REACTIONS OF 1,5-DIKETONES

IX.* REACTION OF 2,2'-METHYLENEDICYCLOHEXANONE WITH HYDRAZINE DERIVATIVES

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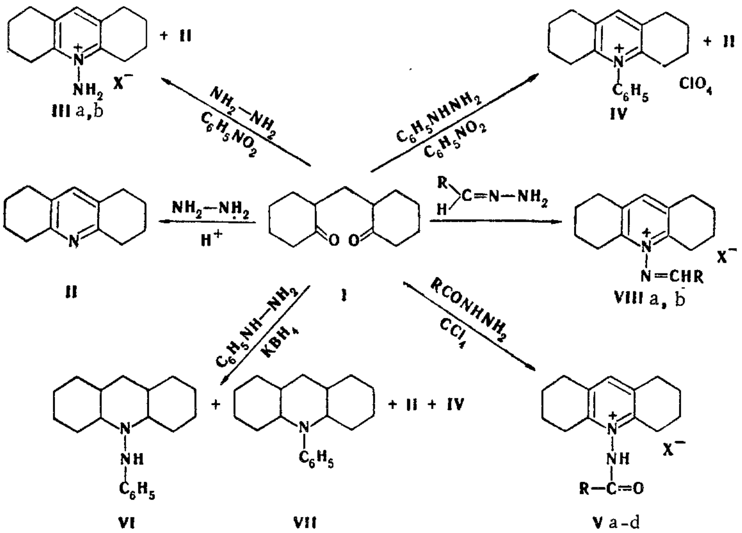
The reaction of 2,2'-methylenedicyclohexanone with hydrazine derivatives, which leads to sym-octahydroacridine, was studied. The possibility of obtaining 10-aminohydroacridine derivatives is demonstrated.

Continuing our study of the reaction of 1,5-diketones with ammonia derivatives, we have investigated the reaction of 2,2'-methylenedicyclohexanone (I) with hydrazine and its derivatives – phenylhydrazine, the hydrazones of several carbonyl compounds, and the hydrazides of acids.

The reaction of diketone I with hydrazine hydrate in acetic acid leads only to sym-octahydroacridine (II); the chief reaction product when a mixture of I and hydrazine hydrate in alcohol is refluxed is also II.

Like the reaction of I with primary amines [2], when the reaction is carried out in the presence of hydride-ion acceptors (nitrobenzene and CCl_4), 10-amino-sym-octahydroacridinium salts (III) are formed. However, their yields do not exceed 30%, since considerable amounts of II are formed along with them. The structure of III is confirmed by the IR spectra (amino group bands at 3300 and 3400 cm^{-1}), the formation of a hydrazone on treatment with p-nitrobenzaldehyde, and by alternative synthesis from sym-octahydroxanthylium perchlorate and hydrazine.



III a $X=ClO_4$; b $X=I$; V a $R=CH_3$, $X=ClO_4$; b $R=C_6H_5$, $X=ClO_4$; c $R=CH_3$, $X=Cl$;
d $R=C_6H_5$, $X=Cl$

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*See [1] for communication VIII.

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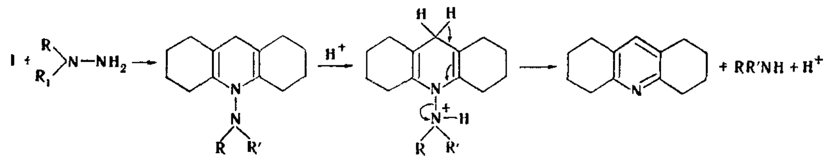
The formation of the corresponding octahydroacridinium salt was not observed when phenylhydrazine was used under the same conditions. The chief reaction product was II, and 10-phenyl-sym-octahydroacridinium salt IV and aniline were also isolated. The formation of these products can be explained by splitting out of aniline from the intermediate 10-phenylaminodecahydroacridine, during which a portion of the aniline reacts with diketone I via the scheme described in [2]. When the hydrazones of benzaldehyde, p-nitrobenzaldehyde, and benzophenone are introduced into the reaction with I, II is also the chief product. The corresponding sym-octahydroacridinium derivatives (VIII) were formed in low yield only with aldehyde hydrazones. In addition, the corresponding carbonyl compounds and their azines were isolated from the reaction mixtures, and ammonia was also detected. This sort of result is apparently explained by splitting out of aldehyde imine or of ketone imine from the intermediately formed decahydroacridine derivative; the imine is then hydrolyzed to give ammonia and a carbonyl compound; the latter reacts with unchanged hydrazone to give the azine. In contrast to the preceding cases, when the hydrazides of acetic and benzoic acid are introduced into reaction with I, the formation of II is not observed; 10-acylaminooctahydroacridinium salts (V) are obtained in good yields here. The IR spectra of these compounds contain absorption bands of a carbonyl group at ~1700 cm^{-1} and of an N−H group at 3180 cm^{-1}, while intense absorption at 1100 cm^{-1} is observed for the perchlorates. Thus this variant is the most convenient for the preparation of 10-aminooctahydroacridinium derivatives.

