β-DICARBONYL COMPOUNDS

COMMUNICATION 20. REACTION OF 2-(ALKYLAMINOMETHYLENE) CYCLOHEXANONES WITH HYDROGEN PEROXIDE*

(UDC 542.91 + 574.5)

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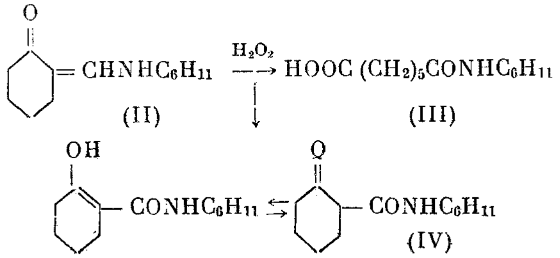
Translated from Izvestiya Akademii Nauk SSSR, Seriya Khimicheskaya, No. 6,
pp. 1054-1060, June, 1962
Original article submitted December 11, 1962

We have shown previously [1] that 2-(methylaminomethylene)cyclohexanone (I) reacts with hydrogen peroxide with formation of a noncrystallizing oil, which on acid hydrolysis gives pimelic acid in 54% yield, based on the original enamine. To determine the mechanism of these transformations it was of interest to establish the nature of the intermediate oily compound. With this object in the present work, in the hope of obtaining more readily crystallizing reaction products, in place of 2-(methylaminomethylene)cyclohexanone we took the corresponding cyclohexylamino compound (II), which was prepared in high yield by the reaction of 2-oxocyclohexanecarboxaldehyde with cyclohexylamine. Actually, when 2-(cyclohexylaminomethylene)cyclohexanone was treated with hydrogen peroxide under the usual conditions, we isolated two crystalline substances, m.p. 93-94° and 111-112° and compositions $C_{13}H_{23}O_3N$ and $C_{13}H_{23}O_4N$, in yields of 44% and 23% respectively, and in accordance with their chemical and physicochemical properties these must have the structures of N-cyclohexylpimelamic acid (III) and N-cyclohexyl-2-oxocyclohexanecarboxamide (IV) solvated with hydrogen peroxide. It is interesting that the cyclic amide (IV) is stable to the action of aqueous hydrogen peroxide and cannot therefore act as a precursor of N-cyclohexylpimelamic acid in its formation from 2-(cyclohexylaminomethylene)cyclohexanone.



The perhydrate of the amide (IV) gives a characteristic reaction for enol with ferric chloride and dissolves in dilute alkali, but it does not dissolve in sodium carbonate solution or dilute mineral acids, and it is hydrolyzed to cyclohexanone when boiled with hydrochloric acid. It loses hydrogen peroxide extremely readily when heated or treated with bases with formation of the nonsolvated form, which repeats all the above reactions of the perhydrate and is converted into the latter immediately on treatment with hydrogen peroxide in acetic acid. Both forms give the same 2,4-dinitrophenylhydrazone, λ_{max} 363 mμ (alcohol), characteristic for the 2,4-dinitrophenylhydrazones of saturated ketones. In the ultraviolet spectra of the cyclic amide (IV) and its solvate, determined in alcohol (Table 1), there is an indistinct maximum corresponding to the conjugated enol form, and this becomes appreciably stronger on transference to chloroform. Similar increase in the enol content of the tautomeric mixture with reduction in the polarity of the solvent is known to be characteristic of cisoid keto-enol compounds. The infrared spectra of the cyclic amide (IV) in mineral oil and in chloroform contain the same carbonyl frequencies of keto and amide groups as the

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* This article is published in accordance with a resolution of the Conference of Chief Editors of Journals of the Academy of Sciences of the USSR, July 12, 1962, as a dissertation paper by L. P. Vinogradova.

TABLE 1. Ultraviolet Spectra

Compound	Solvent	λmax	ε	Compound	Solvent	λmax	ε
(I)	Alcohol	327	17,850	(IV)	CHCl$_3$	255	8200
(II)	Ditto	327	18,300	Perhydrate of (IV)	Alcohol	257	975
(IV)	"	256	1,200	Perhydrate of (IV)	CHCl$_3$	255	5800

TABLE 2. Infrared Spectra

Compound	Solvent	ν, cm^{-1}
(IV)	CHCl$_3$	1635, 1649, 1703
(IV)	Mineral oil	1635, 1649, 1703
Perhydrate of (IV)	CHCl$_3$	1635, 1649, 1703
Perhydrate of (IV)	Mineral oil	1618, 1635
(XI)	Ditto	1642, 1657, 1712
Perhydrate of (XIV)	"	1616, 1632
Methyl ester of (III)	CCl$_4$	1653, 1684, 1745
Ditto (XII)	CCl$_4$	1656, 1680, 1743
" (XV)	CCl$_4$	1657, 1680, 1745
" (XVI)	CCl$_4$	1651, 1680, 1745
" (XIX)	CCl$_4$	1653, 1684, 1747

