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HYDROGEN PEROXIDE CLEAVAGE OF 2-FORMYL-CYCLOALKANONES AND THEIR ENAMINES

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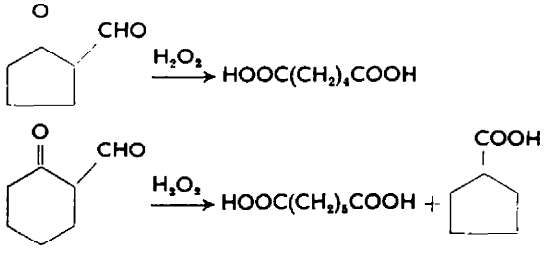
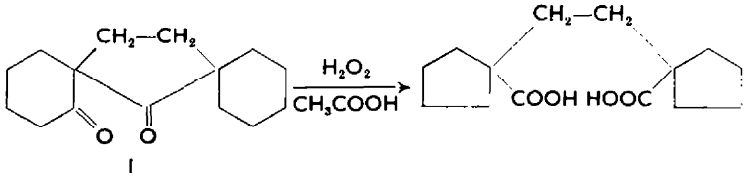
Abstract—2-Formylcycloalkanones and their enamines, on treatment with hydrogen peroxide, give dicarboxylic acids and mono amides containing the same number of carbon atoms as the starting compounds.

IT HAS been shown that 2-formylcyclopentanone and 2-formylcyclohexanone, on treatment with aqueous hydrogen peroxide, undergo an unusual oxidative cleavage to dicarboxylic acids containing the same number of carbon atoms as the starting compounds.[1,2]



It also has been established that the cleavage of the six-membered ketone competes with ring contraction to form a cyclopentane carboxylic acid.

An analogous ring contraction of the spirodiketone (I) has been described by Mannich[3] but without interpretation of the mechanism.

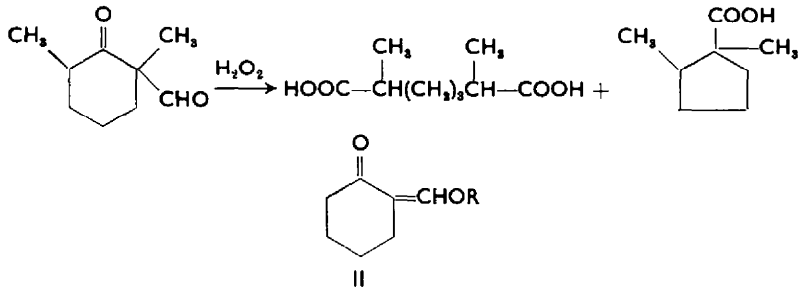


I

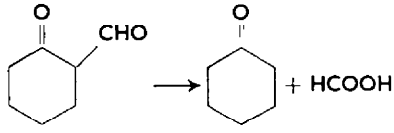
The present communication is concerned with the nature and applications of these interesting transformations.

In the hydrogen peroxide cleavage of 2-formylcycloalkanones only the diketo forms are involved, since the behaviour of the non-enolizable 2-methyl-2-formylcyclohexanone towards hydrogen peroxide is similar to that of the enolizable 2-formylcyclohexanone and different from that of the enol ether (II) which affords exclusively adipic acid.[4,5]

[1] L. P. Vinogradova and S. I. Zavialov, *Izv. Acad. Nauk SSSR, Otd. Chim. Nauk* 1717 (1960).
[2] L. P. Vinogradova and S. I. Zavialov, *Zh. Obsch. Khim.* **30**, 4110 (1960).
[3] C. Mannich, *Ber. Dtsch. Chem. Ges.* **74B**, 1007 (1941).
[4] L. P. Vinogradova and S. I. Zavialov, *Izv. Acad. Nauk SSSR, Otd. Chim. Nauk* 2050 (1961).
[5] L. P. Vinogradova, B. A. Rudenko and S. I. Zavialov, *Izv. Acad Nauk SSSR, Otd. Chim. Nauk* 1436 (1962).

