HYDRAZINOCYANATION OF 2,2'-METHYLENEDICYCLOHEXANONE IN AQUEOUS ALCOHOL

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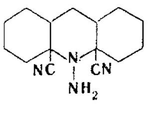
The reaction of 2,2'-methylenedicyclohexanone with HCN and hydrazine in aqueous alcohol was studied at various pH values. Conclusions were drawn regarding the spatial configurations of the reaction products.

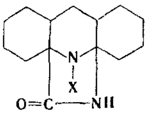
The hydrazinocyanation of 2,2'-methylenedicyclohexanone (I) in acetic acid gives one isomer of 10-amino-11, 14-dicyanoperhydroacridine [1]. It is known that, depending on the reaction conditions, different products are formed during hydrazinocyanation [2, 3].

In the present study we have investigated the hydrazinocyanation of diketone I in aqueous alcohol at different pH values. The reaction of the diketone with KCN and hydrazine hydrate in aqueous alcohol containing 2 moles of acetic acid per mole of diketone (pH 8) gives two stereoisomeric 10-amino-11,14-dicyanoperhydroacridines (IIa, b), the first of which is identical to the product of the reaction in acetic acid. At pH 9 (1 mole of acetic acid per mole of diketone) the reaction products are two stereoisomeric lactams of 10,11-diaminoperhydroacridine-14-carboxylic acid (VIa, b), two stereoisomeric iminoimides of 10-aminoperhydroacridine-11,14-dicarboxylic acid (VIIa, b), and dinitrile IIa. In the absence of acetic acid (pH 10), only lactams VIa, b are formed.

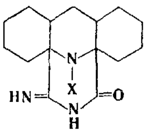
Compounds IIa and IIb, VIa and VIb, and VIIa and VIIb are stereoisomers; this is confirmed by the results of mass spectrometry (m/e 258 for IIa and IIb, 249 for VIa and VIb, and 276 for VIIa and VIIb) and by the IR spectra, which are extremely similar for each pair. The presence of an NH_2 group in VIa, VIb, and VIIa is confirmed by the formation of the corresponding hydrazones (VIIIa, VIIIb, and IXa) on treatment with benzaldehyde. The deamination of VIa and VIb leads to Xa and Xb. Product Xa is identical to the previously described lactam of 11-aminoperhydroacridine-14-carboxylic acid [4]. Compound Xb is the stereoisomer of Xa, as follows from the results of mass spectrometry (m/e 234 for both compounds) and the IR spectra, which are extremely similar. The IR spectra of VIa,b and Xa,b are typical for five-membered lactams: amide band II is absent at 1500-1600 cm^{-1}; the lactam structure of Xa,b is especially graphically revealed when their IR spectra are com-



IIa, b



VIa, b VIIIa,b Xa,b



VIIa,b, IXa, XIIIa

VIa,b, VIIa,b X=NH_2; Xa,b, XIIIa X=H; VIIIa,b,IXa X=N=CH—C_6H_5

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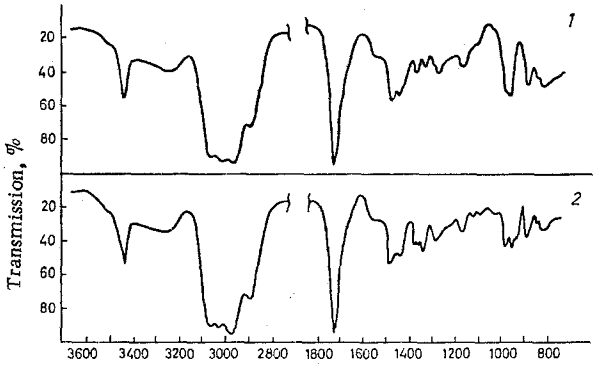
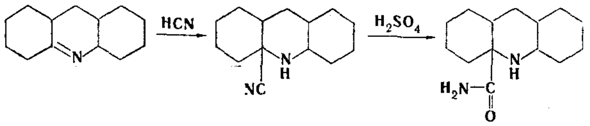


