A New Route to Steroid Ring-C Aromatization from 7-Oxygenated Steroids

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3β-Acetoxy-5α-cholesta-8,14-dien-7β-ol (3), 3β-acetoxy-8α,9α-epoxy-5α-cholestan-7β-ol (6a), and 3β-acetoxy-8α,14α-epoxy-5α-cholestan-7β-ol (8a) have been aromatized with hydrochloric acid in ethanol to afford a 9:1 mixture of 12-methyl-18-nor-5α,17β(H)-cholesta-8,11,13-trien-3β-ol (4) and 12-methyl-18-nor-5α-cholesta-8,11,13-trien-3β-ol (5). By the same acidic treatment 3β-acetoxy-8α,9α-epoxy-5α-cholestan-7α-ol (6c) generates 3β-hydroxy-5α-cholest-8-en-7-one (7a), and 3β-acetoxy-8α,14α-epoxy-5α-cholestan-7α-ol (8c) affords 3β-hydroxy-5α-cholest-8(14)-en-7-one (9a) accompanied by the previously unobserved 3β-hydroxy-5α-cholest-8(14)-en-15-one (10a).

As part of our interest in the synthesis of ring-C benzenoid steroids from readily available precursors we report here a new route to such compounds starting from 7-oxygenated steroids.

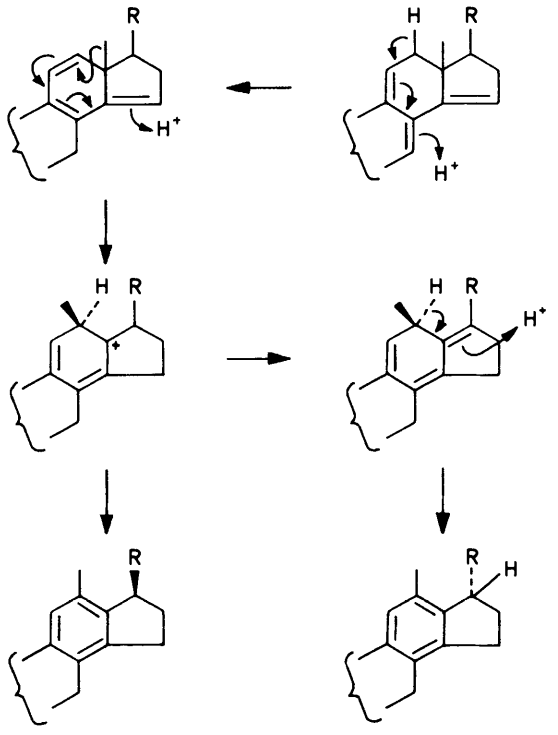
In a previous paper [1] we reported that a number of sterols of the cholestane series, oxygenated in the C- and D-rings, could be converted into ring-C benzenoid steroids by treatment with hydrochloric acid or toluene-*p*-sulphonic acid. The configuration of the side chain was retained in the molecular rearrangement promoted by toluene-*p*-sulphonic acid whilst the side-chain configuration was inverted in the rearrangement promoted by hydrochloric acid. Despite the different products obtained in the reactions with the two acids we isolated in both cases two intermediate trienes, 3β-acetoxy-5α-cholesta-7,9(11),14-triene (1b) and 3β-acetoxy-5α-cholesta-8,-11,14-triene (2), thus strongly supporting the mechanism proposed by Whalley *et al.*[2] (Scheme 1) for a similar aromatization.

With this mechanism in mind we considered that, on treatment with hydrochloric acid, 3β-acetoxy-5α-cholesta-8,14-dien-7β-ol (3) should afford the triene (1b) by elimination of the 7β-hydroxy-group which, on rearrangement and saponification, would give 12-methyl-18-nor-5α,17β(H)-cholesta-8,11,13-trien-3β-ol (4) and 12-methyl-18-nor-5α-cholesta-8,-11,13-trien-3β-ol (5).

To test this hypothesis, compound (3), prepared by sodium borohydride reduction of 3β-acetoxy-5α-cholesta-8,14-dien-7-one,[3] was treated with hydrochloric acid in ethanol at room temperature. Under these conditions the triene (1b) crystallized out as needles from a mixture with the corresponding alcohol (1a). When the reaction was performed in refluxing ethanol the aromatic sterol (4) was obtained in good yield, together with a small amount of the isomer (5).[1]

Since the 8,14-diene system present in compound (3) can be obtained by acidic treatment of an 8α,9α- or 8α,14α-epoxide ring, we treated 3β-acetoxy-8α,9α-epoxy-5α-cholestan-7β-ol (6a) with hydrochloric acid in refluxing ethanol. In this case the aromatic sterol (4) was obtained in 50% yield, together with the known [4] 3β-hydroxy-5α-cholest-8-en-7-one (7a) and a minor amount of compound (5). Analogous treatment of 3β-acetoxy-8α,14α-epoxy-5α-cholestan-7β-ol (8a) afforded the same sterol (4), together with 3β-hydroxy-5α-cholest-8(14)-en-7-one (9a),[4,5] 3β-hydroxy-5α-cholest-8(14)-en-15-one (10a),[6] and a small amount of compound (5).