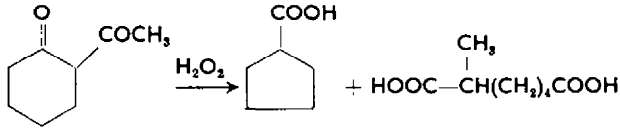


On the other hand, the conversion of 2-formylcycloalkanones to dicarboxylic acids cannot be regarded as a simple hydrolytic reaction, the latter being accompanied by rupture of the exocyclic C—C—bond to give cyclic mono ketones.

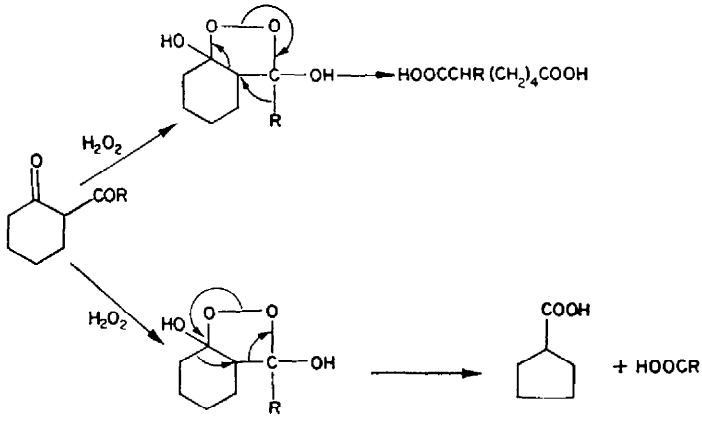


The rather facile oxidation of 2-carboxycyclohexanone by hydrogen peroxide to adipic acid,[4] renders unlikely the intermediate formation of 2-carboxy derivatives with subsequent ring opening.

Finally, it is important to note that the interaction of 2-acetylcyclohexanone with hydrogen peroxide involves not only the ring opening and ring contraction processes, but also the migration of the methyl group to form α-methylpimelic acid.[4]



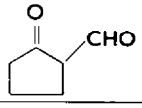
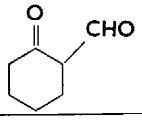
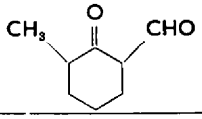
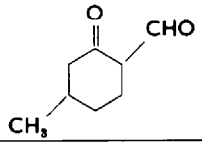
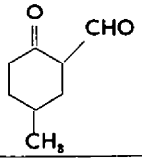
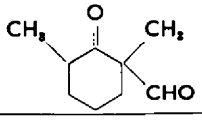
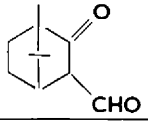
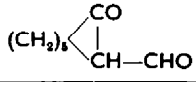
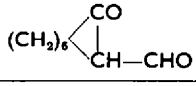
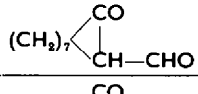
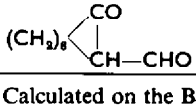
The mechanism of the reaction of 2-acylcycloalkanones with hydrogen peroxide may be considered as a rearrangement of the corresponding peroxides* in two possible



* Attempts to isolate the intermediate peroxides were not successful.[6]

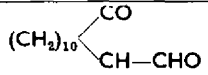
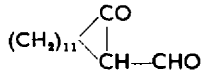
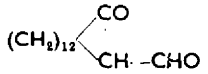
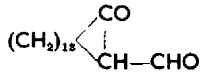
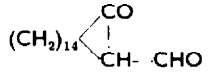
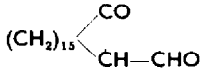
[6] G. Payne, *J. Org. Chem.* **26**, 4793 (1961) and Refs. therein.