Fig. 1. IR spectra (in $CHCl_3$): 1) 10,11-diaminoperhydroacridine-14-carboxylic acid lactam (VIa); 2) 10,11-diaminoperhydroacridine-14-carboxylic acid lactam (VIb).

pared with the spectrum of perhydroacridine-11-carboxamide (XII), which we synthesized via the following scheme:

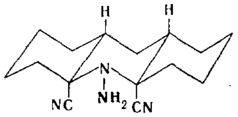


XI XII

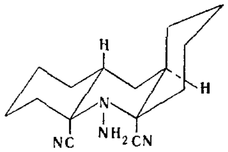
The II amide band appears in the IR spectrum of XII at 1560 cm^{-1}, and there is also a doublet characteristic for primary amides at 3400 and 3500 cm^{-1}.

The previously described [4] iminoimide of perhydroacridine-11,14-dicarboxylic acid is formed when iminoimide VIIa is deaminated.

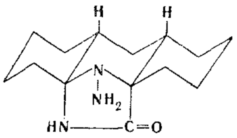
The available data make it possible to state some considerations regarding the spatial configurations of the compounds obtained. As previously demonstrated [1], dinitrile IIa leads to the known 11,14-dicyanoperhydroacridine and consequently has the trans-syn-trans configuration [4]. Isomeric dinitrile IIb has the trans-anti-cis configuration. The configurations of IIa,b are confirmed by the following data: the pure threo form of diketone I [5] undergoes hydrazinocyanation at pH 8 and 0°C to give primarily isomer IIb (IIb : IIa = 9 : 1). When a mixture of the threo and meso forms (formed in the synthesis of the diketone) is used, isomer IIb is obtained in somewhat lower yield than isomer IIa (IIb : IIa = 4 : 6). This serves as an indication of the anti orientation of the hydrogen atoms attached to C_{12} and C_{13} in isomer IIb and of the syn orientation in isomer IIa. By way of analogy, one may cite the results of the hydroamination of diketone I [6], in which β-perhydroacridine is formed from the threo form, while a mixture of α-and β-perhydroacridines is formed from a mixture of the threo and meso forms; the trans-anti-cis configuration was established for the β isomer, while the trans-syn-trans configuration was established for the α isomer [7]. The formation of two stereoisomeric iminoimides (VIIa,b) may serve as an indication of a cis-axial orientation of the CN groups in both dinitriles. Only lacatam VIa is formed in the hydrolysis of dinitrile IIa with dilute alkali; dinitrile IIb gives only lactam VIb. The reaction proceeds readily in both cases (1% alkali solution is sufficient). Since one of the reaction steps is dehydrocyanation, the ease of conversion may serve as an argument in favor of the fact that it originates from the 11 and 12 positions, and the CN group and the H atom attached to C_{12} should consequently be found in the trans orientation for both dinitriles. An examination of all of the possible configurations of dinitriles II with allowance for what has been stated above leads to the conclusion that only a lactam that differs from the lactam from dinitrile IIa can be formed from isomer IIb when it has the trans-anti-cis configuration.



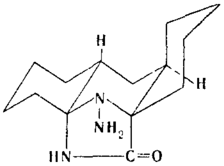
II a



II b



VIa



VIb

Dinitrile IIb is partially converted to isomer IIa on melting and also on prolonged storage; this is in agreement with the proposed configurations of the isomers, since IIa is the more stable isomer.

