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OXIDATION OF CERTAIN CYCLIC CARBONYL COMPOUNDS WITH ALKALINE HYDROGEN PEROXIDE*

HORACE S. ISBELL, HARRIET L. FRUSH, AND ZLATA ORHANOVIC**
Department of Chemistry, The American University, Washington, D.C. 20016 (U. S. A.)
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ABSTRACT

The following cyclic compounds were oxidized at 4° by means of aqueous sodium peroxide in large excess: 2,3,4,6/5-pentahydroxycyclohexanone (**1**); *xylo*-pentahydroxy-2-cyclohexen-1-one (**2**); *xylo*-trihydroxycyclohexane-1,2,3-trione (**3**); reductic acid (**4**); and ninhydrin (**5**). On oxidation, **1**, **2**, and **3** gave carbon dioxide, formic acid, and oxalic acid; in addition, **1** yielded DL-glucaric acid, and **2** and **3** afforded xylaric acid. Compound **4** gave almost equimolecular quantities of carbon dioxide and succinic acid. In addition to a small amount of formic acid, compound **5** gave carbon dioxide and phthalic acid in yields of 92 and 95%, respectively. Reaction mechanisms are proposed.

DISCUSSION

In prior publications, we have shown that, under suitable conditions, alkaline hydrogen peroxide oxidatively degrades aldoses[1], ketoses[2], uronic acids and keto acids[3], as well as hexuloses and hexodiuloses[4], by nucleophilic addition of a hydroperoxide anion to the carbonyl form of the substrate. The resulting adduct (a hydroperoxyhydrin), then decomposes by one or more of the following mechanisms: (*a*) *alpha*-hydroxy peroxide cleavage; (*b*) epoxide-forming, peroxide cleavage; and (*c*) ester-forming, peroxide cleavage[5]. The mode of cleavage depends on the availability of electrons for rupture of the oxygen–oxygen bond of the adduct.

To obtain a better understanding of the peroxide-cleavage reactions, we have now investigated the behavior of the following cyclic compounds: 2,3,4,6/5-pentahydroxycyclohexanone (**1**); *xylo*-pentahydroxy-2-cyclohexen-1-one (**2**); *xylo*-trihydroxycyclohexane-1,2,3-trione (**3**); reductic acid (**4**); and ninhydrin (**5**). Each of the compounds was oxidized by (*a*) aqueous sodium peroxide in large excess, and (*b*) an excess of hydrogen peroxide, with gradual addition of sodium hydroxide. After suitable reaction times, carbon dioxide, formic acid, oxalic acid, and residual acids were determined. A summary of the results is given in Table I.

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*Reactions of Carbohydrates with Hydroperoxides. Part VI. For Parts I to V, see refs. 1–5.

**Present address: Faculty of Technology, University of Zagreb, Zagreb, Yugoslavia.

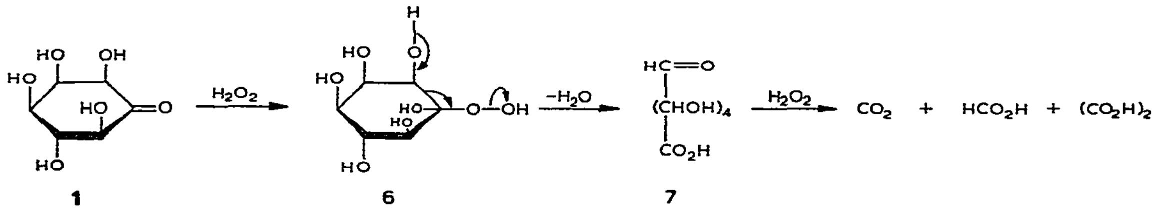
TABLE I

OXIDATION OF COMPOUNDS BY ALKALINE HYDROGEN PEROXIDE[a]

Substrate	*Expt. no.*	*Millimoles formed per millimole of substrate*				*Residual acids*			*Mililatoms of carbon per millimole of substrate*	
						Major constituent identified	*Equivalent wt.*			
		Carbon dioxide	*Formic acid*	*Oxalic acid*	*Residual acid*[b]		*Found*[c]	*Calc.*[d]	*Recovered*	*Theory*
2,3,4,6/5-Pentahydroxy-cyclohexanone	1*a*	0.65	1.65	0.22	0.54	DL-glucaric acid	107	105	5.98	6.0
	1*b*	0.46	1.34	0.16	0.64		106	105	5.96	6.0
Pentahydroxy-2-cyclohexen-1-one	2*a*	0.85	1.43	0.45	0.57	xylaric acid	93	90	6.03	6.0
	2*b*	—	0.11	0.0	0.58		79	90	—	
4,5,6-Trihydroxy-cyclohexane-1,2,3-trione	3*a*	1.12	1.37	0.67	0.43	xylaric acid	92	90	5.98	6.0
	3*b*	—	0.09	0.15	0.94		87	90	—	
Reductic acid	4*a*	0.96	0.0	0.0	1.01	succinic acid	62	59	5.00	5.0
	4*b*	—	0.0	0.0	1.01		57	59	—	
Ninhydrin	5*a*	0.92	0.12	0.0	0.95	phthalic acid	80	83	8.64	9.0
	5*b*	—	0.00	0.0	0.84		83	83	—	

