Regioselectivity of the Reaction of 3-Keto Steroids with Potassium Superoxide

Enrique Alvarez, Cosme G. Francisco, Raimundo Freire,* Rosendo Hernández, José A. Salazar, and Ernesto Suárez
Instituto de Productos Naturales Orgánicos del C.S.I.C., Carretera de La Esperanza 2, La Laguna, Tenerife, Canary Islands, Spain
Carmen Betancor
Departamento de Química Orgánica, Universidad de La Laguna, Tenerife, Canary Islands, Spain

The regioselectivity in the oxidation of different types of 3-keto steroids with potassium superoxide in the presence of 18-crown-6 has been investigated. In all cases, the reaction products are directly related to the enolization process of the substrates. The oxidation of a 2-enolate results in oxidative cleavage of ring A with loss of carbon monoxide to give the lactols (**2**) and (**10**) and the aldehyde (**8**). However, the oxidation of 4-enolates occurs with oxidative cleavage of ring A to give the ketones (**7**) and (**12**), the latter with loss of carbon monoxide.

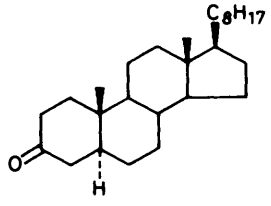
There is a growing interest in the reactivity of the superoxide anion with a variety of substrates, especially in aprotic media. Several recent reviews [1-3] provide evidence of the versatility of this reagent. Thus the superoxide anion behaves as a nucleophile in displacement reactions with alkyl halides, tosylates, acid chlorides, and esters. It is also an effective Brønsted base (pK_a *ca.* 23) and a moderate one-electron reducing agent for sulphur dioxide, several metallic ions, and quinones. In spite of the fact that it is a poor oxidizing agent by itself, through a one-hydrogen abstraction process it can dismutate to species that are good oxidants.[2]

Although Lee-Ruff reports [3] that isolated ketones are inert to $O_2^{\cdot -}$ oxidation, it has been shown that under catalytic phase-transfer conditions it is possible to cleave monocyclic ketones to afford the diacid without loss of carbon atoms.[4] We have recently found that isolated ketones can react with $O_2^{\cdot -}$ to give compounds in which one carbon atom is lacking.[5]

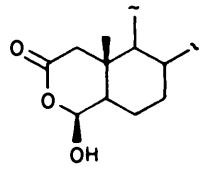
In this paper we report a detailed study of the reactions of $O_2^{\cdot -}$ with several representative 3-keto steroids and the products obtained are discussed on the basis of the mechanisms proposed. The identity of the products was consistent with the spectral data and the chemical evidence obtained (see Experimental section). Thus, treatment of 5α-cholestan-3-one (**1**) with potassium superoxide in dry benzene containing 18-crown-6 led to lactol (**2**), whose i.r. spectrum showed absorptions corresponding to OH (3 570 and 3 370 cm^{-1}) and CO groups (1 720 cm^{-1}). The ^1H n.m.r. spectrum of lactol (**2**) displayed a multiplet at δ_H 5.60, assigned to 4-H, and two doublets at δ_H 2.65 and 2.14 (*J* 18 Hz), corresponding to the AB system of the 1-H_2. The mass spectrum and the analytical data agree with the molecular formula $C_{26}H_{44}O_3$.

Chemical support for structure (**2**) was from reduction of this substance with $LiAlH_4$ to give the diol (**3**), and by methylation with methanolic hydrogen chloride or CH_2N_2 to give the methyl ester (**4**) or the methyl ester (**5**), respectively. In the ^1H n.m.r. spectrum of aldehydo ester (**5**) the signal corresponding to the aldehydic proton is a doublet (*J* 2 Hz), so this function must be at the atom which is C-4 of (**1**), and this led us to conclude that C-3 had been lost from compound (**1**)

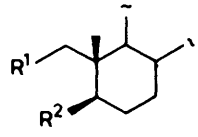
Similar treatment of 17β-hydroxy-4α-methyl-5α-androstan-3-one (**6**)[6] with potassium superoxide followed by methylation with diazomethane afforded a mixture of esters (**7**) (19%) and (**8**) (20%) which was resolved by column chromatography. I.r. data of compound (**7**) showed a broad band at 1 720 cm^{-1} corresponding to a carbonyl group. and its high-resolution mass



(**1**)

