Synthesis of Cycloartenol *via* 19-Oxygenated Lanostanes

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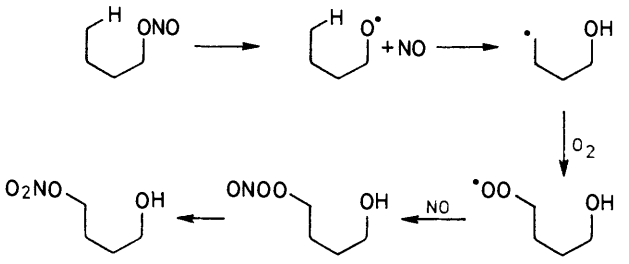
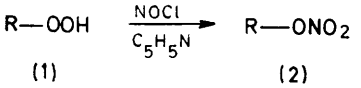
U.v. irradiation of 3β-acetoxy-5α-lanost-24-en-11β-yl nitrite in the presence of oxygen affords 3β-acetoxy-11β-hydroxy-5α-lanost-24-en-19-yl nitrate. Further standard steps then give 3β-acetoxy-5α-lanosta-9(11),24-dien-19-yl methanesulphonate, which is reduced by lithium aluminium hydride in refluxing diethyl ether to afford cycloartenol in good overall yield.

INTRAMOLECULAR hydrogen abstraction by a suitably oriented alkoxyl radical provides the only practical route for the introduction of a functional group on the angular methyl groups of terpenoid compounds. Such radicals are conveniently generated from either a nitrite ester [1] or a hypohalite.[2] Classically, the photolysis of nitrite esters is carried out in an inert atmosphere such that the product (nitroso dimer or oxime) contains a new C–N bond. Subsequent steps are then required to generate the biosynthetically [3] and medicinally [4] more important oxygen-substituted compounds. By conducting the photolysis in the presence of oxygen a new C–O bond can be introduced directly.[5] The mechanism originally postulated to account for this synthetically important modification of the nitrite photolysis reaction (Scheme) has recently received support from the



SCHEME

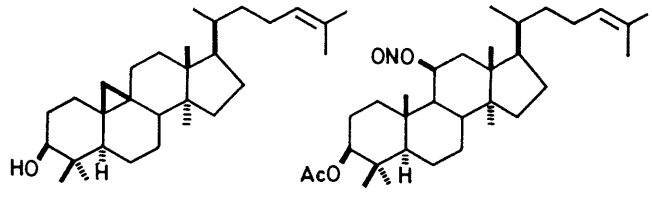
observation that treatment of a (tertiary) hydroperoxide (1) with nitrosyl chloride in pyridine at 0 °C affords in high yield the nitrate ester (2).[6]



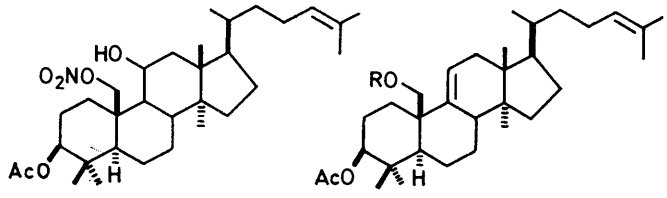
(1) (2)

In the lanosterol series an 11β-alkoxyl radical preferentially abstracts hydrogen from C-19,[7,8] although regeneration of the alkoxyl radical does result in subsequent functionalisation of C-18.[9] This fact was utilised in an elegant synthesis of cycloartenol (3),[7] the parent member of an important group of plant triterpenoids.[10] We now report a method for the synthesis of 19-oxygenated lanostanes, and the application of these compounds to an alternative and efficient synthesis of cycloartenol (3).

Irradiation of an oxygen-saturated solution of 3β-acetoxy-5α-lanost-24-en-11β-yl nitrite [7] (4) in dry carbon tetrachloride afforded 3β-acetoxy-11β-hydroxy-5α-lanost-24-en-19-yl nitrate (5). The use of other solvents (*e.g.* acetonitrile, tetrahydrofuran) [11] led to inferior yields of the nitrate (5). Separation of the nitrate (5) from re-formed 3β-acetoxy-5α-lanost-24-en-11β-ol was



(3) (4)



(5) (6) R = NO_2 (7) R = H

most conveniently achieved following dehydration of the mixture using thionyl chloride in pyridine. Chromatography then gave pure 3β-acetoxy-5α-lanosta-9(11),24-dien-19-yl nitrate (6) in an overall yield from (4) of 40%. Removal of the nitrate group to afford 3β-acetoxy-5α-lanosta-9(11),24-dien-19-ol (7) was readily achieved using zinc dust in acetic acid. The geometry of the homoallylic alcohol (7) suggested that hydride reduction of the derived 19-methanesulphonate would proceed with participation of the double bond and hence formation of the required cyclopropane ring. Indeed, treatment of the alcohol (7) with methanesulphonyl chloride in pyridine and reduction of the crude product by lithium aluminium hydride in refluxing diethyl ether afforded cycloartenol (3) (62%), accompanied by only 5% of 3β,19-dihydroxy-5α-lanosta-9(11),24-diene. When the reduction was carried out in refluxing tetrahydrofuran, the unwanted 3,19-dihydroxy-compound was the major product. Cycloartenol and the derived acetate were both identified by rigorous comparisons with authentic samples.

EXPERIMENTAL

M.p.s were determined for samples in open capillary tubes. N.m.r. data are for deuteriochloroform solutions with tetramethylsilane as internal reference, and were recorded at 90 MHz. Rotations are of solutions in chloroform. I.r.

data are for Nujol mulls. P.l.c. plates were prepared using Merck silica gel GF_{254}. Light petroleum refers to the fraction of b.p. 40—60 °C.

