Ozonolysis of Hydroxymethylene Ketones: the Baeyer–Villiger Reaction as a Source of Anhydride Formation

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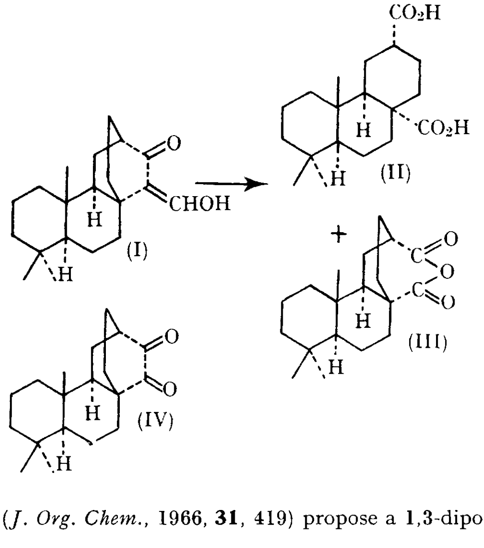
IN the total synthesis of (±)-1,1,12-trimethylperhydrophenanthrene-6,14-dicarboxylic acid (II), we reported[1] that the oxidative ozonolysis[2] of the hydroxymethylene ketone (I) gave (II) and a small amount of the ring-D anhydride (III). When base treatment was omitted during work-up, (III) could be obtained in yields of 36%. That (II) is not a precursor of (III) *via* dehydration was shown by ozonization of (I) in acetic acid–ethyl acetate (1 : 1) to give a mixture of anhydride (III), ν_{max} (KBr) 1800 and 1745 cm.$^{-1}$, and the diketone (IV), ν_{max} (KBr) 1760 and 1730 cm.$^{-1}$ Ozonolysis of (I) in neat methylene chloride also gave a mixture of the anhydride (III) and diketone (IV). Because of the extremely small amount of (I) available for study, the mechanism of this ozonization reaction was explored using the readily available 3-hydroxymethylene derivative (V) of camphor.

It seemed reasonable to suppose that anhydride formation is the result of a Baeyer–Villiger type oxidation of the α-diketone by a peracid generated during ozonolysis. According to the pathway proposed in Scheme 1, the molozonide (a)[3] which is formed by addition of ozone to the olefin (V), is unstable and decomposes to give the diketone (VI) and the zwitterion (b).[4]† The negatively charged



(I) (II) (III) (IV)

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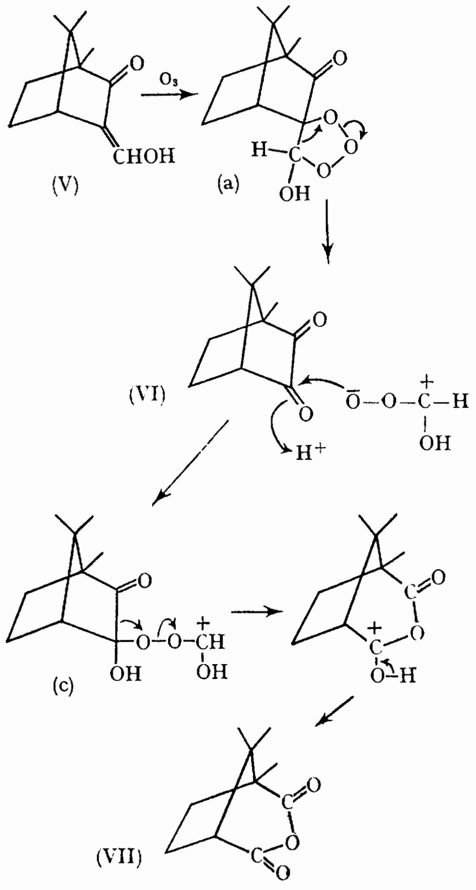
† It is interesting to note that H. Kwart and D. M. Hoffman (*J. Org. Chem.*, 1966, **31**, 419) propose a 1,3-dipolar addition of such a peracid zwitterion $(\mathrm{R{-}\overset{OH}{\underset{+}{C}}{-}O{-}O^{-}})$ in the peroxidation of olefins.

oxygen of (b)† or its tautomeric counterpart, performic acid, may attack (VI) to afford the intermediate (c) which could then rearrange to give the anhydride (VII). The steps from (VI) to (VII) are analogous to those in the Baeyer–Villiger reaction and an intermediate similar to (c) has been proposed by Krakower[5] to explain the abnormal ozonolysis products of fusidic acid and its derivatives.