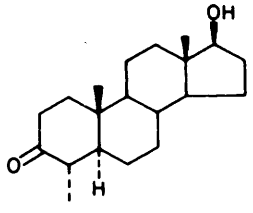


(**2**)

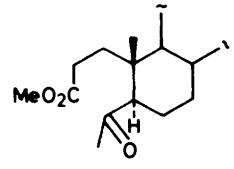


	R^1	R^2
(**3**)	CH_2OH	CH_2OH
(**4**)	CO_2Me	$HC(OMe)_2$
(**5**)	CO_2Me	CHO

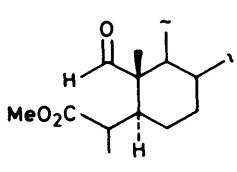
C_8H_{17} = $CH(Me)[CH_2]_3CHMe_2$



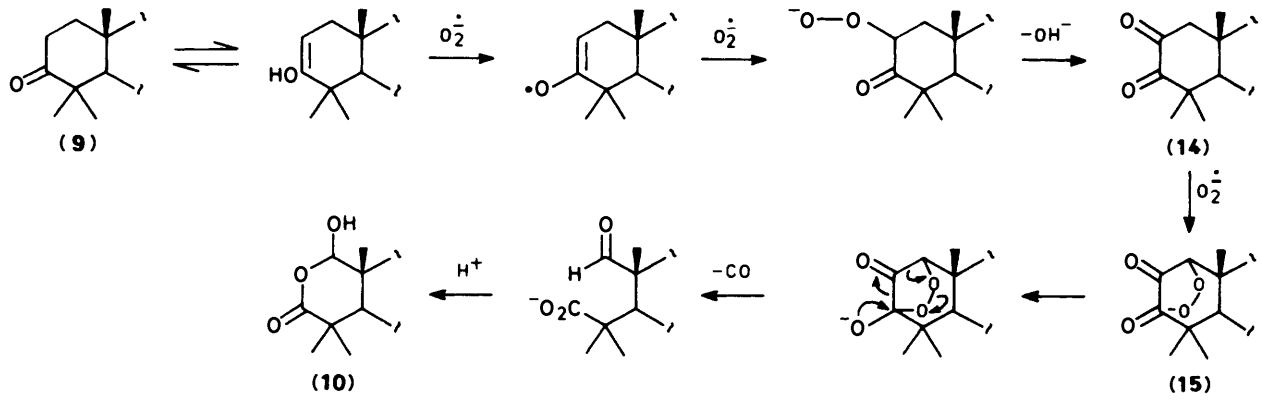
(**6**)



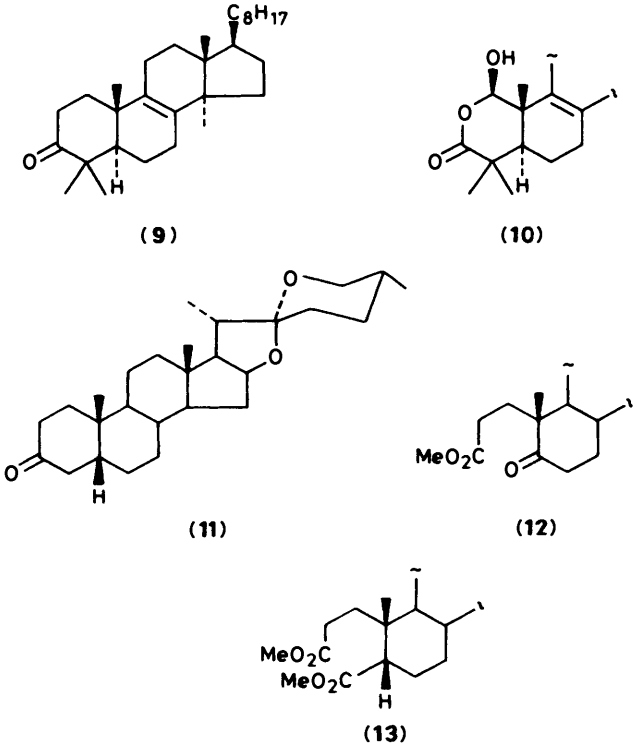
(**7**)



(**8**)



Scheme 1.



spectrum agrees with the molecular formula $C_{21}H_{34}O_4$. In the ^1H n.m.r. spectrum two singlets are observed, at δ_H 3.68 and 2.15, corresponding to a methyl ester and the 4-Me, respectively. Furthermore, the ^{13}C n.m.r. spectrum displayed signals at δ_C 212.0 (C-4) and 174.2 (C-3).