EXPERIMENTAL

Hydrazinocyanation of 2,2'-Methylenedicyclohexanone. A solution of 10.4 g (0.05 mole) of diketone I in 25 ml of alcohol was added at 0° in the course of 1 h to a mixture of 7.8 g (0.12 mole) of KCN, 2.6 ml (0.06 mole) of 99% hydrazine hydrate, 20 ml of water, 10 ml of alcohol, and acetic acid [0.12 mole (pH 8) or 0.06 mole (pH 9)]. When the pH was 10, no acetic acid was added. The mixture was stirred for another 30 min after the addition of the diketone. When the pH was 8, the mixture was diluted to twice its volume with water at the end of the reaction, and the reaction product was removed by filtration, washed with water, and dried. Dinitriles IIa and IIb were separated by column chromatography on Al_2O_3 with elution with hexane–diethyl ether (0 : 0) [sic]. In the case of the pure threo form, the total yield of dinitriles was 91%, and the ratio of IIa to IIb was 1 : 9; in the case of a mixture of the threo and meso forms, the overall yield was 95%, and the ratio of IIa to IIb was 6 : 4.

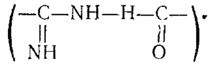
In the case of the pure threo form of the ketone at pH 9, at the end of the reaction, 6.5 g (52%) of lactam VIb was removed by filtration, 20 ml of water was added to the filtrate, and 0.5 g of iminoimide VIIb was separated. Further dilution of the filtrate gave 1.1 g of a mixture in which IIa, VIa, VIb, VIIa, and VIIb were detected by means of thin-layer chromatography (TLC) on Al_2O_3. When a mixture of the threo and meso forms was used, 2.2 g (18%) of lactam VIb, 1 g of iminoimide VIIa, and 6.3 g of a mixture of substances in which IIa, VIa, VIb, VIIa, and VIIb were detected, were isolated.

When the threo form of the diketone was used at pH 10, 7.8 g (63%) of lactam VIb was removed by filtration at the end of the reaction. Dilution of the filtrate with water gave 1.6 g (13%) of a mixture of VIa and VIb. In the case of a mixture of the threo and meso forms, 8.4 g (67%) of lactam VIa was removed by filtration at the end of the reaction, and dilution of the filtrate with water gave 3.6 g (29%) of isomer VIb.

All of the synthesized products were white crystalline substances. Compound IIa was identified by comparison with the previously described [1] preparation.

Compound IIb. This compound had mp 128-130° [from acetone–ether (1 : 30) by freezing out] and m/e 258. Found: N 21.4%. $C_{15}H_{22}N_4$. Calculated: N 21.7%. Mol. wt. 258. IR spectrum (in $CHCl_3$), cm^{-1}: 3380 (NH), 2240 ($C \equiv N$).

10,11-Diaminoperhydroacridine-14-carboxylic Acid Lactam (VIa). This compound had mp 172-174° [dioxane–heptane (1 : 2)] and m/e 249. Found: N 16.8%. Isomeric lactam VIb had mp 233-235° [dioxane–benzene (3 : 2)] and m/e 249. Found: N 16.9%. $C_{14}H_{23}N_3O$. Calculated: N 16.9%. Mol. wt. 249. IR spectra (in $CHCl_3$), cm^{-1}: 3420 (NH_2), 3180 (CO—NH), 1710 (C=O in five-membered lactams).

10-Aminoperhydroacridine-11,14-dicarboxylic Acid Iminoimide (VIIa). This compound had mp 225-226° (from dioxane) and m/e 276. Found: N 20.1%. Isomeric iminoimide VIIb had mp 188-190° [hexane–benzene (2 : 3)] and m/e 276. Found: N 20.4%. $C_{15}H_{24}N_4O$. Calculated: N 20.3%. Mol. wt. 276. IR spectrum (in $CHCl_3$): 1650, 1700 cm^{-1}  $\left(\underset{\|}{\overset{}{-\mathrm{C}}}\!\!\!\!\!\!\underset{\mathrm{NH}}{}{-}\mathrm{NH}{-}\mathrm{H}{-}\underset{\underset{\mathrm{O}}{\|}}{\mathrm{C}}{-}\right)$.