TABLE 1. REACTION OF 2-FORMYLCYCLOALKANONES WITH HYDROGEN PEROXIDE

Starting 2-formylcyclo-alkanone	Reaction products: dicarboxylic acids name	yield %	cycloalkanecarboxylic acids name	yield %
1	2	3	4	5
	adipic acid	90		
	pimelic acid	38	cyclopentane-carboxylic acid	31
	α-methylpi-melic acid	14*	2-methylcyclo-pentanecar-boxylic acid	50
	β-methylpi-melic acid	29*	3-methylcyclo-pentanecar-boxylic acid	23
	γ-methyl pimelic acid	31*	3-methylcyclo-pentanecar-boxylic acid	18
	α, α′-dimeth-ylpimelic acid	25*	1,2-dimethyl-cyclopentane-carboxylic acid	51
	homocamphoric acid	52		
	suberic acid	37	cyclohexane-carboxylic acid	4
	azelaic acid	50	cycloheptane-carboxylic acid	12
	sebacic acid	60		
	1,11-undecane dioic acid	43		

* Calculated on the Basis of the v.p.c. data.[5]

TABLE 1 (*continued*)

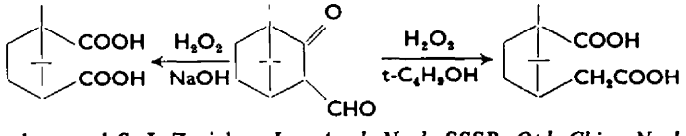
Starting 2-formylcyclo-alkanone	Reaction products: dicarboxylic acids name	yield %	cycloalkanecarboxylic acids name	yield %
1	2	3	4	5
	brassilic acid	58		
	1,14-tetra-decanedioic acid	60		
	1,15-penta-decanedioic acid	44		
	thapsic acid	46		
	1,17-hepta-decanedioic acid	39		
	1,18-octa-decanedioic acid	69		

directions leading to the ring opening and ring contraction.[4,6] This is in good agreement with the above experimental data and the ability of ketones to form hydroxy peroxide compounds.

The hydrogen peroxide cleavage method can be extended to other 2-formylcycloalkanonones (Table 1)[4,5,7,8].

The course of the reaction depends on structural factors and experimental conditions. The ring contraction of C_6—C_8 ketones is responsible for the relatively low yields of the corresponding dicarboxylic acids. In many cases, in particular, under alkaline conditions,[5] 2-formylcycloalkanones undergo to some extent an oxidative degradation to lower dicarboxylic acids and a hydrolytic cleavage to cyclic mono ketones. The best results are obtained by carrying out the reaction at 50–60° in such solvents as water or aqueous t-butyl alcohol.[6,9]

For example, the treatment of 2-formylcamphor with hydrogen peroxide in the presence of alkali[5] gives rise to 62% of camphoric acid, whereas in t-butyl alcohol solution homocamphoric acid is formed in 52%-yield.

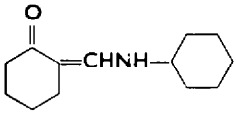
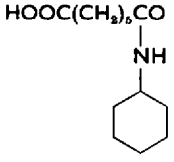
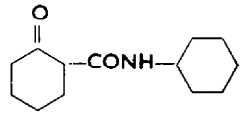
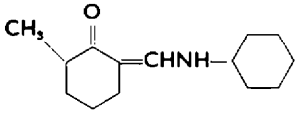
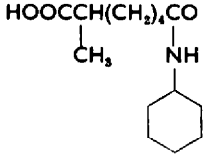
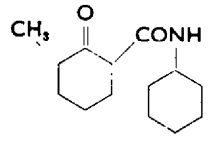
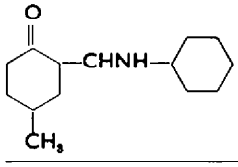
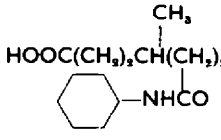
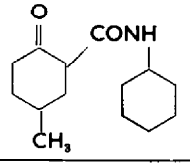


[7] L. P. Vinogradova and S. I. Zavialov, *Izv. Acad. Nauk SSSR, Otd. Chim. Nauk* 1482 (1961).
[8] L. I. Zakharkin, L. P. Vinogradova, V. V. Korneva and S. I. Zavialov, *Izv. Acad. Nauk SSSR, Otd. Chim. Nauk* 1309 (1962).
[9] L. P. Vinogradova and S. I. Zavialov, *Izv. Acad. Nauk SSSR, Otd. Chim. Nauk* 866 (1963).