The structure of compound (**8**) was deduced on the basis of its spectroscopic properties. The i.r. spectrum shows a strong absorption at $\nu_{max.}$ 1 720 cm^{-1}, corresponding to a carbonyl group, and in its ^1H n.m.r. spectrum signals are observed at δ_H 9.15, a one-proton singlet assigned to the aldehydic 1-H, at δ_H 3.55 a singlet attributed to a methyl ester, and at δ_H 1.06 a doublet corresponding to the 3-Me.* The mass spectrum of this product exhibits a molecular ion at *m/z* 337 (*M* + 1, c.i.).

The lactol (**10**) obtained by reaction of 5α-lanost-8-en-3-one (**9**) with KO_2 under the same conditions was identical in all respects with the compound obtained by autoxidation of compound (**9**) with O_2 in the presence of potassium t-butoxide.[7]

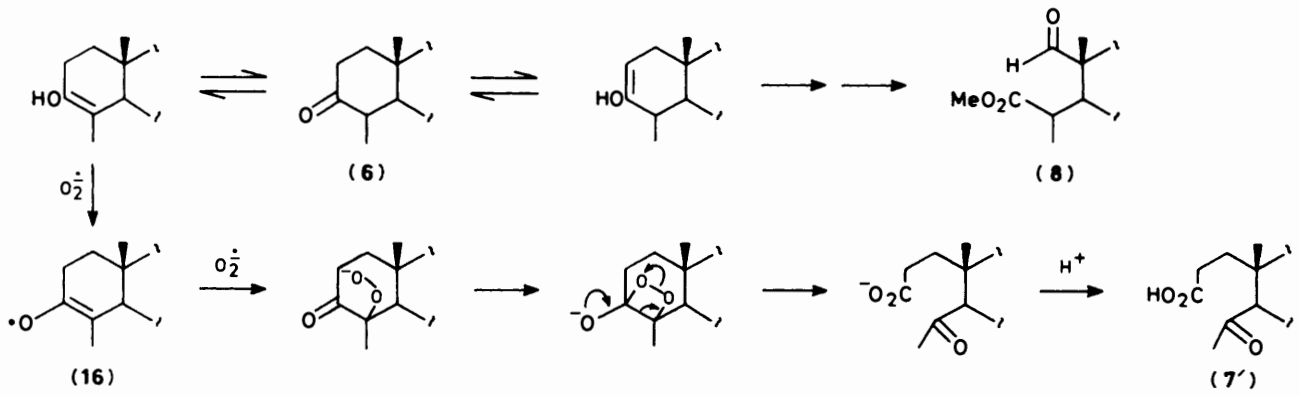
Finally, a mixture of acids was obtained by reaction of (25*R*)-5β-spirostan-3-one (**11**) with KO_2, and after methylation with CH_2N_2 the mixture was resolved by chromatography to give keto ester (**12**) (45%) and diester (**13**) (6%). The i.r. spectrum of compound (**12**) showed bands at $\nu_{max.}$ 1 730 and 1 700 (ester and ketone), 980, 920, 900, 865 cm^{-1} [(25*R*)-spirostan] and ^1H n.m.r. spectrum displayed resonances at δ_H 4.40 (m, 16-H) and 3.65 (s, methyl ester). Its mass spectrum exhibited the molecular ion at *m/z* 446. The minor product (**13**) showed in its i.r. spectrum bands at $\nu_{max.}$ 1 735 (methyl ester), 980, 920, 900, 865 cm^{-1} [(25*R*)-spirostan]. In the ^1H n.m.r. spectrum a singlet appears at δ_H 3.65, corresponding to the two methyl groups of the ester functions, and the mass spectrum shows the molecular ion at *m/z* 490.

The formation of the products (**7**), (**8**), and (**10**) from the ketones (**6**) and (**9**) can be rationalized in the light of the mechanism proposed in Schemes 1 and 2. Thus, in the reaction of lanost-8-en-3-one (**9**) (Scheme 1) the presence of a *gem*-dimethyl group in C-4 leads to enolization of the intermediate diketone (**14**). Subsequent attack by $O_2^{\cdot -}$ leads to peroxy anion (**15**) which undergoes rearrangement and elimination of C-2 to yield lactol (**10**). The obtention of products (**7**) and (**8**), in similar yields, from the reaction of ketone (**6**) is explained by initial enolization of the ketone group which takes place (equally favoured) through C-2 and C-3 (Scheme 2). The formation of keto acid (**7'**) without loss of carbon C-2 is explainable, since the diketone intermediate cannot be formed from the enolate (**16**) because of the presence of the 4-Me group, and nucleophilic attack at C-3 with rearrangement takes place instead.