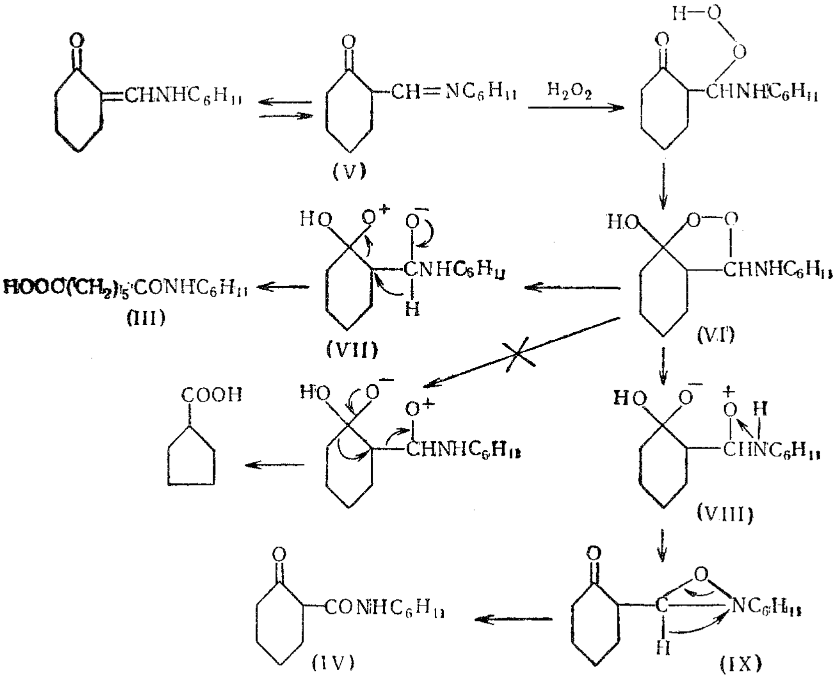
infrared spectrum of the solvate in chloroform (Table 2). In the solid state, however, the solvate shows bands corresponding, in all probability, to the conjugated amide group of the enol form. Since the cyclic amide (IV) and its solvate have identical infrared and ultraviolet spectra in solutions, it may be supposed that such solvents as methanol and chloroform bring about the breakdown of the perhydrate into its components. The structure of N-cyclohexylpimelamic acid is confirmed not only by the elementary analysis, but also by its chemical properties: solubility in sodium carbonate solution, formation of a methyl ester under the action of diazomethane, and acid hydrolysis to pimelic acid. On analogy to 2-oxocyclohexanecarboxaldehyde itself [2, 3], the reaction of the enamine derived from it with hydrogen peroxide may be represented as a process that includes the formation of the cyclic peroxide (VI) and its heterolytic breakdown in two directions with the subsequent rearrangement and stabilization of the cations (VII) and (VIII). The presence of a highly nucleophilic nitrogen atom favors the formation of the isonitrone (IX) from the cation (VIII) and at the same time makes the conversion of the latter into cyclopentanecarboxylic acid difficult.

The proposed scheme is fully in accord with the already described [4] conversion of imines into carboxamides through the intermediate stage of the thermal isomerization of isonitrones. The relative amounts of the amides (III) and (IV) depend on the medium in which the reaction takes place and are, as molar ratios, 1 : 0.3 for water and 1 : 0.5 for aqueous acetic acid. In presence of sodium carbonate 2-(cyclohexylaminomethylene)cyclohexanone does not react with hydrogen peroxide, probably because the alkalinity of the medium prevents the displacement of the enamine-imine tautomeric equilibrium toward the reactive imine form (V) [5].

Analogous transformations occur also in the case of the homologs of 2-(cyclohexylaminomethylene)cyclohexanone (X) and (XIII), with the difference, however, that N-cyclohexyl-3-methyl-2-oxocyclohexanecarboxamide (XI) was found to be incapable of undergoing solvation with hydrogen peroxide.

2-(Methylaminomethylene)cyclohexanone gives only the aliphatic amide (XVI), but 4-methyl-2-(methylaminomethylene)cyclohexanone (XVII) gives not only N,4-dimethylpimelamic acid (XIX), but also traces of N,5-dimethyl-2-oxocyclohexanecarboxamide (XVIII), which was characterized as its 2,4-dinitrophenylhydrazone. On hydrolysis the unpurified N,4-dimethylpimelamic acid is converted into the dicarboxylic acid in 61% yield, based on the original enamine (XVII).

