REACTIONS OF 1, 5-DIKETONES*

I. Cycloaminocyanidation of 2, 2'-Methylenedicyclohexanone and Study of the Properties of the Resultant 11, 14-Dicyanoperhydroacridine

V. A. Kaminskii and M. N. Tilichenko

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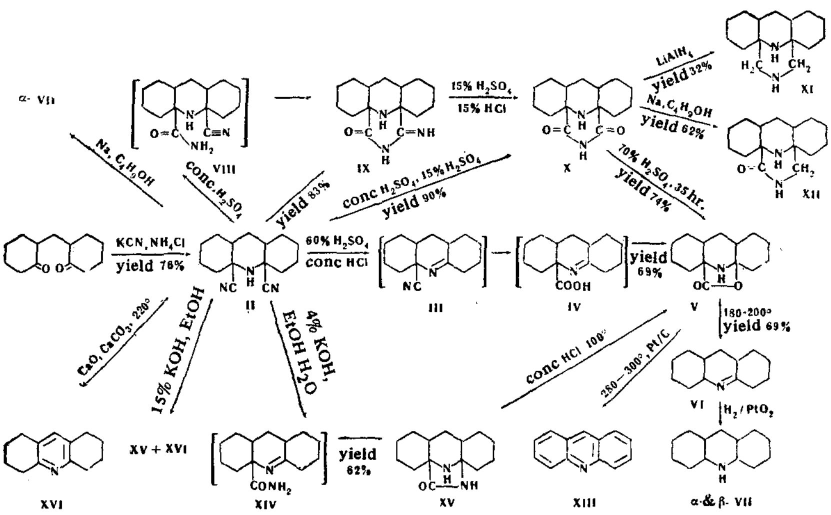
The action of potassium cyanide and ammonium chloride on 2, 2'-methylenedicyclohexanone gives 11, 14-dicyanoperhydroacridine, some of whose reactions are investigated. A number of tetracyclic compounds, representing a union of the hydroacridine system with the appropriate oxazolidine, imidazolidine, and piperazine rings, are synthesized. $\Delta^{10(11)}$-dodecahydroacridine is also obtained. The configuration of 11, 14-dicyanoperhydroacridine is inferred.

Despite the undoubted interest attaching to reactions of 1, 5-diketones, they represent an area of organic chemistry which so far has been little explored. Many reactions typical of monoketones remain almost or completely uninvestigated. An example of such reactions untouched on until recently is aminocyanidation of 1, 5-diketones. Recently the present authors briefly reported that cyanoamination of 2, 2-methylenedicyclohexanone (I) gave 11, 14-dicyanoperhydroacridine (II) [2]. The present paper gives a developed description of the research, which proceeded thus:



The reaction proceeds like aminocyanidation and cyclization (with closure of the piperidine ring), and hence can be called cycloaminocyanidation. This reaction has been found to take place with a number of other 1, 5-diox compounds [3, 5]; aminocyanidation also takes place with 1, 4-dioxo compounds, though with closure of the pyrrolidine ring [5].

Hydrolysis of dicyanide II with 60% sulfuric acid at 120° C, or concentrated hydrochloric acid at 100° C, gives the lactone of 14-hydroxyperhydroacridine-11-carboxylic acid V, a derivative of 5-oxazolidone.

Probably the reaction takes place via stages III and IV. At 280°–300° C in the presence of Pt/C, lactone V is converted to acridine XIII. The structure of V is also confirmed by its IR spectrum, lactone carbonyl (1780 cm^{-1}) and NH group (3280 cm^{-1}) bands being found. In absolute ethanol lactone V titrates with the speed of a free acid, neturalizing one equivalent of alkali. This shows the great readiness with which lactone V isomerizes to acid IV.