The results can be explained by assuming that the cleavage of decahydroacridine derivatives, which leads to II, is facilitated by protonation of the amine nitrogen atom:



In the case of acid hydrazides, the basicity of this nitrogen atom is markedly reduced, and oxidation of the decahydroacridine derivative by the hydride-ion acceptor becomes the major direction of the reaction.

We also carried out the reaction of diketone I with phenylhydrazine in the presence of hydride reducing agents (the hydroamination scheme [3]). Potassium borohydride in alcohol, acetic acid, and in alcohol−acetic acid mixtures, and lithium aluminum hydride in ether were used as the reducing agents. The target product − 10-phenylaminoperhydroacridine (VI) − could be obtained by using potassium borohydride in dilute acetic acid or in an acetic acid−alcohol mixture. The structure of VI was confirmed by hydrogenolysis over a platinized catalyst, which gives the known trans-syn-trans-perhydroacridine and aniline. In addition to VI, the reaction mixture yielded II, two stereoisomeric 10-phenylperhydroacridines (VII), which were described in [4], and IV. The formation of these products can be explained by the fact that the intermediately formed 10-phenylaminodecahydroacridine is only partially reduced by KBH_4, while the remainder splits out aniline via the scheme presented above. Aniline forms VII and IV on reacting with diketone I in a reductive medium.

EXPERIMENTAL

Reaction of I with Hydrazine Hydrate in Acetic Acid. A 2.1-g (0.01 mole) sample of I and 0.7 g (0.014 mole) of hydrazine hydrate were dissolved in 20 ml of 75 CH_3COOH, and the solution was allowed to stand for 36 h, after which it was diluted with water and extracted with chloroform. The aqueous layer was made alkaline with 50% NaOH, and 0.2 g of crystals (fraction I) were separated. The chloroform was removed from the extract by distillation, and the residue was treated with water. The mixture was filtered, and the filtrate was made alkaline with 50% NaOH to give 1.5 g of crystals (fraction II). The crystals of both fractions were identical, with mp 69-70° (from petroleum ether), and did not give a melting-point depression with a genuine sample of octahydroacridine II. The picrate had mp 200° and did not give a melting-point depression with a sample of the picrate of II. The yield of II was 1.7 g (90%).

Reaction of I with Hydrazine in the Presence of Hydride-Ion Acceptors. A. A mixture of 20.8 g (0.1 mole) of I, 6 ml of CH_3COOH, and 50 ml of nitrobenzene was heated to the boiling point, after which 5 g (0.1 mole) of hydrazine hydrate and 50 ml of nitrobenzene were added in portions, and the mixture was refluxed for 2 h. It was then cooled and washed with water (three 50-ml portions). The wash waters were made alkaline to pH 8 with sodium carbonate and extracted with ether; $NaClO_4$ or NaI solution was added to the aqueous layer, and the perchlorate (IIIa) or iodide (IIIb) were isolated in 30% yield. The ether extracts were combined with the nitrobenzene layer, and the mixture was vacuum-evaporated. The residue was treated with 15% HCl, and the acid extract was made alkaline with NaOH and extracted with ether. The ether was evaporated, and the residue was vacuum-distilled to give 4.3 g (22%) of II and 1.5 g of aniline.

B. A mixture of 5.0 g (0.024 mole) of I and 1.2 g (0.024 mole) of hydrazine hydrate in 25 ml of CCl_4 was refluxed for 9 h, after which it was extracted with 15% HCl. The acid extract was made alkaline to pH 8 with sodium carbonate and extracted with ether. As in part A, the aqueous layer yielded IIIa or IIIb in 11-13% yield. The ether extract yielded 53% II.

10-(p-Nitrobenzylideneamino)octahydroacridinium Perchlorate. A mixture of 4.2 g (0.014 mole) of IIIa and 2.1 g (0.014 mole) of p-nitrobenzaldehyde in 30 ml of alcohol was refluxed for 12 h, after which the alcohol was removed by distillation, and the residue was treated with 20 ml of acetone to separate the hydrazone in 53% yield. IR spectrum: 1640 cm^{-1} (C = N), 1360 and 1550 cm^{-1} (NO_2), 1100 cm^{-1} (ClO_4).

Reaction of I with Phenylhydrazine in the Presence of Nitrobenzene. A mixture of 10.2 g (0.05 mole) of I, 5.4 g (0.05 mole) of phenylhydrazine, and 3 ml of CH_3COOH in 50 ml of $C_6H_5NO_2$ was treated as in variant A of the preceding experiment to give 3.3 g (19%) of perchlorate IV (identified by a mixed-melting-point determination with a genuine sample [5]), 3.5 g (38%) of II, and 0.5 g of aniline.

