141. *Ozonolysis of Conjugated Systems. Part III.* Rearrangement Products Formed on Ozonolysis of* 11-*Deoxy-steroidal* 1,4-*Dien*-3-*ones.*[1]

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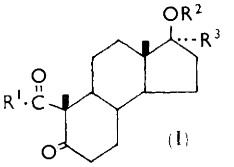
The ozonolysis of 1,2-didehydro-17α-methyltestosterone (II) and the derived 2-diselenide (III) were investigated. In addition to compounds formed by partial cleavage of ring A, rearranged products were obtained. A mechanism for the rearrangement has been suggested.

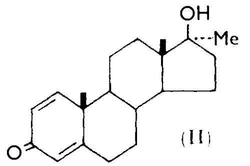
THE differences in the behaviour of steroidal 1,4-dien-3-ones with and without an oxygen function at C-11 on ozonolysis were pointed out in previous papers.[2,3] In the 11-oxygenated series, the cleavage proceeded in a " normal " manner and products of partial or complete rupture of the cross-conjugated system were isolated. In the 11-deoxy-series, considerable amounts of rearranged products were formed. It was suggested that the rearrangement proceeded through a cyclic peroxide, formed from the β-keto-aldehyde (Ia) and encompassing both carbonyl groups.[3-5] To confirm the observations, the ozonolysis of 17β-hydroxy-17α-methylandrosta-1,4-dien-3-one (II) and of the selenide (III) were investigated, and the results are reported here.

17β-Hydroxy-17α-methylandrosta-1,4-dien-3-one (II) was prepared by dehydrogenation of 17α-methyltestosterone with 2,3-dichloro-5,6-dicyano-*p*-benzoquinone.[6] The product (II) was ozonized in ethyl acetate and processed as previously described.[2,3] The ozonolysis proceeded slowly and required 10 hr. for completion. The products were separated into those soluble in ethyl acetate and those soluble in aqueous sodium carbonate. The residue from the ethyl acetate fraction deposited crystals, identified later as the acid (IVa). Chromatography of the mother-liquor on silica gel led to the separation also of products (Va) and (VI).

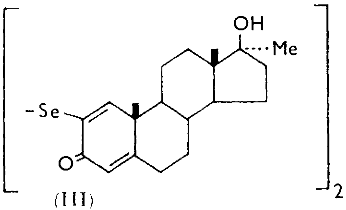


(I)

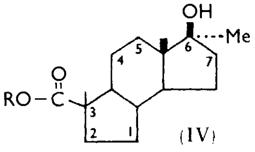
(a: $R^1 = H, R^2 = CO\ Et, R^3 = H$)
(b: $R^1 = H, R^2 = H, R^3 = Me$)
(c: $R^1 = OH, R^2 = H, R^3 = Me$)



(II)

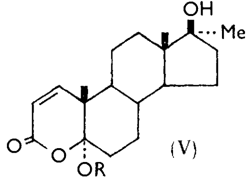


(III)



(IV)

(a: R = H) (b: R = Me)



(V)

(a: R = H) (b: R = Me)

The solid (IVa) showed no selective absorption in the ultraviolet region, had the formula $C_{16}H_{26}O_3$, and gave an infrared spectrum indicative of a carboxylic acid. Its equivalent showed it to be monobasic. That the product was not the β-keto-acid (Ic)

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* Part II, *Tetrahedron*, 1962, **18**, 1013.

[1] For simplicity steroidal nomenclature and numbering have been used in the discussion; generic names and numbering are employed for compounds (IV) and (VI) (see Handbook for Chem. Soc. Authors, *Special Publ. No.* 14, 1960, p. 64).

[2] Caspi, Schmid, and Khan, *Tetrahedron*, 1962, **18**, 767.

[3] Caspi, Taqui Khan, and Balasubrahmanyam, *Tetrahedron*, 1962, **18**, 1013.

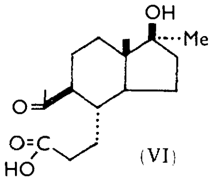
[4] Vinogradova and Zavialov, *Izvest. Akad. Nauk S.S.S.R., Otdel. khim. Nauk*, 1961, 1482.

[5] Payne, *J. Org. Chem.*, 1961, **26**, 4793.