[a] Reaction mixtures and analytical methods given in experimental section. The conditions employed in this and previous papers were chosen to effect complete oxidation of slowly oxidized compounds. Certain members of the group, however, react quickly with hydrogen peroxide in alkaline solution, and do not require the severe conditions used here. [b] Determined by titration. [c] Determined from titration and weight of residual acid. [d] Calculated from formula of major product identified.

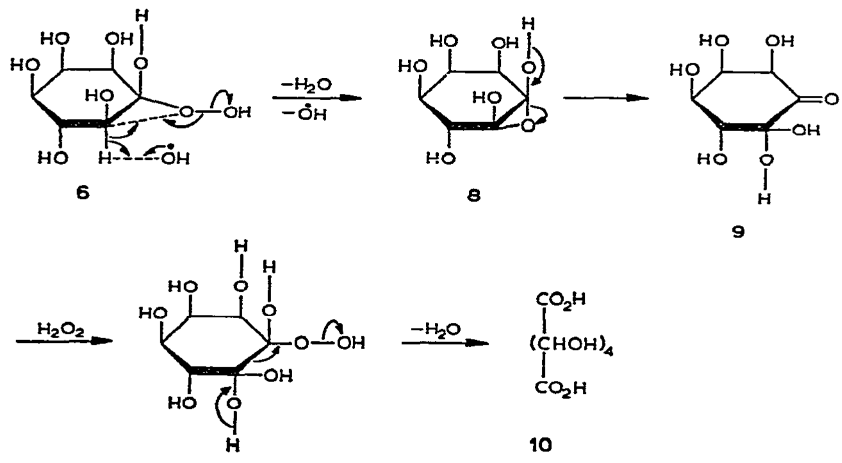
The reactions of **1** with alkaline hydrogen peroxide were investigated because the *alpha* hydrogen atoms are unusually labile; this is shown by the fact that the compound undergoes enolization about 1000 times as rapidly as D-glucose[6]. The results in Table I indicate that **1** reacts by two processes: one yields carbon dioxide, formic acid, and oxalic acid, and the other, a hexaric acid. Presumably, both processes begin with the addition of hydrogen peroxide to the carbonyl group. As depicted in Scheme 1, decomposition of the hydroperoxide adduct (**6**) may take place by *alpha*-hydroxy peroxide cleavage, giving, as the primary product, a hexuronic acid (**7**). This intermediate would be degraded, by reactions reported in ref. 3, to carbon dioxide, formic acid, and oxalic acid. Compound **7** would consist of a hexuronic acid having the DL-*gluco* or DL-*altro* configuration, depending, respectively, on whether the 1–2 or the 1–6 bond of the parent compound **1** had been broken in the *alpha*-hydroxy peroxide cleavage. Neither hexuronic acid was available for comparative studies. However, it was previously shown[3] that, on oxidation with alkaline hydrogen peroxide, the hexuronic acids having the *gluco*, *galacto*, and *manno* configurations yield carbon dioxide, formic acid, and oxalic acid. Under the conditions of experiment 1*a* of Table I, the same three products were obtained from **1** in amounts of 1.41, 3.64, and 0.48 moles, respectively, per mole of that portion of **1** that was not oxidized to a hexaric acid. Under the conditions of experiment 1*b*, the same products were obtained in amounts of 1.28, 3.72, and 0.44 moles, respectively. The results indicate that part of **1** is oxidized to a hexuronic acid, presumably by an *alpha*-hydroxy peroxide cleavage, and subsequently to the end products, carbon dioxide, formic acid, and oxalic acid; the rest is oxidized to a hexaric acid.



Scheme 1.