Reaction of I with Hydrazones in the Presence of CCl_4. Equimolar amounts of I and the hydrazones of, respectively, benzaldehyde (1), p-nitrobenzaldehyde (2), and benzophenone (3) were dissolved in CCl_4, and the mixtures were refluxed for 1-3 h, cooled, and extracted with water (the water extract gave a positive test for ammonia with Nessler's reagent). Ammonium perchlorate solution was then added to the aqueous extract: in cases 1 and 2, perchlorates VIIIa (4% yield) or VIIIb (2% yield), respectively, precipitated. Compound VIIIb was identical to the hydrazone obtained from IIIa and p-nitrobenzaldehyde. In case 3, no perchlorate precipitated. The organic layer in cases 1 and 3 was treated with 15% HCl, and the acid extract was made alkaline with sodium carbonate to give 56% II for case 1 and 86% II for case 3. The organic layer yielded, respectively, 4% benzazine and 7% benzophenone azine, and the residue after separation of the azines was treated with 2,4-dinitrophenylhydrazine to give the hydrazones of, respectively, benzaldehyde (1%) and benzophenone (2%). The isolated azines and dinitrophenylhydrazones were identified by mixed-melting-point determinations with authentic samples.

10-Acylaminooctahydroacridinium Salts (Va-d). A. Perchlorates (Va, b). Equimolecular amounts of I and the hydrazides of acetic or benzoic acids in CCl_4 were refluxed for 1-2 h, after which the mixture was extracted with water. Ammonium perchlorate solution was added to the aqueous extract to isolate, respectively, 63% Va or 79% Vb.

B. Chlorides (Vc, d). Equimolar amounts of the components were dissolved in absolute benzene–CCl_4 (5 : 1), and the solution was refluxed for 2-3 h, after which the solvent was removed by distillation, and the residue was treated with absolute ether to isolate, respectively, 74% Vc and 51% Vd. In the latter case, the residue after treatment with ether was washed out with acetone.

Reaction of I with Phenylhydrazine in the Presence of KBH_4. A solution of 0.03 mole of phenylhydrazine in 10 ml of alcohol and a solution of 1.6 g (0.03 mole) of KBH_4 in 10 ml of water were added simultaneously with stirring in the course of 2-3 min to an ice-cooled solution of 7.0 g (0.03 mole) of I in 20 ml of CH_3COOH, and the mixture was allowed to stand at room temperature for 2 h. The resulting viscous mass was separated and dissolved in 50 ml of petroleum ether, and the solution was washed with 30 ml of acetic acid and water, and the petroleum ether was evaporated. The residue was treated with alcohol, during which it began to crystallize to give 40% of VI. The acetic acid extract was neutralized with sodium carbonate, and the resulting mixture was separated by preparative chromatography on activity-II Al_2O_3 in petroleum ether to give 1.56 g (27%) of II, 0.27 g of trans-anti-cis-VII with mp 127-130°, and 0.1 g of trans-syn-trans-VII with mp 108-109°. The aqueous layer after separation of the indicated mixture yielded 1.0 g (10%) of IV (by treatment with NH_4ClO_4). Compounds II, IV, and VII were identified by mixed melting-point determinations with authentic samples.

Hydrogenolysis of VI. A 3.34-g (0.01 mole) sample of VI in 200 ml of CH_3COOH was hydrogenated over an Adams catalyst. A total of 102 ml of hydrogen was absorbed (the calculated value is 224 ml). The catalyst was separated, and the filtrate was diluted with water to give 1.9 g of VI. The filtrate was treated with 20 ml of HCl (1 : 1), and the hydrochloride of trans-syn-trans-perhydroacridine (0.4 g) was separated. The hydrochloride yielded the base, with mp 89-90°, which was identical to an authentic sample. The filtrate after separation of the hydrochloride was made alkaline with NaOH to give aniline, which was identified as the benzanilide.

TABLE 1. 10-Aminohydroacridine Derivatives

Compound	mp, °C	Empirical formula	Found, %			Calc., %		
			C	H	N	C	H	N
IIIa	148—150	$C_{13}H_{19}ClN_2O_4$	52,1	6,5	9,3	51,6	6,3	9,3
IIIb	106—107	$C_{13}H_{19}IN_2$	—	—	8,6	—	—	8,5
Va	210—211	$C_{15}H_{21}ClN_2O_5$	52,5	6,4	8,2	52,2	6,1	8,1
Vb	203—204	$C_{20}H_{21}ClN_2O_5$	59,1	5,9	6,9	59,0	5,7	6,9
Vc	197—198	$C_{15}H_{21}ClN_2O$	64,2	7,7	—	64,2	7,5	—
Vd	199—200	$C_{20}H_{23}ClN_2O$	69,8	6,5	—	70,1	6,7	—
VI	141—142	$C_{19}H_{28}N_2$	80,5	9,8	—	80,3	9,8	—
VIIIa	183—184	$C_{20}H_{23}ClN_2O_4$	61,4	6,1	—	61,6	5,7	—
VIIIb	219—220	$C_{20}H_{22}ClN_3O_6$	55,5	5,3	10,0	55,1	5,1	9,6

The melting points and the analytical data for the newly prepared substances are presented in Table 1. The IR spectra of $CHCl_3$ solutions of the substances were recorded with a UR-20 spectrophotometer.

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