Photolysis of 3β-Acetoxy-5α-lanost-24-en-11β-yl Nitrite (4) *in the Presence of Oxygen.*—Dry oxygen was bubbled through refluxing, dry carbon tetrachloride (600 ml) for 1 h. After cooling, 3β-acetoxy-5α-lanost-24-en-11β-yl nitrite [7] (5 g) was added. A slow stream of dry oxygen was passed through the solution while it was irradiated at room temperature using a 125 W medium-pressure mercury vapour lamp until no starting material remained (t.l.c.). The solvent was evaporated off and the residue was chromatographed on a column of Merck silica gel 60. Elution with 5% ethyl acetate in light petroleum afforded an oil (2.8 g) consisting mainly of 3β-acetoxy-11β-hydroxy-5α-lanost-24-en-19-yl nitrate, together with 3β-acetoxy-5α-lanost-24-en-11β-ol. This oil in pyridine (30 ml) at 0 °C was treated with thionyl chloride (15 drops). After 10 min the mixture was poured into water and extracted with ether. The extracts were washed with 2N-hydrochloric acid and water, dried, and evaporated. The residue was purified by preparative l.c. to give 3β-acetoxy-5α-lanosta-9(11),24-diene (161 mg, 3%), m.p. (from chloroform–methanol) 154—155°, $[\alpha]_D$ +85° (*c* 0.4) (lit.,[12] m.p. 161—162°, $[\alpha]_D$ +81°) and *3β-acetoxy-5α-lanosta-9(11),24-dien-19-yl nitrate* (2.0 g, 40%), m.p. (from chloroform–methanol) 118—120°, $[\alpha]_D$ +80° (*c* 0.35), $\nu_{max.}$ 1 740, 1 635, 1 620, 1 285, 1 245, and 870 cm^{-1}, δ 0.65 and 0.77 (each 3 H, s, 32- and 18-H_3), 0.93 (6 H, s, 30- and 31-H_3), 1.58 and 1.65 (each 3 H, broad s, 26- and 27-H_3), 2.02 (3 H, s, OAc), 4.4—4.9 (3 H, m, 19-H_2 and 3α-H), 5.08 (1 H, t, 24-H), and 5.4 (1 H, m, 11-H) (Found: C, 72.5; H, 9.7; N, 2.4. $C_{32}H_{51}NO_5$ requires C, 72.55; H, 9.7; N, 2.6%).

3β-Acetoxy-5α-lanosta-9(11),24-dien-19-ol (7).—Zinc dust (5 g) was added to 3β-acetoxy-5α-lanosta-9(11),24-dien-19-yl nitrate (500 mg) in acetic acid (100 ml). The mixture was stirred at room temperature for 4 h, then filtered through Celite, and the solid residue was washed thoroughly with ether. The filtrate was extracted with ether and the extracts were washed with sodium carbonate solution, then water, dried, and evaporated. Crystallisation of the residue from chloroform–methanol afforded *3β-acetoxy-5α-lanosta-9(11),24-dien-19-ol* (420 mg, 92%), m.p. 182—183°, $[\alpha]_D$ +83° (*c* 0.81), $\nu_{max.}$ 3 515, 1 700, and 1 280 cm^{-1}, δ 0.66 and 0.79 (each 3 H, s, 18- and 32-H_3), 0.90 (6 H, s, 30- and 31-H_3), 0.90 (3 H, d, *J* 6 Hz, 21-H_3), 1.60 and 1.68 (each 3 H, broad s, 26- and 27-H_3), 2.04 (3 H, s, OAc), 3.60 (1 H, broad s, exchanged with deuterium oxide, OH), 3.66 (2 H, ABq, *J* 10 and 19 Hz, 19-H_2), 4.55 (1 H, m, 3α-H), 5.10 (1 H, t, 24-H), and 5.40 (1 H, m, 11-H) (Found: C, 79.1; H, 10.9. $C_{32}H_{52}O_3$ requires C, 79.3; H, 10.8%).

Cycloartenol (3).—3β-Acetoxy-5α-lanosta-9(11),24-dien-19-ol (250 mg) in dry pyridine (5 ml) was treated with methanesulphonyl chloride (10 drops) at room temperature for 12 h. The mixture was poured into ice–water and extracted with ether. The extracts were washed with 2N-hydrochloric acid, then water, dried, and evaporated to give crude 3β-acetoxy-5α-lanosta-9(11),24-diene-19-yl methanesulphonate, $\nu_{max.}$ 1 725, 1 340, and 1 170 cm^{-1}.

The crude methanesulphonate in dry ether (25 ml) was treated with lithium aluminium hydride (270 mg) under reflux for 1 h. The excess of lithium aluminium hydride was destroyed by the careful addition of water (0.5 ml) followed by 2N-sodium hydroxide (1 ml). The mixture was filtered through Celite and the solids were washed thoroughly with ether. The ether layer was separated, dried, and evaporated. Preparative t.l.c. of the residue (elution with 10% ethyl acetate in light petroleum) gave cycloartenol (136 mg, 62%), m.p. (from ethyl acetate–methanol) and mixed m.p. with an authentic sample 113—114°, $[\alpha]_D$ +54° (*c* 0.4) (lit.,[13] m.p. 115°, $[\alpha]_D$ +54°). The acetate had m.p. (from chloroform–methanol) 122—123°, $[\alpha]_D$ +57° (*c* 0.3) (lit.,[13] m.p. 122—124°, $[\alpha]_D$ +59°). The more polar product was 3β,19-dihydroxy-5α-lanosta-9(11),24-diene (12 mg, 5%), m.p. (from chloroform–methanol) 220—222°, $[\alpha]_D$ +71° (*c* 0.44).

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