Experimental

M.p.s were determined with a Kofler hot-stage apparatus and are uncorrected. Optical rotations were measured for solutions in $CHCl_3$ on a Perkin-Elmer 141 polarimeter. ^1H N.m.r. spectra were recorded with a Perkin-Elmer R-12B (60 MHz), an R-32 (90 MHz), or a Bruker WP200sy (200 MHz) instrument and ^{13}C n.m.r. spectra on a Varian C.F.T.-20 (20 MHz) instrument for solutions in $CDCl_3$ with Me_4Si as internal reference. I.r. spectra were measured on a Perkin-Elmer 257 instrument in $CHCl_3$ (unless otherwise stated). Low- and high-resolution, and chemical ionization (c.i.) (CH_4) mass spectra were determined with a VG Micromass ZAB-2F spectrometer. T.l.c. was performed on Merck silica gel 60 and column chromatography

* Systematic numbering. This methyl is attached to C-4 of starting material (**6**).



Scheme 2.

on Merck silica gel (0.063—0.2 mm). The spray reagent for t.l.c. was vanillin (1 g) in H_2SO_4–EtOH (4:1; 200 ml).

4β-*Hydroxy*-3-*oxa*-5α-*cholestan*-2-*one* (**2**).—To a stirred solution of 18-crown-6 (0.17 g, 0.64 mmol) in dry benzene (10 ml) under nitrogen at room temperature was added potassium superoxide (0.34 g, 4.78 mmol). After 15 min, a solution of 5α-cholestan-3-one (**1**) (0.37 g, 0.96 mmol) in dry benzene (5 ml) was added *via* a syringe. The resulting mixture was vigorously stirred for 7 h, then cautiously poured into dil. HCl (20 ml) and extracted with chloroform (3 × 30 ml). The combined extracts were washed with brine, dried over Na_2SO_4, and evaporated under reduced pressure. Chromatography of the residue on silica gel with ethyl acetate–benzene (1:9) gave *lactol* (**2**) (108 mg, 28%), m.p. 151—155 °C (from methanol); $[\alpha]_D$ +16° (*c* 0.2); $\nu_{max.}$ 3 570, 3 370 (OH), and 1 720 cm^{-1} (CO); δ_H 5.60 (1 H, m, $w_{\frac{1}{2}}$ 18 Hz, 4-H), 4.95 (1 H, m, $w_{\frac{1}{2}}$ 27 Hz, D_2O-exchangeable, 4-OH), 2.65 and 2.14 (2 H, AB, *J* 18 Hz, 1-H_2), 0.92 (3 H, d, *J* 6 Hz, 20-Me), 0.90 (3 H, s, 10-Me), 0.86 (total 6 H, 2 × d, each *J* 6 Hz, together 25-Me_2), and 0.66 (3 H, s, 13-Me) (Found: C, 77.0; H, 11.0%; M^+, 404. $C_{26}H_{44}O_3$ requires C, 77.18; H, 10.96%; *M*, 404).

A-*Nor*-2,3-*seco*-5α-*cholestane*-2,3-*diol* (**3**).—To a solution of lactol (**2**) (100 mg, 0.25 mmol) in diethyl ether (10 ml) was added a suspension of $LiAlH_4$ (60 mg), in diethyl ether (20 ml), and the mixture was refluxed for 1 h. The excess $LiAlH_4$ was quenched with saturated aqueous Na_2SO_4, the solution was filtered, and the organic phase was concentrated under reduced pressure. The residue was chromatographed [benzene–ethyl acetate (1:1) as eluant] to give the *diol* (**3**) (55 mg, 56%), m.p. 138—140 °C (from methanol); $[\alpha]_D$ +19° (*c* 0.12); $\nu_{max.}$ 3 420 cm^{-1} (OH); δ_H 3.73 (total 4 H, m, $w_{\frac{1}{2}}$ 18 Hz, 2- and 3-H_2), 3.37 (2 H, br s, $w_{\frac{1}{2}}$ 8 Hz, D_2O-exchangeable, 3- and 2-OH), 0.90 (3 H, s, 10-Me), 0.86 (total 6 H, 2 × d, *J* 6 Hz, together 25-Me_2), 0.83 (3 H, d, *J* 6 Hz, 20-Me), and 0.64 (3 H, s, 13-Me); *m/z* 374 (5%, $M^+ - H_2O$), 356 (2, $M^+ - 2H_2O$), and 347 (10, $M^+ - HO[CH_2]_2$) (Found: C, 78.9; H, 12.6. $C_{26}H_{48}O_2$ requires C, 79.53; H, 12.32%).