All the aliphatic amides, apart from N-cyclohexylpimelamic acid, are noncrystallizing oils and were isolated as their methyl esters, the structures of which were confirmed unequivocally by their infrared spectra (Table 2).

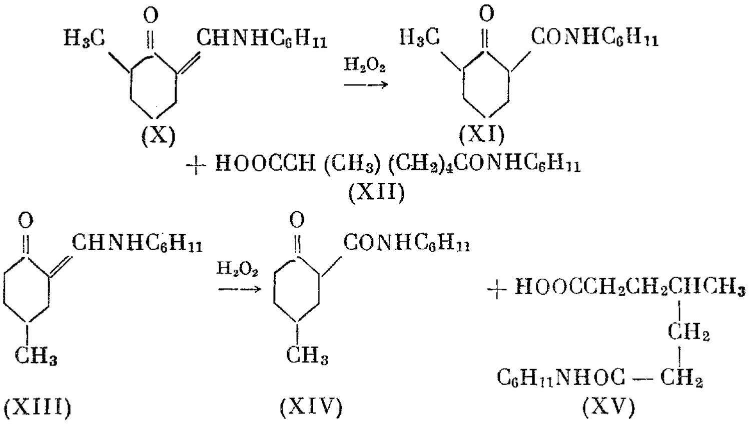


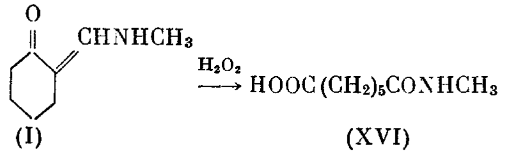
EXPERIMENTAL

2-(Cyclohexylaminomethylene)cyclohexanone (II). 4.9 g of cyclohexylamine was added to 6.2 g of 2-oxocyclohexanecarboxaldehyde, and after two hours the crystalline mass formed was washed with ether cooled to −78°. This gave 9.1 g (90%) of 2-(cyclohexylaminomethylene)cyclohexanone (II), m.p. 74-76°, raised to 76-78° by recrystallization from heptane. R_f 0.70 (thin-layer chromatography on alumina of activity II in 1 : 1 acetone-heptane). Found: N 6.97; 6.85%. $C_{13}H_{21}ON$. Calculated: N 6.76%.

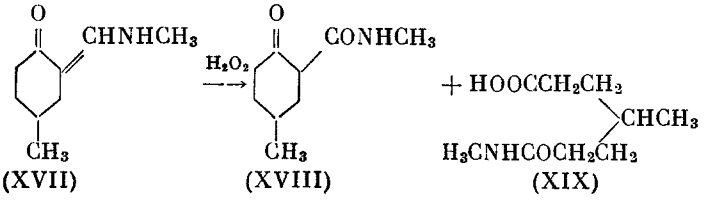
Reaction of 2-(Cyclohexylaminomethylene)cyclohexanone with Hydrogen Peroxide. a) 25 ml of 30% hydrogen peroxide was added to 5 g of 2-(cyclohexylaminomethylene)cyclohexanone in 25 ml of acetic acid at such a rate that the temperature did not rise above 65°. After 12 hours the crystals that had precipitated were filtered off, and we obtained 1.4 g of the perhydrate of N-cyclohexyl-2-oxocyclohexanecarboxamide (IV), m.p. 109-110°. Yield 23%. After recrystallization from benzene it had m.p. 111-112°. Found: C 60.43; 60.57; H 9.09; 9.05; N 5.56; 5.51%. $C_{13}H_{21}O_2N \cdot H_2O_2$. Calculated: C 60.68; H 9.01; N 5.44%. 2,4-Dinitrophenylhydrazone, m.p. 191-193°. Found: C 56.57; 56.50; H 6.26; 6.12; N 17.23; 17.26%. $C_{19}H_{25}O_5N_5$. Calculated: C 56.56; H 6.25; N 17.36%.