At 180° C lactone V splits off a molecule of CO_2, giving the hitherto unknown $\Delta^{10(11)}$-dodecahydroacridine VI; probably this involves prior isomerization to 14-carboxy-$\Delta^{10(11)}$-dodecahydroacridine IV. The structure of VI is confirmed by its IR spectrum, and by catalytic hydrogenation. The IR spectrum has a band at 1670 cm^{-1} (>C═N—) but not a N—H bond band. On hydrogenation, one molecule of hydrogen is absorbed to give a mixture of known α- and β-perhydroacridines [6]. Hydroacridine VI readily undergoes autooxidation; Cohen and Witkop [7] found the same sort of thing with $\Delta^{1(9)}$-octahydroquinoline, the bicyclic analog of VI.

Treatment of dicyanide II with concentrated sulfuric acid converts it to the imidoimide of 11, 14-perhydroacridinedicarboxylic acid IX; the latter is probably formed by isomerization of cyanoamide VIII. Iminoimide IX is readily hydrolyzed by dilute mineral acids to the imide of 11, 14-perhydroacridinedicarboxylic acid X. If treatment is first with concentrated, then with 15% sulfuric acid, the change from dicyanide II to imide X is effected in a single phase. Some other dicyanides are hydrolyzed sim-

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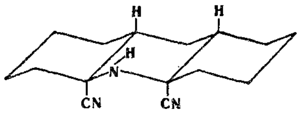
*For previous papers see [1]

ilarly [8, 9]. The imide X proved to be very resistant to hydrolysis; 35 hours heating in 70% sulfuric acid led only to destructive hydrolysis, involving splitting off the elements of formic acid and formation of lactone V.

Lithium aluminum hydride reduction of imide X gives 11, 14-dimethyleneiminoperhydroacridine XI. Reduction with sodium in butanol gives the lactam of 14-aminomethylperhydroacridine-11-carboxylic acid XII.

In alkaline solution dicyanide II undergoes changes that depend on the reaction conditions. Thus the action of a 4% aqueous ethanolic solution of alkali gives the lactam of 14-aminoperhydroacridine-11-carboxylic acid XV; obviously the process goes through stage XIV. Heating (100° C) lactam XV with concentrated hydrochloric acid converts it to lactone V. The action of more concentrated alkali on dicyanide II gives mainly sym-octahydroacridine XVI, and some lactam XV. The octahydroacridine XVI is also formed by heating (220° C) dicyanide II with CaO + $CaCO_3$ mixture. Treatment of dicyanide II with sodium in butanol gives α-perhydroacridine (α-VII).

The ease with which ring closure takes place in the conversions II → IX and II → X shows that both cyanide groups in II are cis-axial. That the cyano groups are axial is confirmed by the transformations II → IV and II → XV. Dehydrocyanidation, taking place under the above reaction conditions, with splitting off of one (II → III and II → XIV → XV) and two (II → VII and II → VII and II → XVI) molecules of HCN, can be taken to indicate that the H atom at the nitrogen and H atoms at C_{12} and C_{13} are trans with respect to the CN groups. Formation from II of α-perhydroacridine (II → V → VI → VII), where the C_{12} and C_{13} hydrogens are known to be cis, is evidence in favor of their being cis in the above case too. Hence it follows that the configuration of dicyanide II is probably that shown in formula XVII, corresponding to one of the two theoretically possible meso forms of II.



XVII

EXPERIMENTAL

11, 14-Dicyanoperhydroacridine (II). A mixture of 25 g methylenedicyclohexanone I in 250 ml EtOH and 28 g 60% KCN plus 13. 5 g NH_4Cl in 300 ml water was kept at 55°–65° C for 5 hr. The crystals of dicyanide II were filtered off with suction, washed with 50% EtOH, and then with water. Yield 21. 9 g (76%), colorless quadrilateral and hexagonal tablets, soluble in benzene, dioxane, acetone, and $CHCl_3$, slightly soluble in ether and cold EtOH, almost insoluble in heptane, mp 168°–170° C. Found: C 73. 82; 74. 01; H 8. 85; 8. 76; N 17. 19; 17.9%, calculated for $C_{15}H_{21}N_3$: C 74.07; H 8.64; N 17.29%. IR spectrum in (KBr): cm^{-1}: 3320 (N–H), 2240 (very weak).