Methyl 3,3-*Dimethoxy*-A-*nor*-2,3-*seco*-5α-*cholestan*-2-*oate* (**4**).—Lactol (**2**) (0.31 g, 0.76 mmol) was dissolved in dry methanol, and a few drops of a saturated solution of hydrogen chloride in methanol were added. The mixture was stirred at room temperature for 12 h, and was then poured into water. After the usual work-up (chloroform for extraction) the crude material was purified by column chromatography [ethyl acetate–benzene (95:5) as eluant] to afford the amorphous *acetal* (**4**) (0.25 g, 70%); $\nu_{max.}$ 1 730 cm^{-1} (CO); $\delta_H(C_6D_6)$ 4.44 (1 H, d, *J* 4 Hz, 3-H), 3.41 (3 H, s, MeOCO), 3.30 and 3.24 (total 6 H, 2 × s, 2 × 3-OMe), 2.70 and 2.46 (2 H, AB, *J* 15 Hz, 1-H_2), 0.98 (3 H, d, *J* 6 Hz, 20-Me), 0.96 (3 H, s, 10-Me), 0.93 (total 6 H, 2 × d, each *J* 6 Hz, 25-Me_2), and 0.66 (3 H, s, 13-Me); δ_C 172.3 (C-2), 106.9 (C-3), 56.6 (C-17 or -14), 56.3 (C-14 or -17) 55.5, 54.4, and 50.9 (3 × OMe), 49.1 (C-5 or -9), 45.6 (C-5 or -9), 42.4 (C-13), 41.4 (C-1), 40.0 (C-16), 39.6 (C-24), 38.7 (C-10), 36.2 (C-22), 35.8 (C-20), 35.6 (C-8), 31.4 (C-7), 28.3 (C-12), 28.0 (C-25), 24.2 (C-15), 23.9 (C-23), 22.8 (C-27), 22.5 (C-26), 21.3 (C-11), 21.1 (C-6), 18.7 (C-21), 16.6 (C-19), and 12.0 (C-18); *m/z* 464 (c.i., M^+) 449 (0.5%, $M^+ - CH_3$), 433 (0.5, $M^+ - CH_3O$), and 75 [100, $HC(OMe)_2^+$] (Found: C, 74.8; H, 11.4. $C_{29}H_{52}O_4$ requires C, 74.95; H, 11.28).

Methyl-3-*Oxo*-A-*nor*-2,3-*seco*-5α-*cholestan*-2-*oate* (**5**).—Lactol (**2**) (96 mg, 0.23 mmol) was methylated with an excess of an ethereal solution of diazomethane and the product was purified by column chromatography [benzene–ethyl acetate (8:2) as eluant] to give the amorphous *methyl ester* (**5**) (90 mg, 91%); $\nu_{max.}$ 1 730 cm^{-1} (CO); δ_H 9.89 (1 H, d, *J* 2 Hz, 3-H), 3.62 (3 H, s, CO_2Me), 2.75 and 2.46 (2 H, AB, *J* 15 Hz, 1-H_2), 0.94 (3 H, d, *J* 6 Hz, 20-Me), 0.90 (3 H, s, 10-Me), 0.86 (total 6 H, d, *J* 6 Hz, 25-Me_2), and 0.66 (3 H, s, 13-Me); *m/z* 418 (0.5%, M^+), 390 (3, $M^+ - CO$), 359 (0.3, $M^+ - MeO_2C$), 345 (2, $M^+ - MeOCOCH_2$), and 316 (42, $M^+ - MeOCOCH_2 - CHO$) (Found: 418.3451 M^+, $C_{27}H_{46}O_3$ requires *M*, 418.3447).