An attempt to achieve the ring opening of 2-formyltetralone-1 led to the formation of α-tetralone.

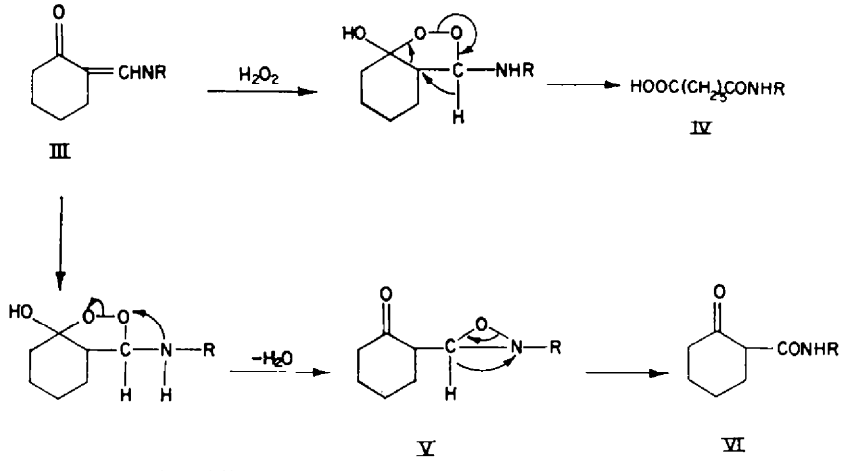
2-Formylcycloalkanone enamines are similar to β-dicarbonyl compounds in their reaction with hydrogen peroxide, undergoing a ring opening to dicarboxylic acid

TABLE 2. REACTION OF 2-FORMYLCYCLOALKANONE ENAMINES WITH HYDROGEN PEROXIDE

Starting enamines	Reaction products: monoamide formula	yield %	cyclic ketoamide formula	yield %
		50		19
		49		20
		36		33

mono amides (Table 2). But in this case, instead of ring contraction, there is formation of cyclic β-ketoamides.[10]

These transformations can be represented as proceeding through an intermediate peroxide rearrangement stage according to the following scheme:



III IV V VI

The strong nucleophilic character of the nitrogen atom hinders the electronic

[10] L. P. Vinogradova, G. A. Kogan and S. I. Zavialov, *Izv. Acad. Nauk SSSR, Otd. Chim. Nauk* 1061 (1964).

shift which leads to ring contraction and favours the ring closure of an isonitrone system (V), followed by its isomerization to the cyclic amide (VI). The latter compound is stable to hydrogen peroxide under the usual conditions and it cannot be, therefore, an intermediate in the formation of the open-chain amide (IV) from the enamine (III).

The hydrogen peroxide cleavage of 2-formylcycloalkanones and their enamines provides a valuable route to dicarboxylic acids and mono amides on the basis of cyclic ketones.

EXPERIMENTAL

Reaction of 2-formylcycloalkanones with hydrogen peroxide (*Table* 1). Hydrogen peroxide (0·22 mole; 30%) was added to a solution of 0·20 mole 2-formylcycloalkanone[4-11] in 50 ml t-butyl alcohol at such a rate that the temp did not rise above 65°. When no longer exothermic, the mixture was allowed to stand at room temp for 12 hr. The excess peroxide was decomposed in the usual manner[4] and the solvents removed on a steam bath. The acids were isolated from the residue by crystallization or vacuum distillation and identified by v.p.c. and by mixed m.ps with authentic samples.[5]