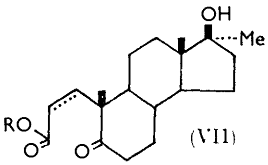
[6] Elks, Oughton, and Stephenson, *Proc. Chem. Soc.*, 1959, 6.

was evident from elemental analysis and from recovery of the starting material when it was boiled with aqueous acetic acid containing some phosphoric acid.[2,3] Absence of a ketone group was confirmed by optical rotatory dispersion, which gave a plain (negative) curve.[7,3] On treatment with diazomethane, the ester (IVb) was formed. The presence of three tertiary methyl groups was shown by the nuclear magnetic resonance spectrum which had bands at τ 8·80, 8·88, and 9·15. In addition, a strong band at τ 8·53, assigned to the methylene groups of the hydroindacene ring structure, was present.[8] Evolution of carbon monoxide when (IVa) was heated with concentrated sulphuric acid provided conclusive evidence for the presence of a tertiary carboxyl group,[9,10] in further support of the assigned structure. By analogy with the previous observations [2,3] and the proposed mechanism,[3] it is suggested that ozonolysis of the dienone (II) gave initially the β-keto-aldehyde (Ib) which, with an excess of ozone or hydrogen peroxide, formed in the reaction medium, was converted into the cyclic intermediate (VIII). The collapse of the peroxide (VIII) in the manner indicated gave the acid (IVa). A carbonium-ion mechanism, as has been postulated, precludes assignment of the configuration at the carbon bearing the geminal carboxyl and the methyl group.

From the chromatography of the mother-liquor, after the initial elution of an additional amount of acid (IVa), a solid was obtained which was predominantly the lactol (Va). This absorbed ultraviolet light (217 mμ) and had the correct analysis for $C_{19}H_{28}O_4$. Its structure follows from its reduction to the known compound (VIIa; no double bond at C-1).* The assignment of the lactol structure, and of the α-hydroxyl at C-5, rests on evidence previously presented.[2,3] However, the infrared spectrum had a weak band at 1740 cm.$^{-1}$



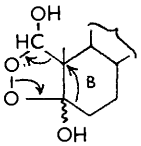
(VI)

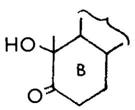


(VII)

(a: R = H) (b: Δ^1; R = Me)

(VIII)





(IX)

in addition to the main strong band at 1700 cm.$^{-1}$, indicating that the compound exists at least partly in the open keto-acid form. The lactol was converted by diazomethane into the keto-ester (VIIb). Evidence in support of the open-ring structure (VIIb) was provided by infrared spectroscopy which showed two carbonyl bands, at 1720 and 1695 cm.$^{-1}$. This is in contrast to similar cases previously reported [2,3] in which the " esters " existed in the lactol ether form (Vb) and gave a single carbonyl band.

The crystalline fraction eluted last from the column was compound (VI) which exhibited no selective absorption in the 205—240 mμ region. The infrared spectrum had bands at 3500, 3200br, 2700sh, and a single carbonyl band at 1700 cm.$^{-1}$. Analysis, however, showed it to have the composition $C_{16}H_{26}O_4$, and a titration indicated a monocarboxylic acid. The appearance of a Cotton effect (peak at 327 mμ; negative) in the optical rotatory dispersion curve indicated the presence of a ketone,[7] and permitted accommodation of all four oxygen atoms. Nuclear magnetic resonance spectroscopy showed, among others, bands at τ 7·81, 8·80, and 9·11 for three methyl groups. The bands at 9·11 and 8·80 were assigned to the tertiary methyls at C-13 and C-17, respectively (steroid numbering). The location of the third methyl group as far downfield as 7·81 could be reconciled only with

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* *Added in proof:* Lactol (Va) has recently been prepared by Pappo and Tung (*Tetrahedron Letters*, 1962, 365)

[7] Djerassi, " Optical Rotatory Dispersion," McGraw-Hill, New York, 1960, p. 3, and ref. therein.

[8] Moniz and Dixon, *J. Amer. Chem. Soc.*, 1961, **83**, 1671.

[9] Bistrzycki and Mauron, *Ber.*, 1907, **40**, 4370.

[10] Cornforth, Gore, and Popjak, *Biochem. J.*, 1957, **65**, 94.

an acetyl group, which was corroborated by a positive iodoform reaction. The nuclear magnetic resonance spectrum of the crude product, recovered from the haloform reaction, was now without a band in the τ 7·8 region. That this product was a dicarboxylic acid was evident from the spectrum of its dimethyl ester which had a band at τ 6·21 equivalent to 6 protons. The loss of the 19-methyl group establishes conclusively the location of the ketone group at C-10, and confirms the proposed structure. The formation of the keto-acid can be rationalized by assuming that the aldehyde (Ib) underwent a Baeyer–Villiger bond scission to yield the 10-hydroxy-5-ketone (IX) which was then cleaved to give the keto-acid (VI) whose indicated configuration is based on the premise that the preferred diequatorial (8α,9β) arrangement of substituents will be retained.

