AUTOOXIDATION OF STERIOD KETO ACIDS AND KETO ALDEHYDES

G. S. Grinenko and V. I. Bayunova

UDC 547.589:542.943

In recent years steroid hydroperoxides have attracted the attention of research workers in connection with the possibility of their use as intermediates for the preparation of steroid hydroxyketones, diketones, and other compounds, e.g., in the method for the 17α -hydroxylation of pregnanes [1], the 11β -hydroxylation of $\Delta^{5(10)}$ -3-ketosteroids [2, 3], in the synthesis of ecdysone through 2,3-diketosteroids [4, 5], in the preparation of 3-keto-6-hydroxy- Δ^4 -steroids [6], in the conversion of pregnanes to androstanes [7], etc. In addition, several steroid hydroperoxides have shown high physiological activity. Thus, compounds with formulas I have contraceptive action with a new biological mechanism [8, 9].



The oxidation of the ketones by air oxygen (autooxidation) is primarily used for the preparation of steroid hydroperoxides. In the process, ketones which form stable enols are readily oxidized to α -hydroperoxyketones. For most ketones, enolization is favored under alkaline conditions, and autooxidation is therefore carried out in the presence of alkoxides [1, 4-6] or amines [2]. 17α -Hydroperoxy-20-ketones of the pregnane series [1], 5α -hydroperoxy-6-ketones [1], etc., which contain a tertiary hydroperoxy group, were obtained in this manner. As a consequence of the ease of dehydration of the secondary hydroperoxy group to form a keto group, autooxidation in this case gives diketones [4, 5].

The oxidation of β , γ -unsaturated ketones is accomplished chiefly by illumination with fluorescent lamps. This route was used to obtain 10-hydroperoxides (I) from $\Delta^{5(10)}$ -3-ketones (II) [8, 10]. We now report the unusual autooxidation of 4-androstene-3,17-dione-19-carboxylic acid (IVb) and 19-aldehyde (IVa), which takes place at the quaternary C₁₀ carbon atom bonded to a carboxyl or aldehyde group. We have found that acetone solutions of these compounds are readily oxidized by oxygen in the air to form hydroperoxide V. This conversion amounts to 60-80% after 7-8 days, and the hydroperoxide is isolated in 50-57% yield. The reaction proceeds better in the dark, since the possibility of photoxidation is excluded.



Ordzhonikidze All-Union Scientific-Research and Pharmaceutical-Chemistry Institute, Moscow. Translated from Khimiko-Farmatsevticheskii Zhurnal, Vol. 6, No. 2, pp. 25-27, February, 1972. Original article submitted June 29, 1970.

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The structure of V was established on the basis of its ability to oxidize potassium iodide (iodometric titration) [11] and from the UV and IR spectra. The absorption maximum of this compound in the UV region is shifted to the short-wave side by 8 nm as compared with the maxima of the acid and aldehyde (IVa, b). A hypsochromic shift under the influence of a hydroperoxy group [10] was observed for Ia and Ib. The IR spectrum of a dilute solution in carbon tetrachloride has an intense band at 3535 cm^{-1} , characteristic for the OH group, including hydroperoxides [12], and characteristic bands for the carbonyl groups at 1740 and 1687 cm⁻¹. Structure V was confirmed by converting it to the known 4-estren- 10β -ol-3,17-dione (VI) [13] by reduction of the hydroperoxy group with trimethyl phosphite. Alcohol VI, obtained in quantitative yield via the method described in [13], was converted to estrone (VII) in 80% yield. The mechanism of this unusual autooxidation is being studied.

The tendency for autooxidation of IVa and IVb, which are used as intermediates in the production of 19-norsteroids [14], is the reason for the decreased yield in the oxidation of III in the presence of air.

EXPERIMENTAL

The specific rotation in chloroform was determined, and the UV spectra in 96% ethanol and the IR spectra of mineral oil suspensions were obtained. The NMR spectra were obtained with an IMC-100 spectrometer with an operating frequency of 100 MHz.

10β-Hydroperoxy-4-estrene-3,17-dione (V). a) A suspension of 2 g of IVa in 5 ml of acetone was allowed to stand in the dark at room temperature with access to the air; acetone was added periodically to keep the suspension at its original volume. After 3 days all the aldehyde had dissolved. After 7 days no more than 20% of the starting compound remained, according to thin-layer chromatography [fixed layer of silica gel, benzene – methanol (25:2)]. The solution was evaporated in vacuo, and the residue was crystal-lized from 8 ml of benzene to give 1.14 g of V. Recrystallization from benzene – methanol (3:1) yielded 0.7 g of V with mp 165-166° (dec.). Recrystallization from methanol gave an analytically pure sample with mp 166-166.5° (dec.) and $[\alpha]_{\rm D}$ +146°. UV spectrum: $\lambda_{\rm max}$ 236 nm, log ε 4.2. IR spectrum (cm⁻¹): 3340 (OOH), 1740 (CO), 1687 (=C-CO), 1635 (C=C). NMR spectrum: 0.853 ppm (18 CH₃), 5.91 ppm (4 H). Found %: C 70.81; H 7.75. C₁₈H₂₄O₄. Calc. %: C 71.05; H 7.94.

The mother liquors were evaporated, and the residue (1.2 g) was chromatographed on 30 g of silica gel; 0.4 g of the starting compound was first eluted with benzene-ether (9:1), followed by 0.46 g of V with mp 163-165° (dec.). The overall yield of V was 57.2% based on IVa.

b) A suspension of 16 g of IVb in 160 ml of acetone was allowed to stand at room temperature in the dark for 8 days (the acid dissolved completely after 3 days). The solvent was removed by vacuum distillation, and the residue was dissolved in benzene-chloroform (4:1). The solution was extracted with 5% sodium carbonate, washed with water until it gave a neutral reaction, and evaporated in vacuo. Crystallization of the residue (9.6 g) from benzene gave 6.5 g of V with mp 164-165.5° (dec.).

The mother liquors were evaporated, and the residue (3.1 g) was chromatographed on 90 g of silica gel; elution with benzene-ether (9:1) gave first 1.16 g of V and then 0.5 g of a compound with mp 198-200° and $[\alpha]_{\rm D}$ +147° (mp 204-206° and $[\alpha]_{\rm D}$ +147° according to the literature). IR spectrum (cm⁻¹): 3440, 1730, 1680, 1630. Found %: C 74.85; H 8.46. C₁₈H₂₄O₃. Calc. %: C 74.94; H 8.38.

Acidification of the sodium carbonate extract yielded 6.5 g of starting acid IVb. The overall yield of V was 50% based on acid IVb and 84% based on the recovered acid.

 $\frac{4-\text{Estren}-10\,\beta-\text{ol}-3,17-\text{dione (VI)}}{\text{of V in 5 ml of methanol.}}$ Trimethyl phosphite (0.5 ml) was added dropwise to a suspension of 1 g of V in 5 ml of methanol. The reaction mixture was stirred for 30 min and poured into a mixture of ice and water. The resulting precipitate was filtered to give a quantitative yield of VI with mp 197-199° and $[\alpha]_D + 148^\circ$ (cl, chloroform), the IR spectrum of which was identical to that of the sample obtained previously.

Estrone (VIII). A solution of 0.2 g of VI in 10 ml of acetone containing 4 drops of concentrated hydrochloric acid was refluxed for 1 h, vacuum evaporated to 5 ml, and 5 ml of water was added to give 0.16 g of VII with mp 255-256°, the IR spectrum of which was identical to that of an authentic sample.

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