17β-*Hydroxy*-4α-*methyl*-5α-*androstan*-3-*one* (**6**).—A solution of testosterone (4.0 g, 13.88 mmol) in tetrahydrofuran (80 ml) was treated with a solution of lithium metal (0.24 g) in liquid ammonia (200 ml), followed by addition of a solution of methyl iodide (18 ml) in diethyl ether (70 ml) according to the method of R. E. Schaub.[6] After purification of the crude material by column chromatography [benzene–ethyl acetate (97:3) as eluant] the ketone (**6**) (1.40 g, 33%) was obtained, m.p. 203—205 °C (from ethyl acetate–n-hexane); $\nu_{max.}$ 3 450 (OH) and 1 700 cm^{-1} (CO); δ_H 3.61 (1 H, t, 17-H), 1.05 (3 H, s, 10-Me), 0.94 (3 H, d, *J* 6 Hz, 4-Me), and 0.73 (3 H, s, 13-Me); δ_C 213.7 (C-3), 81.7 (C-17), 54.2 (C-9), 53.7 (C-5), 50.9 (C-14), 45.1 (C-4), 43.0 (C-13), 39.3 (C-1), 38.0 (C-2), 36.7 (C-12), 36.5 (C-10), 35.0 (C-8), 31.5 (C-7), 30.5 (C-16), 25.5 (C-6), 23.4 (C-15), 21.0 (C-11), 12.8 (C-20 or -19), 11.5 (C-19 or -20), and 11.2 (C-18); *m/z* 304.2376 (44%, M^+. Calc. for $C_{20}H_{32}O_2$: 304.2401), 289.2235 (6, $M^+ - CH_3$. Calc. for $C_{19}H_{29}O_2$: 289.2166), 286.2324 (8.7, $M^+ - H_2O$. Calc. for $C_{20}H_{30}O$: 286.2295), and 271.2051 (14, $M^+ - CH_3 - H_2O$. Calc. for $C_{19}H_{27}O$: 271.2060).

Methyl 17β-*Hydroxy*-4-*methyl*-4-*oxo*-3,4-*seco*-5α-*androstan*-3-*oate* (**7**) *and Methyl* 17β-*Hydroxy*-3-*methyl*-1-*oxo*-A-*nor*-1,2-*seco*-5α-*androstan*-2-*oate* (**8**).—To a stirred solution of 18-crown-6 (0.52 g, 1.97 mmol) in dry benzene (8 ml) at room

temperature was added potassium superoxide (1.40 g, 19.7 mmol). After 15 min, a solution of 17β-hydroxy-4α-methyl-5α-androstan-3-one (**6**) (0.60 g, 1.97 mmol) in dry benzene (15 ml) was added *via* a syringe. The resulting mixture was vigorously stirred for 6 h, then cautiously poured into dil. HCl and extracted with ethyl acetate (3 × 30 ml). The combined extracts were washed with brine, dried over Na_2SO_4, and evaporated under reduced pressure. The recovered product was methylated with an excess of an ethereal solution of diazomethane to give two major products, which were separated by medium-pressure liquid chromatography (m.p.l.c.) [benzene–ethyl acetate (90:10)] to afford the *aldehydo ester* (**8**) (less polar; 0.13 g, 20%), m.p. 128—130 °C (from methanol); $\nu_{max.}$ 3 600 (OH) and 1 720 br cm^{-1} (C=O); δ_H 9.15 (1 H, s, 1-H), 3.61 (1 H, t, 17-H), 3.55 (3 H, s, MeOCO), 1.06 (3 H, d, *J* 7 Hz, 3-Me), 0.96 (3 H, s, 10-Me), and 0.68 (3 H, s, 13-Me); δ_C 206.1 (C-1), 177.1 (C-2), 81.8 (C-17), 54.3 (C-10), 51.8 (MeO), 51.1 (C-14), 46.5, 43.2 (C-13), 43.0, 40.4, 36.5 (C-12), 34.3 (C-8), 31.0 (C-7), 30.5 (C-16), 23.4 (C-15), 23.2 (C-6), 23.0 (C-11), 15.5 (C-20 or -19), 11.2 (C-18), and 8.2 (C-19 or -20); *m/z* (c.i.) 337 (3%, $M^+ + 1$), 305.2123 (6, $M^+ - CH_3O$. $C_{19}H_{29}O_3$ requires 305.2115), 289.2135 (0.3, $M^+ - COH - H_2O$. $C_{19}H_{29}O_2$ requires 289.2166), 287.1911 (2, $M^+ - CH_3O - H_2O$. $C_{19}H_{27}O_2$ requires 287.1960), 249.1782 (4, $M^+ - C_4H_7O_2$. $C_{16}H_{25}O_2$ requires 249.1852), and 231.1784 (2, $M^+ - C_4H_7O_2 - H_2O$. $C_{16}H_{23}O$ requires 231.1748; and the amorphous *methyl ester* (**7**) (more polar; 0.13 g, 19%), $[\alpha]_D$ −15° (*c* 0.5); $\nu_{max.}$ 3 600 (OH) and 1 720 (C=O); δ_H 3.68 (3 H, s, CH_3O), 3.63 (1 H, m, $w_{\frac{1}{2}}$ 12 Hz, 17-H), 2.15 (3 H, s, 4-Me), 1.02 (3 H, s, 10-Me), and 0.73 (3 H, s, 13-Me); δ_C 212.0 (C-4), 174.2 (C-3), 81.6 (C-17), 56.4 (C-9), 51.7 (MeO), 51.0 (C-14), 47.9 (C-5), 42.8 (C-13), 38.5 (C-10), 36.5 (C-12), 34.9 (C-8), 33.0 (C-6), 31.6 (4-Me), 30.7 (C-7), 30.4 (C-16), 27.9 (C-1 or -2), 24.5 (C-2 or -1), 23.3 (C-15), 20.0 (C-11), 17.1 (C-19), and 11.1 (C-18); *m/z* 350.2435 (3%, M^+. $C_{21}H_{34}O_4$ requires *M*, 350.2457), 332.2324 (5, $M^+ - H_2O$. $C_{21}H_{32}O_3$ requires 332.2351), and 318.2167 (10, $M^+ - CH_3OH$. $C_{20}H_{30}O_3$ requires 318.2195).