Initially, attempts had been made to prepare the dienone (II) by dehydrogenation of 17α-methyltestosterone with selenium dioxide. However, in t-butyl alcohol in the presence of pyridine [11] the major product was the diselenide [12] (III), whose structure was assigned on the basis of elemental analysis, ultraviolet absorption (296, 258, and 305 mμ), and infrared spectroscopy. The diselenide was ozonized and processed as described for the dienone (II). The residue of the ethyl acetate fraction consisted almost exclusively of the acid (IVa). The product recovered from aqueous sodium carbonate resisted crystallization and was boiled with a mixture of acetic and phosphoric acid.[2,3] Neutral and acidic fractions were also obtained. From the former a small amount of a solid, m. p. 159—160°, was obtained, and is under investigation.

EXPERIMENTAL

Infrared spectra were taken for materials in potassium bromide in paper blotters. Ultraviolet spectra were taken for methanol solutions on a Cary model 14 spectrophotometer. M. p.s were determined on a hot stage and are corrected. Nuclear magnetic resonance spectra were determined for deuterated chloroform or deuterated methanol solutions with tetramethylsilane as internal standard, on a Varian model V4300B high-resolution spectrometer. The spectra were calibrated by using a Hewlett-Packard model 200 CRD wide-range oscillator, together with a Hewlett-Packard model 521 CR electronic counter. Analyses were made by Dr. W. J. Kirsten, Uppsala, Sweden, and J. F. Alicino, Metuchen, N.J., U.S.A.

17β-*Hydroxy*-17α-*methylandrosta*-1,4-*dien*-3-*one* (II).—To a solution of 17α-methyltestosterone (19·9 g.) in dry dioxan (400 ml.) was added 2,3-dichloro-5,6-dicyano-*p*-benzoquinone, and the mixture was refluxed for 22 hr. The cooled solution was filtered and concentrated to a residue which was dissolved in methylene chloride–ether (1 : 3); the solution was washed successively with 2N-sodium hydroxide and water, dried (Na_2SO_4), and concentrated to a residue which yielded the *product* (II) (11·9 g.), m. p. 152—154° (from acetone), $\lambda_{max.}$ 247 mμ (ε 12,700), $\varepsilon_{max.}$ 3500, 1660, 1630, 1600 cm.$^{-1}$ (Found: C, 80·4; H, 9·55. $C_{20}H_{28}O_2$ requires C, 79·95; H, 9·4%).

Di-(17β-*hydroxy*-17α-*methyl*-3-*oxoandrosta*-1,4-*dien*-2-*yl*) *Diselenide* (III).—17α-Methyltestosterone (25 g.) in dry t-butyl alcohol (700 ml.) was refluxed with pyridine (14 ml.) and selenium dioxide (8 g.) for 6 hr. More selenium dioxide (4 g.) was then added, and the boiling was continued for 16 hr. The t-butyl alcohol was removed and the residue was dissolved in methylene chloride–ether (1 : 3). The organic solution was successively washed with sodium hydroxide solution, a freshly prepared solution of ammonium sulphide, aqueous ammonia, dilute hydrochloric acid, aqueous sodium hydrogen carbonate, and water. The methylene chloride–ether solution was dried and concentrated, to yield the *product* (9·96 g.), m. p. 160—161° (from methanol–methylene chloride), $[\alpha]_D^{24}$ +325·2° (in methanol), $\lambda_{max.}$ 246 (16,200), 258 (16,600), and 305 mμ (ε 1065), $\nu_{max.}$ 3580, 1645, 1625, 1595 cm.$^{-1}$ (Found: C, 63·5; H, 7·3. $C_{40}H_{54}O_4Se_2$ requires C, 63·5; H, 7·1%).

Ozonolysis of 17β-*Hydroxy*-17α-*methylandrosta*-1,4-*dien*-3-*one* (II).—A solution of the dienone (II) (4·48 g.) in ethyl acetate (100 ml.) at −70° was treated with ozonized oxygen. Samples were removed at intervals, and when the band at about 240 mμ disappeared leaving

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[11] Edwards, Ringold, and Djerassi, *J. Amer. Chem. Soc.*, 1960, **82**, 2318.

