

THE HYDROPEROXIDATION OF CYCLOHEX-3-ENONES

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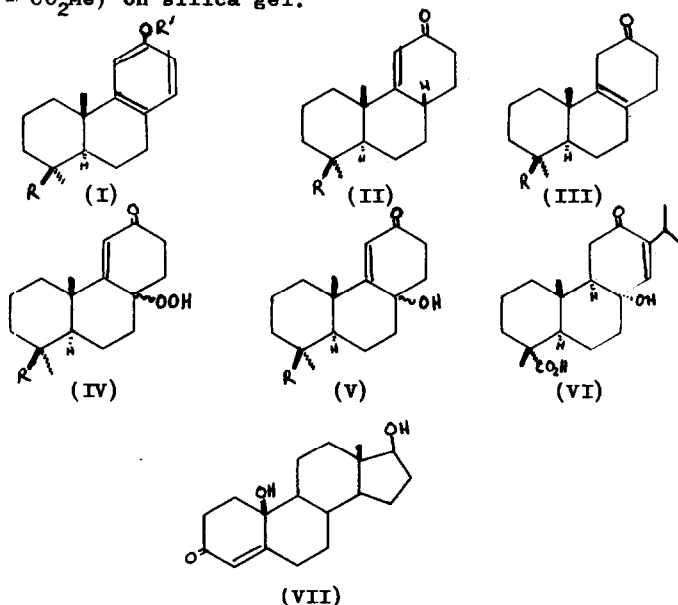
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The hydroperoxidation of ketones in the α -position,⁽¹⁾ and of conjugated ketones in the γ -position,⁽²⁾ by molecular oxygen, has been observed by a number of workers. Further, the autoxidation of a steroidal $\beta\gamma$ -unsaturated ketone to yield a γ -hydroperoxy-conjugated ketone has been reported.⁽³⁾ In connection with a proposed synthesis of the atisine carbon skeleton,⁽⁴⁾ we had occasion to chromatograph on silica gel, mixtures of the ketones (II) and (III), ($R = CO_2H$). Elution with ether yielded moderate quantities of a more polar substance to which we have assigned the 8- ξ -hydroperoxy-podocarp-8(11)-en-12-one-4- β -carboxylic acid structure (IV, $R = CO_2H$). The recent paper by Shapiro and co-workers⁽⁵⁾ describing a similar sequence of reactions in the steroid field, has prompted us to present some of our results in this preliminary form.

The starting material for these reactions was O-methylpodocarpic acid (I, $R = CO_2H$, $R' = Me$), which was obtained directly from podocarpic acid in high yield by addition of dimethyl sulphate to a strongly alkaline solution of the acid. The details of this process, which is markedly simpler than other published preparations of O-methylpodo-

carpic acid,⁽⁶⁾ will be presented elsewhere. Reduction with lithium in a variety of ammonia or amine media^(cf. 7) gave, after carefully controlled hydrolysis, a mixture of the ketones (II and III, $R = CO_2H$), in which the non-conjugated isomer predominated. The products of further reduction were also observed. On chromatography on silica gel the ketones were clearly separated and, in addition, the hydroperoxide (IV, $R = CO_2H$) was obtained in about 5% yield. This substance had m.p. 189° ; methyl ester (obtained by reaction with diazomethane), m.p. $160-161^\circ$. The ester was also obtained in small yield during chromatography of the ketones (II and III, $R = CO_2Me$) on silica gel.



The ester (IV, R = CO₂Me) was used in an investigation of the structure of these hydroperoxides, the details of which are as follows. Elemental analysis supported the formula C₁₈H₂₆O₅. In the ultraviolet region there appeared a band at 234 mμ (ε 14,600) as compared with the absorption of the ketone (II, R = CO₂Me) at 240 mμ (ε 14,500). A similar hypsochromic shift has been observed in the case of 10-β-hydroxyketone (VII) as compared with testosterone,⁽⁸⁾ and in the case of the ketol (VI) derived from levopimaric acid.⁽⁹⁾ The infrared spectrum (nujol) showed ν_{max} at 3300 (OH), 1730 (CO₂Me), 1680 (C=O), 1615 (C=C) and 915 cm.⁻¹ The band at 915 cm.⁻¹ was present in the spectra of all the hydroperoxides (IV) but was absent from the spectra of all other compounds in this series. Although it falls outside the normal range of 820-890 cm.⁻¹ (10) Therefore, it seems reasonable to assign this band to the -O-O- stretching mode. The peroxide nature of the compound was indicated by a positive starch-iodide test. Reduction with either zinc in acetic acid, or with sodium iodide to the alcohol (V, R = CO₂Me) m.p. 174°, followed by dehydration with sulphuric acid in acetic acid, gave methylpodocarpate (I, R = CO₂Me, R' = H). The configuration at C₈ cannot be assigned with certainty at the moment. The optical rotatory dispersion curves for the ketones (II and IV, R = CO₂Me) show Cotton effects of the same sign, but this result must be treated with caution since the C₈-substituents are not in a position where their effect can readily be predicted by the Octant Rule. Experiments to clarify this point are in hand.

It has been found that the hydroperoxides (IV,

R = $-\text{CO}_2\text{H}$, $-\text{CO}_2\text{Me}$ or $-\text{CH}_2\text{OH}$) can be produced from the appropriate $\beta\gamma$ -unsaturated ketones in fair yield by standing under oxygen in ethereal solution for some days. The same result is achieved more efficiently by bubbling oxygen through a solution of the ketones in carbon tetrachloride, at room temperature, with irradiation by a fluorescent lamp. In an endeavour to prepare these compounds by an alternative route, we treated the ketones (II) or (III) with potassium tert.-butoxide in tert.-butanol solution, under an atmosphere of oxygen. (cf.1) The uptake of one mole. of oxygen was observed, but the only isolated product was the phenol (I, R' = H). That the peroxide (IV) is not an intermediate in this oxidation is shown by the fact that on treatment with tert.-butoxide in tert.-butanol solution, no phenol is obtained, instead, a carboxylic acid being produced. The nature of this rearrangement product, and the mechanism of the oxidation to phenol are being investigated.

It has been found that the yield of hydroperoxide is considerably increased by the addition of free radical generators such as benzoyl peroxide. Also, in the dark, the reaction proceeds well in the presence of benzoyl peroxide after heating to about 60° . In the absence of such an initiator, no reaction occurs in the dark. Finally, in the presence of diphenylpicrylhydrazyl, the light induced reaction is completely suppressed, indicating that it is a free radical chain process. In the absence of normal free radical generators, the nature of the initiation process is in doubt. The possibility that it may involve the photo-excitation of the carbonyl group is difficult to reconcile with the

observation that in the presence of small quantities of acetone, the reaction is largely suppressed.

We are continuing our investigations of this and of other points in the formation and chemistry of these hydroperoxides, and are studying the extension of the reaction to simpler cyclohexenones.

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