1β-*Hydroxy*-2-*oxa*-5α-*lanost*-8-*en*-3-*one* (**10**).—To a stirred solution of 18-crown-6 (0.18 g, 0.68 mmol) in dry benzene (8 ml) under nitrogen at room temperature was added potassium superoxide (0.5 g, 7.0 mmol). After 15 min a solution of 5α-lanost-8-en-3-one (**9**) (0.59 g, 1.38 mmol) in dry benzene (10 ml) was added. The reaction mixture was stirred for 24 h, and then poured into dil. HCl (50 ml) and extracted with chloroform (3 × 30 ml). The extracts were combined, washed with brine, dried (Na_2SO_4), and evaporated to dryness under reduced pressure. Column chromatography [benzene–ethyl acetate (90:10) as eluant] gave the previously described lactol (**10**)[7] (0.354 g, 60%), m.p. 170—171 °C (from methanol); $[\alpha]_D$ +70° (*c* 0.02); $\nu_{max.}$ 3 400 (OH) and 1 720 cm^{-1} (C=O); δ_H 5.60 (1 H, m, $w_{\frac{1}{2}}$ 12 Hz, 1-H), 4.65 (1 H, m, $w_{\frac{1}{2}}$ 12 Hz, D_2O-exchangeable, 1-OH), 1.28, 1.23, and 1.11 (total 9 H, 3 × s, 14-Me and 4-Me_2), 0.90 (3 H, s, 10-Me), 0.85 (total 6 H, 2 × d, each *J* 6 Hz, together 25-Me_2), and 0.70 (3 H, s, 13-Me); δ_C 179.3 (C-3), 137.7 (C-8), 128.4 (C-9), 100.6 (C-1), 50.5 (C-17), 49.9 (C-14), 44.5 (C-13), 40.7 (C-4), 40.1 (C-10), 39.5 (C-24), 39.0 (C-5), 36.5 (C-22 and -20), 30.9 (C-15 or -16), 30.7 (C-16 or -15), 28.9 (C-29), 28.0 (C-25 and -7), 25.8 (C-12), 24.1 (C-23 and -19), 23.5 (C-28), 22.8 (C-26 or -27), 22.5 (C-27 or -26), 20.6 (C-6), 18.7 (C-21), 18.4 (C-11), 17.5 (C-30), and 15.9 (C-18); *m/z* 444 (0.5%, M^+), 429 (1, $M^+ - CH_3$), 426 (1, $M^+ - H_2O$), 416 (13, $M^+ - CO$), 328 [9, $M^+ - (CH_3)_2CCO_2CHOH$].