[12] Baran, *J. Amer. Chem. Soc.*, 1958, **80**, 1687.

only some end absorption (10 hr.) the reaction was stopped. Water (25 ml.) was added and the mixture was shaken at room temperature for 16 hr. The ethyl acetate phase was partitioned with a sodium carbonate solution into " neutral " (2·49 g.) and " acidic " (2·4 g.) fractions.

The neutral residue crystallized from methanol–ether to yield the acid (IV) (250 mg.). The mother-liquor was chromatographed on silica gel. Fractional elution with ethyl acetate–chloroform (3 : 7) allowed separation of the acid (IV) (890 mg.), the lactol (V) (277 mg.), and finally the keto-acid (VI) (530 mg.). Chromatography of the acidic residue (2·4 g.) gave additional amounts of (IVa) and (Va).

Ozonolysis of Di-(17β-*hydroxy*-17α-*methyl*-3-*oxoandrosta*-1,4-*dien*-2-*yl*) *Diselenide* (III).—A solution of the diselenide (3·01 g.) in ethyl acetate (110 ml.) at −70° was treated with ozonized oxygen, and the course of the reaction was followed by ultraviolet spectroscopy. The reaction was terminated (3·5 hr.) after the disappearance of the bands at 246 and 258 mμ, and the solution shaken with water (25 ml.) for 16 hr. Separation by sodium hydrogen carbonate solution gave a " neutral " (1·29 g.) and an " acid " (1·78) fraction. The neutral fraction crystallized on trituration with ethyl acetate. The acidic fraction resisted crystallization, and was refluxed for 1·5 hr. with a mixture of acetic acid (20 ml.) and N-phosphoric acid (0·8 ml.).[2] The volatile components were removed under reduced pressure, then the residue was dissolved in ethyl acetate and resolved by sodium hydrogen carbonate into " neutral " (0·89 g.) and acidic (0·76 g.) fractions. From this neutral fraction a small amount of solid, m. p. 159—161° was obtained.

Perhydro-6β-*hydroxy*-3ξ,5aβ,6α-*trimethyl*-as-*indacene*-3-*carboxylic Acid* (IVa).—The samples of *acid* (IVa) obtained in the various fractions from ozonolysis of (II) and (III) had m. p. 235—238° alone or in admixture, and all had identical infrared spectra. A sample, crystallized from methanol–ether, had m. p. 239—241°; rotatory dispersion, $[\alpha]_{500}$ −29°, $[\alpha]_{400}$ −38·7,° $[\alpha]_{300}$ −98° (*c* 0·31 in dioxan at 27°); $\lambda_{max.}$ no specific absorption in the 205—240 mμ region; $\nu_{max.}$ 3450, 3200br, 2640, 1700 cm.$^{-1}$; nuclear magnetic resonance, τ 8·53, 8·80, 8·88, and 9·15 (in deuteromethanol) (Found: C, 72·0, 71·9; H, 9·65, 9·9%; equiv., 277. $C_{16}H_{26}O_3$ requires C, 72·1; H, 9·8%; equiv., 266).

A mixture of the acid (50 mg.), acetic acid (7 ml.), and N-phosphoric acid (1 ml.) was boiled for 1 hr., but only the unchanged starting material was recovered.

Methyl Perhydro-6β-*hydroxy*-3ξ,5aβ,6α-*trimethyl*-as-*indacene*-3-*carboxylate* (IVb).—A solution of the acid was treated with an excess of ethereal diazomethane. Removal of the solvent left the *ester* (IVb), m. p. 60—62° (crystallized with great difficulty from ethyl acetate), $[\alpha]_D^{24}$ −18·6° (*c* 0·48 in dioxan), $\nu_{max.}$ 3400, 1725 cm.$^{-1}$, nuclear magnetic resonance, τ 6·34, 8·58, 8·78, 8·88, and 9·16 (Found: C, 73·5; H, 9·7. $C_{17}H_{28}O_3$ requires C, 72·8; H, 10·1%).

Evolution of Carbon Monoxide from the Acid (IVa).—Concentrated sulphuric acid (2 ml.) was added to the acid (IVa) (16·3 mg.) and the mixture was heated at 95° for 1·5 hr. The evolving gases were swept out with nitrogen through a train of apparatus consisting of a tube filled with ascarite, a U-tube containing iodine pentoxide at 120°, and an absorption trap with a half-saturated solution of barium hydroxide. Barium carbonate was precipitated, and iodine deposited in the cool part of the U-tube. In a blank experiment with sodium hydrogen carbonate neither iodine nor barium carbonate was formed.