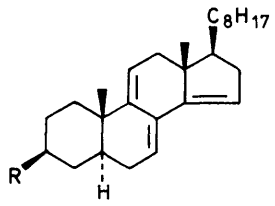
The formation of the ketones (7a) and (9a) by acidic treatment of compounds (6a) and (8a), respectively, parallels the formation of the analogous 8- and 8(14)-unsaturated ketones (7b) and (9b) by acidic treatment of the epimeric 8α,9α-epoxy-5α-cholestan-7α-ol (6b) and 8α,14α-epoxy-5α-cholestan-7α-ol (8b).[7]



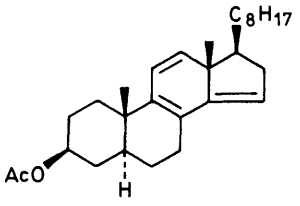
Scheme 1

In order to check if the acidic treatment of 3β-acetoxy-8α,9α-epoxy-5α-cholestan-7α-ol (6c) and 3β-acetoxy-8α,14α-epoxy-5α-cholestan-7α-ol (8c) afforded the unsaturated ketones without causing ring-C aromatization we subjected both epoxy-alcohols to the action of hydrochloric acid in ethanol. Thus, compound (6c) afforded the unsaturated ketone (7a) whilst the epoxy-alcohol (8c) was transformed into the ketone (9a), together with the rather unexpected isomeric ketone (10a). Products of ring-C aromatization were not observed in either reaction.

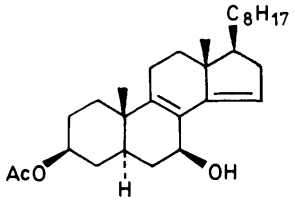
The different behaviour of the epimeric 7α- and 7β-hydroxy-epoxides to acidic treatment can be reasonably explained by inspection of Dreiding models of the appropriate compounds. It appears that in the case of the 7α-hydroxy-compound (6c) the 7β-hydrogen is antiparallel to the C(8)–O bond and hence, in the opening of the epoxide ring by the acid, it can easily undergo a 1,2-shift from the 7β- to the 8β-position with the (therefore preferred) formation of a 9α-hydroxy-7-



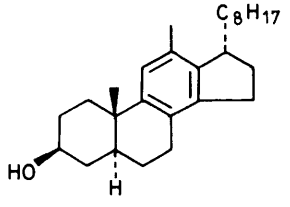
(1)
a ; R = OH
b ; R = OAc



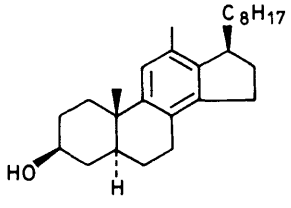
(2)



(3)

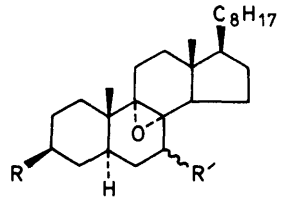


(4)

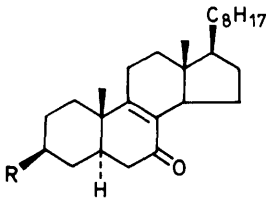


(5)

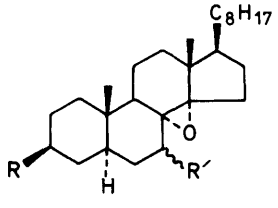
For compounds (1)—(12), C_8H_{17} = CH(Me)[CH_2]$_3$CHMe$_2$



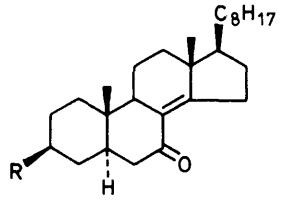
(6)
a ; R = OAc , R′ = β—OH
b ; R = H , R′ = α—OH
c ; R = OAc , R′ = α—OH



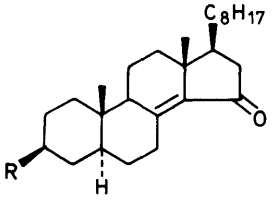
(7)
a ; R = OH
b ; R = H



(8)
a ; R = OAc , R′ = β—OH
b ; R = H , R′ = α—OH
c ; R = OAc , R′ = α—OH



(9)



(10)

a ; R = OH
b ; R = H

ketone which in turn affords the unsaturated ketone (7a) by dehydration.

The 7α-hydrogen of the 7β-hydroxy-isomer (6a) cannot undergo such a 1,2-shift and so the opening of the 8α,9α-epoxide ring to give an 8(14)-ene system [3] prevails over the direct formation of compound (7a), which in this case can originate only by a non-concerted mechanism.