Dehydrogenation. a) In the presence of CaO + $CaCO_3$. 1 g Dicyanide II was heated to 220° C with 5 g CaO + $CaCO_3$ (1:1). HCN was found in the vapor evolved (Feigl's test [10] with Cu acetate, and with Cu acetate and benzidine acetate). After cooling the products were extracted with ether, the ether taken off, and the residue converted to picrate. Picrate mp 198°–199° C (ex EtOH), mixed mp established its identity as sym-octahydroacridine picrate. Treatment of the picrate with 10% NaOH gave the free base, mp 69° C, undepressed mixed mp with authentic sym-octahydroacridine.

b) By treatment with Na/K alloy in BuOH. 7 g Na containing 2%K was rapidly added to 5 g dicyanide II in 100 ml BuOH, and the mixture heated on an oil bath (150° C). After the alloy had dissolved, the mixture was cooled, acidified with 10% HCl, and the BuOH steam distilled off. When its removal was effected, 1. 5 g perhydroacridine (α-VII) hydrochloride, slighly soluble in water, came down. Decomposition with alkali gave the base itself, mp 88° C, undepressed mixed mp with authentic α-perhydroacridine.

Lactone of 14-hydroxyperhydroacridine-11-carboxylic acid (V). 9.5 g Dicyanide II was refluxed for 2-1/2 hr with 50 ml 60% H_2SO_4 cooled, cracked ice added (~30 g), and ammonia added until the solution was slightly alkaline. The precipitate was filtered off with suction and dried without washing it, after which it was treated with 6 successive portions (10–15 ml each) of boiling heptane. On cooling lactone V came down from the heptane extracts, yield 6. 4 g, colorless rods, soluble in EtOH, ether, acetone, benzene, boiling heptane, and hot water; sparingly soluble in cold heptane, mp 128°–129° C (ex heptane). Found: C 70.96; 70.91; H 8.76; 8.97; N 5.76; 5.77%; M 255; 259.* calculated for $C_{14}H_{21}NO_2$: C 71. 48; H 8. 94; N 5. 96%, M 235.

IR spectrum (in KBr), cm^{-1}: 1780 (–C=O in 5-membered ring lactones), and 3280 (N–H).

Hydrochloride, mp 194°–196° C. Found: Cl 13. 50%, calculated for $C_{14}H_{21}NO_2 \cdot HCl$: Cl 13. 20%.

Dehydrogenation. 1 g V was heated to 280°–300° C with 0. 3 g Pt/C. 515 ml hydrogen and 0. 175 g CO_2 were collected (in an ascarite tube); theoretical 572 ml H_2 and 0. 187 g CO_2. The dehydrogenation product was extracted with ether and purified by distillation, mp 109° C. Mixed mp showed it to be idential with acridine.

$\Delta^{10(11)}$-Dodecahydroacridine (VI). 6 g Lactone V was dry distilled under vacuum (2 mm); there was vigorous frothing when the bath was at 180° C, and at 200° C distillate started coming over. The distillate was slowly redistilled in a current of N, and 3. 4 g (69. 4%) was collected, colorless oily liquid, bp 117°–122° C (2 mm), n_D^{20} 1. 5270, d_4^{20} 1. 010. Found: C 80. 69; 80. 37; H 10. 83; 10. 90%**; MR_D 58. 09, calculated for $C_{13}H_{21}N$: C 81. 67; H 11. 00%; MR_D 58. 63.

Picrate mp 150°–152° C (ex EtOH). Found: N 13.06; 13.26%, calculated for N 13.06; 13.26%: $C_{13}H_{21}N \cdot C_6H_3N_3O_7$: N 13.33%.

Oxygen absorption. Shaking 0. 55 g amine VI in 25 ml heptane in a vessel connected with a gas buret, and containing O_2, 0. 75 mole of the latter per mole of amine were absorbed in 2 hr, half the gas being, for example absorbed in the first 15 min. 0. 4 g crystalline material came out of the solution, and the substance liberated iodine from an acetic acid solution of NaI. When amine VI was kept in air it oxidized rather quickly to a crystalline product.