The mother solution (after the isolation of the cyclic amide) was vacuum-evaporated to dryness, and the residue was treated with water and excess of sodium carbonate. The alkaline solution was filtered and acidified with hydro-





(I) (XVI)



(XVII) (XVIII) (XIX)

chloric acid, and there was a precipitate of 2.6 g (44%) of N-cyclohexylpimelamic acid (III), m.p. 91-93°. After recrystallization from benzene it had m.p. 93-94°. Found: C 65.16; 64.88; H 9.53; 9.48; N 5.80; 5.81%. $C_{13}H_{23}O_3N$. Calculated: C 64.70; H 9.61; N 5.80%.

b) A mixture of 1 g of 2-(cyclohexylaminomethylene)cyclohexanone and 10 ml of 15% hydrogen peroxide was stirred for 12 hours at 20°. The crystals obtained were carefully ground with sodium carbonate solution and then filtered off. We isolated 0.19 g (19%) of N-cyclohexyl-2-oxocyclohexanecarboxamide (IV), m.p. 93-94° (from heptane). Found: C 69.66; 69.59; H 9.44; 9.33; N 6.31; 6.33%. $C_{13}H_{21}O_2N$. Calculated: C 69.92; H 9.48; N 6.27%.

The 2,4-dinitrophenylhydrazone melted at 191-193° and melted without depression in admixture with the 2,4-dinitrophenylhydrazone prepared from the solvate of N-cyclohexyl-2-oxocyclohexanecarboxamide. On acidification of the alkaline mother solution we obtained 0.6 g (50%) of N-cyclohexylpimelamic acid, m.p. 87-88°.

The reactions of hydrogen peroxide with the homologs of 2-(cyclohexylaminomethylene)cyclohexanone were carried out analogously. Liquid amides were isolated by extraction with chloroform and were identified with the aid of their methyl esters.

Elimination of Hydrogen Peroxide from the Perhydrates of N-Cyclohexyl-2-oxocyclohexanecarboxamide. 0.88 g of the perhydrate of the cyclohexylamide (IV) was heated at a residual pressure of 2-3 mm at a temperature of 110-120° for 40 minutes. Hydrogen peroxide was seen to distill over. Crystallization of the residue from heptane gave 0.5 g (66%) of N-cyclohexyl-2-oxocyclohexanecarboxamide (IV), m.p. 92-94°. The perhydrate readily loses hydrogen peroxide when mixed with an aqueous solution of sodium carbonate or hydroxide. The amide (IV) is completely solvated almost instantaneously when aqueous hydrogen peroxide is added to its acetic acid solution.

Hydrolysis of N-Cyclohexyl-2-oxocyclohexanecarboxamide. A mixture of 0.7 g of N-cyclohexyl-2-oxocyclohexanecarboxamide, 4 ml of acetic acid, and 15 ml of 20% hydrochloric acid was refluxed for 16 hours. Extraction of the cooled solution with ether gave cyclohexanone, identified as its 2,4-dinitrophenylhydrazone (m.p. 160-161°).

Hydrolysis of N-Cyclohexylpimelamic Acid. Boiling of 3.7 g of N-cyclohexylpimelamic acid with 40 ml of 20% hydrochloric acid for 16 hours gave 1.3 g (54%) of pimelic acid, m.p. 97-99°.

Methyl N-Cyclohexylpimelamate. By treating 0.2 g of N-cyclohexylpimelamic acid with ethereal diazomethane we obtained 0.2 g (95%) of the methyl ester, m.p. 59-60° ("frozen out" from ethereal solution with solid carbon dioxide). Found: N 5.65; 5.78%. $C_{14}H_{25}O_3N$. Calculated: N 5.49%.

2-(Cyclohexylaminomethylene)-4-methylcyclohexanone (XIII). This was prepared by the action of cyclohexylamine on 5-methyl-2-oxocyclohexanecarboxaldehyde [6]. Yield 87%; m.p. 55-56° ("frozen out" from ethereal solution with solid carbon dioxide). Found: N 6.39; 6.50; $C_{14}H_{23}ON$. Calculated: N 6.33%.

Reaction of 2-(Cyclohexylaminomethylene)-4-methylcyclohexanone with Hydrogen Peroxide. When treated with hydrogen peroxide in acetic acid as described above, 3 g of 2-(cyclohexylaminomethylene)-4-methylcyclohexanone gave 1.2 g (33%) of the perhydrate of N-cyclohexyl-5-methyl-2-oxocyclohexanecarboxamide (XIV), m.p. 117-119°. After this had been precipitated from acetic acid solution with aqueous hydrogen peroxide, the melting point was raised to 124-126°. Found: N 5.04; 5.17. $C_{14}H_{23}O_2N \cdot H_2O_2$. Calculated: N 5.16%. 2,4-Dinitrophenylhydrazone, m.p. 225-226°. Found: N 16.79; 16.91%. $C_{20}H_{27}O_5N_5$. Calculated: N 16.78%. The mother solution remaining after the isolation of the cyclic amide (XIV) was diluted with water, and extraction with chloroform gave oily N-cyclohexyl-4-methylpimelamic acid (XV), which was converted by the action of diazomethane into its methyl ester, b.p. 199-201° (3 mm) and m.p. 43°. Yield 36%, based on the original enamine. Found: N 5.10; 5.02%. $C_{15}H_{27}O_3N$. Calculated N 5.20%. By the reaction of 2-(cyclohexylaminomethylene)-4-methylcyclohexanone with aqueous hydrogen peroxide and the above-described treatment of the reaction mixture we obtained the solvate of N-cyclohexyl-5-methyl-2-oxocyclohexanecarboxamide and methyl N-cyclohexyl-4-methylpimelate in yields of 20% and 46%, respectively.