SCHEME 1.

Compounds (VI) and (VII) have been isolated (by g.l.c.) from the reaction of (V) with ozone in various solvents and their structures established by comparison with authentic 3-ketocamphor (VI) and camphoric acid anhydride (VII), respectively.

The Table summarizes the percentages of (VI) and (VII) obtained by the ozonolysis of (V) in various solvents. The high yield of (VII) in reaction 1 is consistent with the general acid catalysis observed in the Baeyer–Villiger reaction.[6] The ease with which pyridine *N*-oxide is formed by oxidation of pyridine with various peracids[7] suggests that the predominance of (VI) obtained in reaction 2 is probably the result of the pyridine acting as a scavenger for peracid(s) generated during ozonolysis. The low yield of (VII) in reaction 3 can be explained in terms of hydroperoxide formation.[8] The presence of peracid(s) is demonstrated by ozonolysis of (V) in methylene chloride containing an excess of cyclohexanone (reaction 4), part of which was converted into 6-hexanolactone by the Baeyer–Villiger oxidation.[9,10] Cyclohexanone and (VI) were unaffected by overozonization in neat acetic acid and methylene chloride.

TABLE

Solvent	3-Keto-camphor (VI) (%)	Camphoric acid anhydride (VII) (%)
1 Acetic acid	41	56
2 Methylene chloride–pyridine (1 : 1)	96	0·04
3 Methanol	75	0·08
4 Methylene chloride–cyclohexanone (9 : 1)	56	0·14
5 Methylene chloride	70	0·13

Other peracids may be present in this system. Bernatek has reported[11] that carboxylic acids react with ozonides to produce peracids and Story has shown[10] that peracids are produced early in a normal ozonolysis by oxidation of aldehydes. In neutral solvents, 3-hydroxymethylenecamphor (V) is known to exist in equilibrium with its isomer, 3-formylcamphor (VIII),[12]‡ which may be oxidized to the peracid (IX) as described by Story. Then, the anhydride (VII) could also be formed by the pathway described in Scheme 2. All the steps are analogous to those in Scheme 1 with the exception of the peracid involved. The small amount of camphor (X) isolated in reaction 5 substantiates Scheme 2. The near quantitative combined yields of (VI) and (VII) in reactions 1 and 2, however, suggest that the equilibrium must lie far to the left in acidic and basic solvents (*i.e.*, to the side of the hydroxymethylene derivative).

‡ By integrating the aldehydic proton, τ 9·77 (doublet) and vinyl proton, τ 6·80, we obtained the aldehyde: hydroxymethylene ratio in $CDCl_3$ of 37 : 63.

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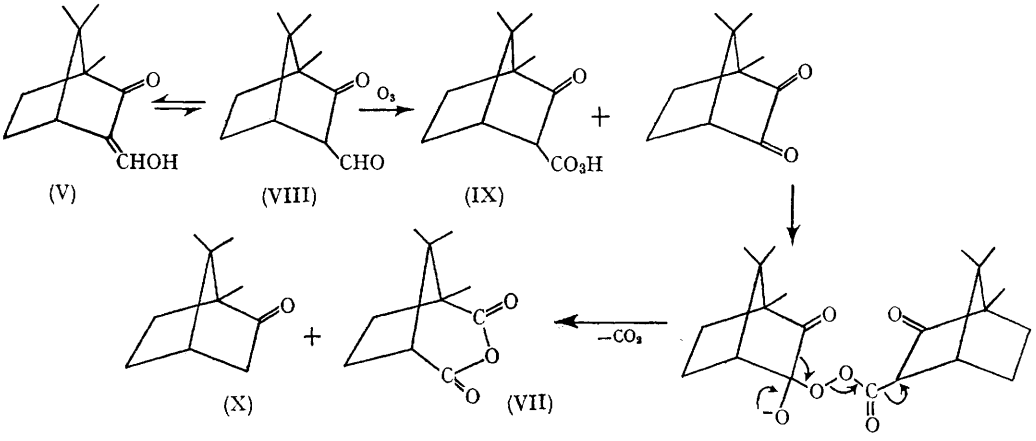

SCHEME 2.

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