Hydrogenation. 1.5 g Amine VI was hydrogenated in dioxane, using 0. 1 g PtO_2, 168 ml H_2 was absorbed (theoretical 175 ml). The catalyst was filtered off, the filtrate saturated with HCl gas, then diluted with water, and 0. 55 g α-perhydroacridine hydrochloride precipitated. It was dissolved in hot water, the solution made alkaline, and the base (α-VII) was obtained, mp 89°–90° C, the literature [6] gives mp 90°–91° C.

Making alkaline the solution remaining after removing the salt gave 0. 5 g β-perhydroacridine (β-VII), mp 50°–51° C. The literature [6] gives mp 48°–51° C. Mixed mps with known specimens confirmed that these compounds were α- and β-perhydroacridine.

Iminoimide of 11, 14-perhydroacridinedicarboxylic acid (IX). 10 g Dicyanide II was carefully dissolved, with cooling in 40 ml conc. H_2SO_4, and the solution left for 24 hr at room temperature.

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*By titrating in absolute EtOH.

**Obviously the low analysis is solely due to the compound's readily oxidizing in contact with air.

Then it was kept for 1.5 hr at 50°–60° C, cooled and added dropwise to a constantly stirred mixture of ice and conc. ammonia. The precipitated iminoimide IX was separated off, and washed with water, yield 8.9 g (83%), white hexagonal platelets, soluble in dioxane, AcOH, and benzene, slightly soluble in ether, insoluble in heptane and water. Mp 263°–265° C (dioxane-water 1:1). Found: C 68.79; H 8.98; N 15.89%, calculated for $C_{15}H_{23}N_3O$: C 68.96; H 8.81; N 16.09%.

IR spectrum (in KBr): cm^{-1}, 3280, 1650 (RCONHR); 1540 $(\overset{\overset{NH}{\diagup}}{C}{=}N)$.

Imide of 11, 14-perhydroacridinedicarboxylic acid (X). a) 20 g Dicyanide II was treated with 75 ml conc. H_2SO_4, as above, then the solution poured in 800 ml water, the whole refluxed for 1-1/2 hr, cooled, excess conc. ammonia added, and the precipitate of imide X separated off, yield 19.5 g (90%), colorless rods, soluble in EtOH, acetone, dioxane, $CHCl_3$, and benzene, slightly soluble in ether and heptane, insoluble in water, soluble in 10% NaOH and reprecipitated on neutralization, mp 201°–202° C (EtOH-water 1:1). Found: C 68.66; H 8.64; N 11.11%, calculated for $C_{15}H_{22}N_2O_2$: C 68.70; H 8.40; 10.68%. IR spectrum(in KBr), cm^{-1}: 3200, 1730, 1700 (CONHCO).

b) 2 g Iminoimide IX was heated with 100 ml 15% H_2SO_4 for 1.5 hr, and the products were made alkaline with conc. ammonia, giving 1.6 g imide X.

Imide sulfate. This was prepared by dissolving imide X in conc. H_2SO_4 then diluting with water, when the slightly soluble sulfate came down, mp 303°–305° C (ex EtOH). Found: N 8.84%, calculated for $C_{15}H_{22}N_2O_2 \cdot 1/2H_2SO_4$: N 9.00%.

Conversion of imide X to lactone V. 3 g Imide was dissolved in 15 ml conc. H_2SO_4, 14 ml water added, the resultant solution refluxed for 35 hr, and the gaseous reaction products passed through washbottles connected in series and containing 33% KOH solution, conc. H_2SO_4, and 0.005 N $PdCl_2$. In the latter, 20 min after boiling began, Pd black appeared due to reaction with CO. After refluxing the products were neutralized with $BaCO_3$, filtered, and the filtrate evaporated, to give 2 g (74%) lactone V, mp 128°–129° C (ex heptane). Mixed mp showed its identity with the previously prepared lactone V.

