIe	5,81	7,48 ... 6,80	5,14	4,72	3,79	2,45 ... 1,70 m	5,3	1,8
IIIf	6,22	7,45 ... 7,07	5,25	4,70	—	1,05 (3H), 0,97 (3H)	5,2	1,8

The composition and structures of the products were established by their elemental analyses and spectral data (Tables 1 and 2). The IR spectra of the 5-oxohexahydroquinolines (IIIa-h) showed characteristic absorption for $\nu_{C=C}$ in the 1,4-dihydropyridine ring at 1640-1645 and 1675-1680 cm^{-1}. Conservation of the carbonyl group is shown by the presence of absorption at 1660-1670 cm^{-1}. The absorption at 3280-3300 cm^{-1} is attributed to N—H stretching vibrations.

The PMR spectra of the 5-oxohexahydroquinolines (IIIa-c, e, h) show, in addition to multiplets for the aromatic protons (7.48-6.64 ppm) and the alicyclic protons (2.59-1.7 ppm), doublets for the 3-H protons (5.13-5.24 ppm) and 4-H (4.74-4.68 ppm), together with a characteristically broad singlet for the N—H proton (5.74-6.22 ppm).

EXPERIMENTAL

IR spectra were obtained on a UR-20 in vaseline grease and perchloro-1,3-butadiene. PMR spectra were obtained on a Varian-80FTA in $CDCl_3$ at 30°C and a concentration of 0.1 mole/liter, internal standard HMDS. The progress of the reactions was followed by TLC on Silufol 254 plates in the system hexane—ether—chloroform (2:1:1), visualized with iodine vapor. The elemental analyses for C, H, and N were in agreement with the calculated values.

7,7-Dimethyl-2,4-diphenyl-5-oxo-1,4,5,6,7,8-hexahydroquinoline (IIIf, $C_{23}H_{23}NO$). A. A suspension of 5 g (13 mmole) of the triketone (If) in 50 ml of absolute ethanol was saturated with ammonia for 18 h at 0°C, then at 80°C until all the starting material (If) had reacted. The mixture was then cooled, and the crystalline solid which separated was filtered off, washed with ethanol, dried, and recrystallized from ethanol—dioxane (1:1). Yield 3 g (57%).

Obtained similarly were the 5-oxohexahydroquinolines (IIIa-e, g, h) (Table 1).

B. A mixture of 5 g (13 mmole) of the triketone (If) and 50 ml of absolute ethanol, previously saturated with 20 g of ammonia, was heated in a sealed ampul or an autoclave for 20 h at 50-60°C. The mixture was then cooled, and the crystalline solid which separated was filtered off, dried, and recrystallized from ethanol—dioxane (1:1).

Obtained similarly were 5-oxohexahydroquinolines (IIIa-c, e, g).

C. A mixture of 3 g (8 mmole) of the triketone (If), 35 ml of 25% aqueous ammonia, and 20 ml of ethanol was heated for 20 h at 60-70°C in a sealed ampul. The crystalline solid which separated on cooling the reaction mixture was filtered off, dried, and recrystallized from ethanol—dioxane (1:1). Yield 2.6 g (92%).

D. A mixture of 5 g (16 mmole) of the chromene (IIa) and 100 ml of absolute ethanol, saturated with 20 g of ammonia, was heated for 20 h at 50-60°C in a sealed ampul. The mixture was then cooled, and the crystalline solid which separated was filtered off, dried, and recrystallized from ethanol—dioxane (1:1). Yield 3.71 g (75%).

Obtained similarly were the 5-oxohexahydroquinolines (IIIb-d).

2-Phenyl-4-(4-methoxyphenyl)-2-hydroxy-5-oxo-1,2,3,4,5,6,7,8-octahydroquinoline (VIb, $C_{22}H_{23}NO_3$). A mixture of 5.25 g (15 mmole) of the chromeme (IIb) and 100 ml of absolute ethanol, saturated with 20 g of ammonia, was heated for 20 h at 50-60°C in a sealed ampul. The mixture was cooled, and the crystalline solid which separated was filtered off, dried, and recrystallized from ethanol. Yield 3.72 g (68%).

7,7-Dimethyl-2,4-diphenyl-5-oxo-5,6,7,8-tetrahydroquinoline Oxime (Vf, $C_{23}H_{22}N_2O$). A mixture of 4 g (10 mmole) of the hexahydroquinoline (IIIf) and 0.91 g (13 mmole) of hydroxylamine hydrochloride in 40 ml of absolute ethanol was boiled for 10 h. The mixture was then cooled, poured into 100 ml of 2% aqueous sodium hydroxide, and the solid which separated was filtered off, washed with water, dried, and recrystallized from ethanol. Yield 4.1 g (95%).

Oximes (Va-c, e, g, h) were obtained similarly, and identified by mixed melting points with samples obtained as described in [6].

LITERATURE CITED

1. V. G. Kharchenko and S. N. Chalaya, 1,5-Diketones [in Russian], Izd. Sarat. Un-ta, Saratov (1977), p. 48.
2. M. Yu. Lidak. Khim. Geterosikl. Soedin., No. 1, 5 (1985).
3. V. G. Kharchenko, L. I. Markova, T. D. Kazarinova, and L. M. Yudovich, Khim. Geterosikl. Soedin., No. 7, 915 (1985).
4. V. G. Kharchenko, L. I. Markova, N. S. Smirnova, K. M. Korshunova, and G. I. Rybina, Zh. Org. Khim., 18, 2184 (1982).
5. U. Eisner and I. Kuthan, Chem. Rev., 72, 1 (1972).
6. L. I. Markova, T. D. Kazarinova, L. M. Yudovich, and V. G. Kharchenko, Khim. Geterotsikl. Soedin., No. 2, 209 (1990).

DIAZOCARBONYL DERIVATIVES OF HETEROCYCLES.

7.* SYNTHESIS, PROPERTIES, AND STRUCTURE OF 2,4-DIAZIDO-6-DIAZOACETYLPYRIMIDINE

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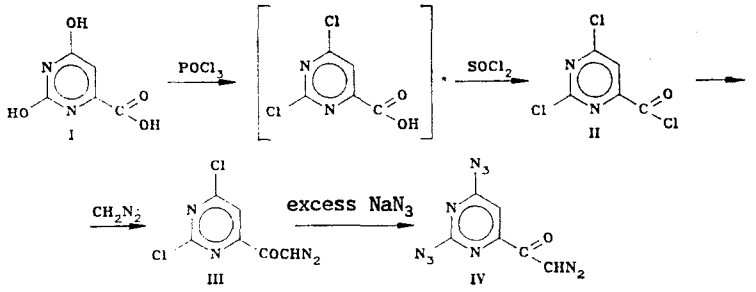
The reaction of 2,4-dichloro-6-diazoacetylpyrimidine with sodium azide to give 2,4-diazido-6-diazoacetylpyrimidine has been examined, and the crystal structure of the latter, and its 1,3-dipolar cycloadditions at the carbonyl group, studied.

In order to obtain novel heterocyclic derivatives of diazoketones, and to study their reactions in which the diazo-group is conserved, we have now synthesized 2,4-dichloro-6-diazoacetylpyrimidine, and examined its reaction with sodium azide.

We have previously reported the nucleophilic replacement of chlorine in some aliphatic diketones [2]. Reactions resulting in the replacement of chlorine by the azide function in chloropyrimidines are well known [3]. This reaction has been carried out for the first time with a diazocarbonyl derivative of dichloropyrimidine.



*For Communication 6, see [1].

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