Reaction of Lactams VIa,b and Iminoimide VIIa with Benzaldehyde. A mixture of 0.02 mole of N-amino derivative and 0.6 ml of benzaldehyde in 3 ml of n-propanol was refluxed for 20 min to give 67% VIIIa, 67% VIIIb, and 68% IXa. All of the hydrazones obtained were light-yellow crystalline substances. Compound VIIIa had mp 201-201.5° (from ethanol). Found: C 75.4; H 8.3; N 12.5%. Compound VIIIb had mp 221-222° (from ethanol). Found: C 74.9; H 8.0; N 12.6%. $C_{21}H_{27}N_3O$. Calculated: C 74.8; H 8.0; N 12.5%. Compound IXa had mp 211-215° (from heptane). Found: C 72.6; H 7.9; N 15.6%. $C_{22}H_{28}N_4O$. Calculated: C 72.5; H 7.7; N 15.4%.

Deamination of Lactams VIa,b and Iminoimide VIIa. A solution of 0.1 g of $NaNO_2$ in 2 ml of water was added in the course of 5 min to a cooled (7-12°) solution of 0.35 g of VIa in a mixture of 2.5 ml of 98% acetic acid and 1 ml of concentrated HCl. The resulting precipitate was washed with 98% acetic acid and dissolved in water. The solution was made alkaline with 20% KOH to give 0.12 g of 11-aminoperhydroacridine-14-carboxylic acid lactam (Xa) with mp 200-202°, which, according to the IR spectrum and mixed-melting-point determination, was identical to an authentic sample [4]. A 4.24-g sample of VIb similarly yielded 1.44 g of isomeric lactam Xb with mp 196-200° (from benzene) and m/e 234. Found: N 11.8%. $C_{14}H_{22}N_2O$. Calculated: N 12.0%. Mol. wt. 234. See Fig. 1 for the IR spectrum. Deamination of 1.57 g of VIIa gave 1.06 g of perhydroacridine-11,14-dicarboxylic acid iminoimide (XIIIa), which was identified by a mixed-melting-point determination with an authentic sample [4].

11-Cyanoperhydroacridine (XI). A solution of 2.4 g of KCN in 5 ml of water was added to a solution of 5.5 g of $\Delta^{10(11)}$-dodecahydroacridine [4] in 30 ml of 98% acetic acid, and the mixture was stirred for 1 h, neutralized with saturated K_2CO_3 solution, and filtered to give 3.1 g (51%) of XI with mp 125-127° (from ethanol). Found: C 76.9; H 10.1; N 13.0%. $C_{14}H_{22}N_2$. Calculated: C 77.0; H 10.1; N 12.8%. IR spectrum, cm^{-1}: 3330 (NH), 2220 ($C \equiv N$).

Perhydroacridine-11-carboxylic Acid Amide (XII). A 0.5-g sample of nitrile XI was dissolved in 4 ml of concentrated H_2SO_4, and the solution was held at room temperature for 36 h, poured into a mixture of ice and 12 ml of concentrated NH_4OH, and filtered to give 0.47 g (90%) of amide XII with mp 176-178° (from ethanol). Found: C 71.7; H 10.3; N 11.5%. $C_{14}H_{24}N_2O$. Calculated: C 71.2; H 10.2; N 11.9%.

Alkaline Hydrolysis of 10-Amino-11,14-dicyanoperhydroacridines (IIa and IIb). A. A 2-g sample of IIa was refluxed for 6 h in a mixture of 30 ml of ethanol and 20 ml of 2% KOH solution. According to TLC on Al_2O_3, the mixture consisted of only VIa and the starting dinitrile. The mixture was cooled to give 0.82 g of a mixture of IIa and VIa. Evaporation of the residue gave 0.35 g of VIa with mp 171-173°, which was identified by means of an authentic sample.

B. A 0.085-g sample of IIb was refluxed for 2 h in a mixture of 5 ml of ethanol and 2 ml of 2% KOH, after which the mixture was evaporated to dryness, and the residue was crystallized from ethanol to give 0.03 g of VIb with mp 220-224°, which did not depress the melting point of an authentic sample.

The IR spectra were recorded with a UR-20 spectrometer, while the mass spectra were recorded with an MKh-1303 spectrometer.

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