11, 14-Dimethyleneiminoperhydroacridine (XI). 2.5 g Imide X was put in an extractor joined to a flask containing a suspension of 1.7 g $LiAlH_4$ in 100 ml ether, which was then gently refluxed. In 8 hr the imide was carried over into the solution. Excess reagent was decomposed with water, and the residue after removing the ether treated with dil. HCl. The acid solution was made alkaline, when it gave 0.7 g (32%) base, purified by vacuum distillation (2 × 10^{-1} mm). Colorless platelets, soluble in EtOH, acetone, benzene and heptane, insoluble in water, mp 86°–87° C. Found: C 76.54; 76.61; H 11.15; 11.12; N 11.66; 11.94%, calculated for $C_{15}H_{26}N_2$: C 76.92; H 11.11; N 11.96%.

IR spectrum (in KBr), cm^{-1}: 3300 (>N–H), no carbonyl absorption band. Picrate mp 232° C (decomp). Found: N 16.38; 16.18%, calculated for $C_{15}H_{26}N_2 \cdot 2C_6H_3N_3O_7$: N 16.18%.

Lactam of 14-aminomethylperhydroacridine-11-carboxylic acid (XII). 7.5 g Na was quickly added to a boiling solution of 5 g imide X in 140 ml BuOH, the whole boiled vigorously for 25 min, when the Na dissolved completely. The solution was cooled, acidified with HCl, and the BuOH steam distilled off. The precipitate of hydrochloride of base XII was filtered off, yield 2.1 g (39%). The filtrate was made alkaline, when 1.1 g base XII came out. Total yield 62%. The compound was soluble in EtOH, benzene, and dioxane, slightly soluble in ether and heptane, insoluble in water, mp 227.5°–229° C (benzene-heptane 1:1). Found: C 72.13; H 9.93; N 11.10%, calculated for $C_{15}H_{24}N_2O$: C 72.58; H 9.68; N 11.29%. IR spectrum (in KBr), cm^{-1}: 1670 (>C=O, in 6-membered ring lactones), 3200, 3080 (—N—H). Hydrochloride mp 340° C (decomp). Found: Cl 11.9%, calculated for $C_{15}H_{24}N_2O \cdot HCl$: Cl 12.4%.

Lactam of 14-aminoperhydroacridine-11-carboxylic acid (XV). 3 g Dicyanide II in 40 ml EtOH was heated to boiling, 4 ml 50% KOH solution added dropwise, the mixture refluxed for 10 hr, made acid with AcOH, and then evaporated to dryness. The dry residue was extracted with water, and the aqueous extract made alkaline with ammonia. 1.8 g (62%) crystals of lactam XV was obtained, colorless rods, readily soluble in EtOH and $CHCl_3$, moderately soluble in benzene, acetone, and dioxane, slightly soluble in ether, insoluble in water and heptane, mp 208°–209° C ($CHCl_3$-heptane 1:2). Found: C 71.39; H 9.60: N 11.70%, calculated for $C_{14}H_{22}N_2O$: C 71.0; H 9.40; N 11.97%.
IR spectrum (in KBr), cm^{-1}: 1710 (C=O in 5-membered lactam rings), 3190, 3080, (N—H).

Refluxing 0.5 g lactam XV in 10 ml conc. HCl for 3 hr gave 0.25 g lactone V mp 128°–129° C (undepressed mixed mp with known V).

Action of 15% KOH on dicyanide II. A solution of 5 g dicyanide II in 60 ml 15% KOH (ethanolic) was refluxed for 25 hr, then diluted with 150 ml water, the solution extracted with ether, the extract evaporated to dryness, and the residue treated with heptane, when 0.5 g heptane-insolubles and 2 g heptane-solubles were obtained. The first was the lactam XV, mp 208°–209° C, undepressed mixed mp with a known specimen, while the second was sym-octahydroacridine XVI, mp 69°–71° C, undepressed mixed mp with a known specimen.

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Far Eastern State University, Vladivostok