5α,17β-*Dihydroxy*-17α-*methyl*-4-*oxa-androst*-1-*en*-3-*one* (Va).—The *lactol* (Va) eluted from the chromatographic columns of the " neutral " and " acidic " fractions from the ozonolysis of (II) had m. p. 200—203°, alone or in admixture, and gave identical infrared spectra. A sample, crystallized from ethyl acetate, had m. p. 204—207°; rotatory dispersion, $[\alpha]_{450}$ +398°, $[\alpha]_{350}$ +1143°, $[\alpha]_{300}$ +2430° (*c* 0·022 in dioxan at 24°); $\lambda_{max.}$ 217 mμ (ε 7500); $\nu_{max.}$ 3400, 1740sh, 1700s, 1620 cm.$^{-1}$ (Found: C, 70·7; H, 8·8. $C_{19}H_{28}O_4$ requires C, 71·2; H, 8·8%).

Methyl 17β-*Hydroxy*-17α-*methyl*-5-*oxo*-3,5-*seco*-4-*nor-androst*-1-*en*-3-*oate* (VIIb).—A solution of the lactol (Va) in methanol was treated with an excess of ethereal diazomethane. Removal of the solvent gave the *ester* (VIIb), m. p. 174—175° (from ethyl acetate–methanol); rotatory dispersion, $[\alpha]_{450}$ +23·9°, $[\alpha]_{350}$ +74·7°, $[\alpha]_{300}$ +234·15° (*c* 0·40 in dioxan at 27°); $\nu_{max.}$ 3580, 1720, 1695, 1625, 1200, and 1175 cm.$^{-1}$ (Found: C, 72·3; H, 9·5. $C_{20}H_{30}O_4$ requires C, 71·8; H, 9·0%).

17β-*Hydroxy*-17α-*methyl*-5-*oxo*-3,5-*seco*-4-*norandrostan*-3-*oic acid* (VIIa).—A solution of the lactol (Va) (15 mg.) in ethyl acetate (4 ml.) was agitated for 45 min. at room temperature with 10% palladium–charcoal (30 mg.) in an atmosphere of hydrogen. The catalyst was separated, and concentration of the filtrate gave the acid (VIIa), m. p. 189—190° (from ethyl acetate) undepressed on admixture with authentic (VIIa) prepared by ozonolysis of 17α-methyltestosterone.[13] The samples had identical infrared spectra.

5β-*Acetylperhydro*-1β-*hydroxy*-1α,7aβ-*dimethylinden*-4α-*ylacetic Acid* (VI).—A sample, crystallized from ethyl acetate, had m. p. 132—133°; rotatory dispersion, $[\alpha]_{450}$ −34·6, $[\alpha]_{350}$ −213°, $[\alpha]_{300}$ −425°, " min." $[\alpha]_{313}$ −832° (*c* 0·96 at 28° in dioxan); $\lambda_{max.}$, no selective absorption in the 205—240 mμ region; $\nu_{max.}$ 3450, 3200br, 2700br sh, 1700, 1165 cm.$^{-1}$; nuclear magnetic resonnance, τ 7·81, 8·80, and 9·11 (in deuteromethanol) (Found: C, 68·0; H, 9·5%; equiv., 294. $C_{16}H_{26}O_4$ requires C, 68·05; H, 9·3%; equiv., 282).

Haloform Reaction on the Keto-acid (VI).—The keto-acid (VI) (57 mg.) was dissolved in 2N-sodium hydroxide (2 ml.), and a 15% solution of iodine in 10% aqueous potassium iodide was added until a faint yellow colour persisted. After about 2 min. a copious precipitate of iodoform was formed which was identified by its odour and colour reaction with aqueous alkali and pyridine.[14]

The iodoform was removed and the filtrate extracted with chloroform. The aqueous phase was acidified with sulphuric acid and extracted with methylene chloride–ether (1 : 3). The extract was washed with sodium hydrogen sulphite solution and water, dried, and concentrated to a residue (44 mg.). The residue was chromatographed on silica gel and the diacid was eluted with ethyl acetate–hexane (3 : 1) as a glass. Its nuclear magnetic resonance spectrum had bands at τ 3·16, 8·75, and 9·04. The dicarboxylic acid was then treated with an excess of ethereal diazomethane. The crude diester showed, among others, a band at τ 6·21.

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[13] Gut and Uskokovic, *J. Org. Chem.*, 1961, **26**, 1943; Bolt, *Rec. Trav. chim.*, 1951, **70**, 940.

[14] Feigl, " Spot Tests in Organic Analysis," 5th edn., Elsevier, Amsterdam, 1956, p. 313.