Reaction of 2-formylcyclooctanone with hydrogen peroxide. Hydrogen peroxide (4·6 ml; 30%) was added to a solution of 5 g 2-formylcyclooctanone in 6 ml t-butyl alcohol, the temp being held 50–60° by external cooling. After standing at room temp for 12 hr and decomposition of the excess peroxide the solvents were removed on a steam bath. The solid residue was washed with water to give 2·5 g azelaic acid, m.p. and mixed m.p. 97–100°. The mother liquor was concentrated to dryness and the residue distilled *in vacuo* to give 0·3 g azelaic acid, m.p. 99–100°, 0·3 g cyclooctanone, b.p. 52–55°/2 mm, n_D^{20} 1·4680, and 0·5 g cycloheptan carboxylic acid, b.p. 98–100°/1 mm, n_D^{20} 1·4700, amide, m.p. 192–193° from aqueous methanol (reported[12] m.p. 195°).

Reaction of DL-*2-formylcamphor with hydrogen peroxide.* Hydrogen peroxide (5 ml; 30%) was added to a solution of 6·5 g DL-2-formylcamphor in 20 ml t-butyl alcohol. After standing at room temp for 12 hr the mixture was diluted with water and the precipitate recrystallized from aqueous acetic acid to give 4 g DL-homocamphoric acid, m.p. 231–232° (reported m.p. 233°).[13]

Preparation of 2-formylcyclononanone. Cyclononanone (1·8 g) and 2·1 g ethyl formate were added to a sodium methoxide prepared from 0·65 g Na in 10 ml dry ether. The reaction mixture was kept at room temp for 12 hr and then treated with cold water. The alkaline layer was acidified with HCl, extracted with ether and dried ($MgSO_4$). Distillation yielded 1·5 g (71%) 2-formylcyclononanone, b.p. 84–86°/2 mm, n_D^{19} 1·5200 (Found: 71·3; H, 9·7. $C_{10}H_{16}O_2$ requires: C, 71·4; H, 9· 6%)

Reaction of 2-formylcyclononanone with hydrogen peroxide. Hydrogen peroxide (1 ml; 30%) was added to a solution of 1·4 g 2-formylcyclononanone in 2 ml t-butyl alcohol. The reaction was very exothermic and the temp rose to 60°. The reaction mixture was kept at room temp for 12 hr and then diluted with water. The resulting crystalline product was filtered off and yielded 0·97 g sebacic acid, m.p. and mixed m.p. 127–129°.

Reaction of 2-formylcyclotetradecanone with hydrogen peroxide. Using the above procedure, 0·18 g cyclotetradecanone was converted into 0·16 g crude 2-formyl derivative which was treated with 0·1 ml 30% H_2O_2 to give 0·08 g 1·15-pentadecanedioic acid, m.p. 109–111° (reported m.p. 113°).[14]

Reaction of 2-formylcycloalkanone enamines with hydrogen peroxide (*Table* 2). Hydrogen peroxide (0·05 mole; 30%) was slowly added to 0·024 mole 2-formylcycloalkanone enamine[10] in 25 ml water or acetic acid, the temp being kept at 60–65°. After the completion of the exothermic reaction, the mixture was allowed to stand at room temp for 12 hr. The mono amide and the cyclic β-ketoamide were separated by treatment with Na_2CO_3 followed by crystallization, esterification and vacuum distillation. The properties and mode of isolation of the amides are reported in Ref 10.

Acknowledgements—The authors wish to acknowledge their indebtedness to G. A. Kogan for spectroscopic investigations, to B. A. Rudenko for v.p.c. analysis and to L. I. Zakharkin and S. Z. Taits for the samples of cyclic ketones.

[11] V. Prelog, L. Ruzicka and O. Metzler, *Helv. Chim. Acta* **30**, 1882 (1947).
[12] W. Reppe, O. Schichting, K. Klager and T. Toepel, *Liebig's. Ann.* **560**, 1 (1948).
[13] A. Lapworth and F. Royle, *J. Chem. Soc.* 750 (1920).
[14] R. Lukes and K. Blaha, *Chem. Listy* **46**, 721 (1952).