Methyl (25R)-5-*Oxo*-A-*nor*-3,5-*secospirostan*-3-*oate* (**12**) *and Dimethyl* (25R)-3,4-*Seco*-5β-*spirostane*-3,4-*dioate* (**13**).—To a stirred solution of 18-crown-6 (0.423 g, 1.6 mmol) in dry benzene (10 ml) under nitrogen at room temperature was added potassium superoxide (0.66 g, 9.28 mmol). After 15 min a solution of (25*R*)-5β-spirostan-3-one (**11**) (0.817 g, 1.97 mmol) in dry benzene (5 ml) was added *via* a syringe. The mixture was stirred for 2 h, then poured into dil. HCl, and worked up in the usual way with EtOAc. The recovered product was methylated with an excess of an ethereal solution of diazomethane giving two major products, which were separated by column chromatography [benzene–ethyl acetate (7:93)] to afford the *diester* (**13**) (less polar; 55 mg, 6%), m.p. 190—192 °C (from benzene–n-hexane); $[\alpha]_D$ −35° (*c* 0.2); $\nu_{max.}$ 1 735 (CO), 980, 920, 900, and 865 cm^{-1} (25*R*-spirostan); δ_H 4.40 (1 H, m, $w_{\frac{1}{2}}$ 18 Hz, 16-H), 3.65 (total 6 H, 2 × s, 2 × MeOCO), 3.46 (2 H, m, $w_{\frac{1}{2}}$ 12 Hz, 26-H_2), 0.96 (3 H, d, *J* 6 Hz, 20-Me), 0.96 (3 H, s, 10-Me) and 0.77 (3 H, s, 13-Me); *m/z* 490.3289 (7%, M^+. $C_{29}H_{46}O_6$ requires 490.3295), 459.3046 (2, $M^+ - CH_3O$. $C_{28}H_{43}O_5$ requires 459.3111), 344.2360 (27, $C_{22}H_{32}O_3$ requires 344.2352), and 139.1114 (100, $C_9H_{15}O$ requires 139.1122); and the *methyl ester* (**12**) (more polar; 0.395 g, 45%), m.p. 105—107 °C (from methanol); $[\alpha]_D$ −48° (*c* 0.2); $\nu_{max.}$ 1 735, 1 700 (CO), 980, 920, 900, and 865 cm^{-1} (25*R*-spirostan); δ_H 4.40 (1 H, m, $w_{\frac{1}{2}}$ 18 Hz, 16-H), 3.66 (3 H, s, MeOCO), 3.45 (2 H, m, $w_{\frac{1}{2}}$ 12 Hz, 26-H_2), 1.12 (3 H, s, 10-Me), 0.97 (3 H, d, *J* 6 Hz, 20-Me), 0.84 (3 H, s, 13-Me), and 0.79 (3 H, d, *J* 6 Hz, 25-Me); *m/z* 446.3033 (6%, M^+, $C_{27}H_{42}O_5$ requires 446.3032), 431.2858 (1, $M^+ - CH_3$. $C_{26}H_{39}O_5$ requires 431.2798), 415.2858 (4, $M^+ - CH_3O$. $C_{26}H_{39}O_4$ requires 415.2848), and 387.2531 (4, $C_{24}H_{35}O_4$ requires 387.2536).

Acknowledgements

This work was supported by the Investigation Programme of the Comisión Asesora de Investigación Científica y Técnica.

References

1 D. T. Sawyer and J. S. Valentine, *Acc. Chem. Res.*, 1981, **14**, 393.
2 D. T. Sawyer and M. J. Gibian, *Tetrahedron*, 1979, **35**, 1471.
3 E. Lee-Ruff, *Chem. Soc. Rev.*, 1977, **6**, 195.
4 M. Lissel and E. V. Dehmlow, *Tetrahedron Lett.*, 1978, 3689.
5 E. Alvarez, C. Betancor, R. Freire, A. Martin, and E. Suárez, *Tetrahedron Lett.*, 1981, **22**, 4335.
6 R. E. Schaub and M. J. Weis, *Chem. Ind.* (*London*), 1961, 2003.
7 R. Hanna and G. Ourisson, *Bull. Soc. Chim. Fr.*, 1961, 587.

Received 19*th September* 1985; *Paper* 5/1621