2-(Cyclohexylaminomethylene)-6-methylcyclohexanone (X). This was prepared by the action of cyclohexylamine on 3-methyl-2-oxocyclohexanecarboxaldehyde [6]. Yield 56%; m.p. 78-79° ("frozen out" from ethereal solution with solid carbon dioxide). Found: N 6.18; 5.99%. $C_{14}H_{23}ON$. Calculated: N 6.33%.

Reaction of 2-(Cyclohexylaminomethylene)-6-methylcyclohexanone with Hydrogen Peroxide. By the treatment of 2-(cyclohexylaminomethylene)-6-methylcyclohexanone with aqueous hydrogen peroxide by the above-described method we obtained: 1) N-cyclohexyl-3-methyl-2-oxocyclohexanecarboxamide (XI) in 20% yield; m.p. 137-139° (after precipitation from acetic acid solution with water). Found: N 6.04; 6.15%. $C_{14}H_{23}O_2N$. Calculated: N 5.90%. 2,4-Dinitrophenylhydrazone, m.p. 196-197°. Found: N 16.88; 16.97%. $C_{20}H_{27}O_5N_5$. Calculated: N 16.78%.

2) Methyl N-cyclohexyl-2-methylpimelamate; yield 49%, based on the original enamine; b.p. 194-196° (3 mm); n_D^{20} 1.4760. Found: N 5.03; 5.11%. $C_{15}H_{27}O_2N$. Calculated: N 5.20%.

Reaction of 2-(Methylaminomethylene)cyclohexanone with Hydrogen Peroxide. By the reaction of 2-(methylaminomethylene)cyclohexanone (I) [1] with hydrogen peroxide in acetic acid and subsequent methylation with diazomethane we obtained methyl N-methylpimelamate in 28% yield, based on the original enamine; b.p. 170-171% (3 mm); n_D^{20} 1.4610. Found: N 7.69, 7.47%. $C_9H_{17}O_3N$. Calculated: N 7.48%.

When the reaction was carried out in an aqueous medium the yield of the methyl ester was 35%.

4-Methyl-2-(methylaminomethylene)cyclohexanone (XVII). This was prepared by the action of 30% aqueous methylamine solution on 5-methyl-2-oxocyclohexanecarboxaldehyde. Yield 91%; b.p. 130-132° (5 mm); m.p. 99-100°. Found: N 9.25; 9.42%. $C_9H_{15}ON$. Calculated: N 9.14%.

Reaction of 4-Methyl-2-(methylaminomethylene)cyclohexanone with Hydrogen Peroxide. When the reaction was carried out in acetic acid we obtained contaminated methyl N,4-dimethylpimelamate, b.p. 150-170° (2 mm), and oily N,5-dimethyl-2-oxocyclohexanecarboxamide (XVIII), 2,4-dinitrophenylhydrazone, m.p. 200-201°, λ_{max} 362 mμ (alcohol). Found: N 20.03; 19.85%. $C_{15}H_{19}O_5N_5$. Calculated: N 20.05%. In the reaction of 4-methyl-2-(methylaminomethylene)cyclohexanone with aqueous hydrogen peroxide only the aliphatic amic acid (XIX) was formed.

Preparation of 4-Methylpimelic Acid from 4-Methyl-2-(methylaminomethylene)cyclohexanone. 2 g of 4-methyl-2-(methylaminomethylene)cyclohexanone was treated as described above with hydrogen peroixde in aqueous acetic acid. The solution obtained was vacuum-evaporated to dryness, and the residue was boiled for seven hours with 20 ml of 20% hydrochloric acid. Ether extracted 1.4 g of 4-methylpimelic acid [b.p. 180-183° (3 mm), b.p. 51-53°], containing, according to analysis by gas-liquid chromatography [7], traces of 3-methyladipic acid.

SUMMARY

By the reaction of 2-(alkylaminomethylene)cyclohexanones with hydrogen peroxide mixtures of substituted pimelamic acids and 2-oxocyclohexanecarboxamides are formed.

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