Presumably, the hexaric acid is formed by the epoxide-forming, peroxide cleavage reaction of Scheme 2. The first step in the process, removal of the labile hydrogen atom of **6**, may be accomplished by reaction with either a hydroxyl ion or a hydroxyl radical. The electron pair released from the hydrogen atom in the ionic mechanism (or the lone electron in the radical mechanism) moves to the electron-deficient peroxide oxygen atom, forming epoxide **8** and releasing a hydroxyl ion or a hydroxyl radical. Compound **8** decomposes to a hydrated, *alpha* diketone (**9**) that reacts with additional alkaline hydrogen peroxide, ultimately yielding a hexaric acid (**10**).

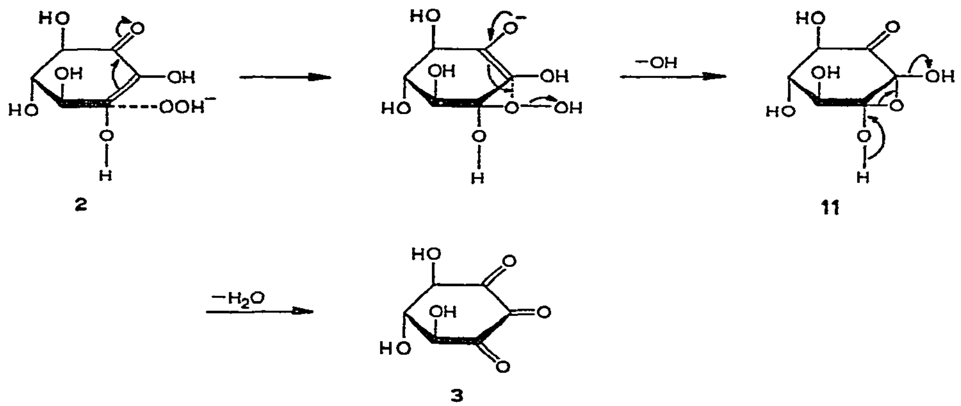
Experimentally, under the conditions of experiment 1*a*, **1** gave **10** in 54% yield,



Scheme 2.

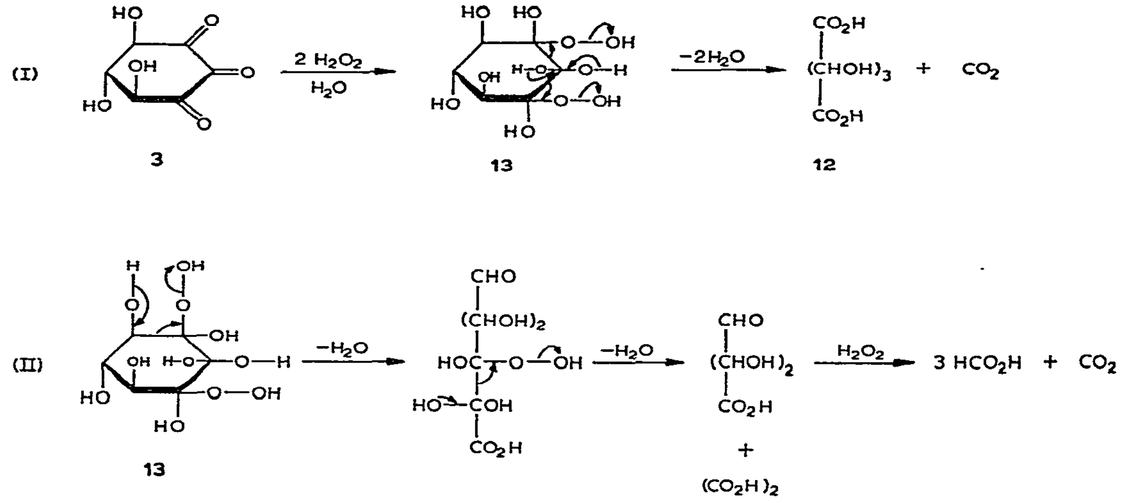
and, under the conditions of experiment 1*b*, in 64% yield. Compound **10** could have either the DL-*gluco* or the DL-*talo* configuration, depending on whether, in the formation of **8**, the labile hydrogen atom was removed from one side or the other of the ketone group of the original substrate. DL-Glucaric acid was separated from the reaction mixture in high yield, and identified as its crystalline calcium salt. DL-Talaric acid, although it may have been present in small amounts, was not identified.

Prior workers have established that, on treatment with alkaline hydrogen peroxide[7,8], *alpha,beta* unsaturated ketones afford epoxides. Hence, it was of interest to examine the behavior of *xylo*-pentahydroxy-2-cyclohexen-1-one (**2**), the enolic form of diketo-*myo*-inositol. Treatment of **2** with a molar equivalent of sodium peroxide gave a strong qualitative test for **3**. Thus, it appeared that the oxidation of **2** proceeds, at least in part, through **3**. Presumably, the reaction involves the formation of epoxide **11** (see Scheme 3).



Scheme 3.

With a large excess of aqueous sodium peroxide, both **2** and **3** gave carbon dioxide, formic acid, oxalic acid, and xylaric acid (**12**) in the yields given in Table I. When treated with sodium peroxide, compound **3** presumably yields the bis(hydroperoxide) (**13**) (see Scheme 4). One mole of this may decompose by reaction sequence I to one mole each of carbon dioxide and **12**, or, by reaction sequence II, to one mole of carbon dioxide, three moles of formic acid, and one mole of oxalic acid. The amount of **12** found indicates that, with aqueous sodium peroxide, 57% of **2**, and 43% of **3** were degraded, presumably by reaction sequence I. The portion of **2** degraded by reaction sequence II gave carbon dioxide, formic acid, and oxalic acid in yields of 0.65, 3.33, and 1.00 moles, respectively, per mole of substrate, whereas the portion of **3** gave yields of 1.21, 2.40, and 1.17 moles per mole. The theoretical yields for the three products are, respectively, 1.0, 3.0, and 1.0 moles per mole. The low yield of formic acid and the high yield of oxalic acid from **3** may arise from the epoxide-forming, periodate-cleavage reaction of the intermediate glyceruronic acid[3]. The difference in the results for **2** and **3** suggests that **2** may not have reacted entirely through **3** as an intermediate. The values indicate that, with aqueous sodium peroxide as the oxidant, a substantial portion of both **2** and **3** is degraded by reaction sequence II.

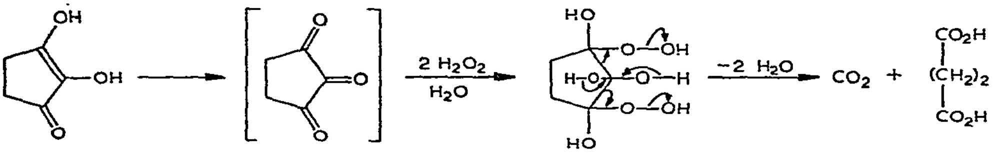


Scheme 4.

With an excess of hydrogen peroxide and alkali, the yields of formic acid and oxalic acid from **2** and **3** were much lower than those obtained with sodium peroxide as the oxidant. The reactions were very sensitive to contaminants, especially traces of heavy metals. Carbon dioxide was not determined for experiments 2, 3, 4, and 5 in the *b* series.

Reaction sequence II of Scheme 4 initially involves the hydroxyl group of C-4 or C-6 of **13**, the peroxide adduct of **3**. With a compound lacking these hydroxyl groups, this sequence would not be possible, and the compound should be degraded entirely by a sequence analogous to I. It was, therefore, of interest to study the degradation of reductic acid (4) and ninhydrin (5).

Presumably, on treatment with alkaline hydrogen peroxide, 4 is converted into an epoxide that decomposes to cyclopentane-1,2,3-trione. As depicted in Scheme 5, reaction of this with additional hydrogen peroxide yields carbon dioxide and succinic acid by a process analogous to sequence I of Scheme 4. Experimentally, 4 gave almost quantitative yields of carbon dioxide and succinic acid.



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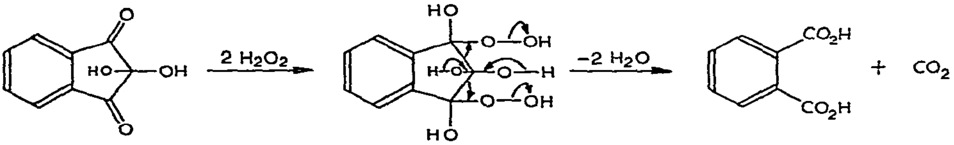
Scheme 5.

By a similar mechanism (see Scheme 6), 5 should afford carbon dioxide and phthalic acid. As shown in Table I, these products were obtained in high yield. The reaction is in accord with the previously known degradations of di- and poly-ketones by alkaline hydrogen peroxide[8].



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Scheme 6.

All of the reactions considered here presumably begin with the addition of hydroperoxide anion to a carbonyl form of the substrate. The resulting hydroperoxide adduct decomposes in various ways, according to the availability of electrons for rupture of the oxygen–oxygen bond of the peroxide. In the complete absence of heavy-metal catalysts, the decomposition reactions are slow, and depend in large measure on contaminants the presence of which is difficult to control. Probably, most of the decompositions are homolytic reactions involving hydroxyl radicals formed from hydrogen peroxide[9].

EXPERIMENTAL

General. — The following compounds were prepared by the methods cited: 2,3,4,6/5-pentahydroxycyclohexanone[10] (1); *xylo*-pentahydroxy-1-cyclohexen-1-

one[10] (2); *xylo*-trihydroxycyclohexane-1,2,3-trione[10] (3); reductic acid[11] (4); DL-glucaric acid[12] (10); and xylaric acid[13] (12). Other compounds and reagents were commercially available, A.C.S.-certified products. Melting points were determined with a Kofler hot stage apparatus, and i.r. spectra were recorded, for potassium bromide pellets, with a Perkin–Elmer Infracord model 137 spectrophotometer. Cations were removed with Amberlite IR-120 (H^+) ion-exchange resin. Evaporations were conducted at 40–50° in a rotary, vacuum evaporator.

Oxidation measurements of Table I. — Reaction mixtures for experiments designated *a* were prepared by dissolving each substrate (2 millimoles) in ice-cold 1M sodium peroxide (50 ml). The mixtures were kept for 24 h at 4°, and then diluted to 100 ml with carbon dioxide-free water. Carbon dioxide, formic acid, and oxalic acid were determined on aliquots of the reaction mixture by conventional methods, as described in ref. 3.

Reaction mixtures for experiments designated *b* were prepared by placing 2 millimoles of the substrate in a 100-ml volumetric flask containing 10 ml of ice-water and 6 ml of 30% hydrogen peroxide. The flask was immersed in an ice bath, and 0.25M sodium hydroxide was added dropwise during 1 h, to give a final volume of 100 ml. The mixtures were kept for 48 h at 4°, and then formic acid and oxalic acid were determined on aliquots by methods previously described.

Separation and identification of individual acids. — A portion of each of the reaction mixtures in series *a* and *b* was used for separation of the residual acids. The solution was warmed with activated carbon and Celite (0.3 g of each) until evolution of oxygen ceased. The solids were filtered off, the filtrate was passed through a column of Amberlite IR-120 (H^+) cation-exchange resin, and the eluate was evaporated under diminished pressure to a thick syrup; this was dissolved in water, and 5 ml of 1M calcium acetate was added. After several hours, the resulting calcium oxalate was filtered off, the filtrate was passed through a column of the cation-exchange resin, and the effluent evaporated to a syrup. Volatile acids were removed by successive addition and evaporation of three 5-ml portions each of water and toluene. The residual acid was dried to constant weight, and its neutralization equivalent was determined by titration with 0.1M potassium hydroxide. The various acids were regenerated by passage through the cation-exchange resin, and were identified by the following procedures.

The residual acid from **1** was neutralized with calcium carbonate, and the suspension was filtered while hot. The residue was thoroughly washed with hot water, and the filtrate was concentrated under diminished pressure to ~10 ml. The resulting crystalline salt was separated, washed with cold water, and dried. The i.r. spectrum of the product was essentially the same as that of calcium DL-glucarate prepared from DL-glucose[12]. A solution of the salt obtained from **1** was passed through a column of Amberlite IR-120 (H^+), and half of the eluate was neutralized with potassium hydroxide. The two portions were combined, and evaporated to a syrup, from which crystalline potassium hydrogen DL-glucarate separated. The equivalent weight of the acid salt (248) was determined by titration with 0.1M potassium hydroxide.

The residual acid from **2** and from **3** crystallized on concentration of the solution. Each was recrystallized from 0.1 ml of water by the addition of about 0.4 ml of acetic acid. After storage over sodium hydroxide, a satisfactory crop of crystals was separated, washed with acetic acid, and dried over sodium hydroxide. The melting point of each product, either alone, or mixed with authentic xylaric acid was 150–152° (lit.[13] m.p. 152°). The neutralization equivalent was determined by titration with 0.1M potassium hydroxide. The i.r. spectrum was essentially the same as that of the authentic acid.

On concentration, the residual acid from **4** gave a crystalline residue, which was extracted with ether. The m.p. (182°), neutralization equivalent (59), and i.r. spectrum were in agreement with those of authentic succinic acid.

The dry, residual acid from **5** was diluted with water to 100 ml. A 40-ml aliquot of the solution was neutralized with 0.1M potassium hydroxide, and combined with 40 ml of the acid solution. The mixture was evaporated to a syrup, which crystallized. After recrystallization from aqueous ethanol, its neutralization equivalent (204) agreed with that of potassium hydrogen phthalate.

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