Inspection of the Dreiding model of compound (8c) shows that in this case the 7β-hydrogen does not lie in the same plane as the C(8)—O bond and so the unsaturated ketone (9a) cannot form by a route similar to that assumed for (7a). It appears reasonable that an acidic opening of the epoxide ring of compound (8c) to afford the 14-ene-7α,8α-diol (11) (Scheme 2) could explain the formation of compounds (9a) and (10a). The 7-ketone (9a) could originate from the diol (11) by a 1,2-shift of the 7β-hydrogen, as occurs in the formation of a steroidal 7-ketone from a 7α,8α-diol,[8] followed by the conjugation of the double bond. The ketone (10a) could be formed by an allylic isomerization of compound (11) to the diol (12) which is known to afford the 8(14)-unsaturated ketone (10a) in the presence of mineral acid.[9]

The formation of compounds (9a) and (10a) from the 7β-hydroxy-compound (8a) probably involves a more complex mechanism and the dehydrative elimination of the 7β-hydroxy-group occurs with the opening of the epoxide ring to afford the triene (1a).

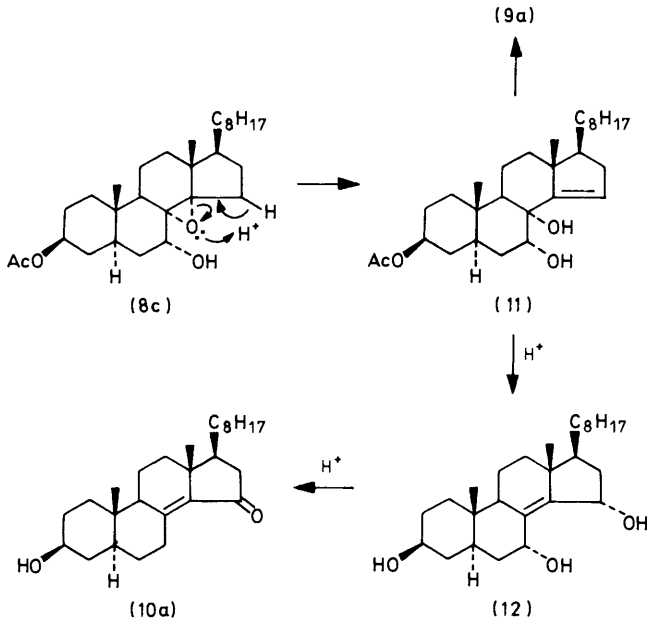
The direct production of the unsaturated ketone (10a) by treatment of compound (8c) with hydrochloric acid was unexpected in view of the previous work of Midgley and Djerassi.[7] These authors subjected the crude reaction mixture from 5α-cholest-7-ene with *m*-chloroperbenzoic acid to the action of hydrochloric acid and they isolated 9α-hydroxy-5α-cholestan-7-one as well as compounds (9b) and (10b). The formation of compound (10b) was explained as being due to the action of the organic acid preceding the treatment with hydrochloric acid. Our results suggest that the enone (10b) could also be formed by an opening of the epoxide ring of compound (8b) with mineral acid.

Experimental

All m.p.s are uncorrected. I.r. spectra were recorded on a Perkin-Elmer 157 spectrophotometer for solutions in chloroform or for Nujol mulls. U.v. spectra were recorded on a Varian 635 spectrophotometer.

^{1}H N.m.r. spectra were recorded on a Varian XL-100 spectrometer in $CDCl_3$ solutions with Me_4Si as internal standard. Mass spectra were recorded on a Varian 112 S mass spectrometer (direct inlet). The progress of all reactions, and eluates from column chromatography (silica gel; 230—400 mesh), were monitored by t.l.c. on E. Merck silica gel HF_{254} plates; spots were visualized by spraying with 70% sulphuric acid followed by heating.

Preparation of 3β-*Acetoxy*-5α-*cholesta*-8,14-*dien*-7β-*ol* (3), 3β-*Acetoxy*-8α,9α-*epoxy*-5α-*cholestan*-7β-*ol* (6a), and 3β-*Acetoxy*-8α,14α-*epoxy*-5α-*cholestan*-7β-*ol* (8a), *by Reduction of the Corresponding* 7-*Ketones*.—A solution of sodium borohydride (0.8 g) in water (0.5 ml) and methanol (10 ml) was slowly added to a swirled solution of the required 7-ketone (1 g) in methanol (40 ml). The mixture was left at room



Scheme 2.

temperature for 2 h with occasional agitation and was then poured into ice–water and extracted with diethyl ether. The extract was washed successively with water, 5% hydrochloric acid, 5% aqueous sodium hydrogen carbonate, and water and was then dried (Na_2SO_4) and evaporated to dryness to yield a crude product which, on chromatography on silica with hexane–ethyl acetate (7 : 3, v/v) as eluant, yielded the desired alcohol. Thus prepared were 3β-*acetoxy*-5α-*cholesta*-8,14-*dien*-7β-*ol* (3) (from 3β-acetoxy-5α-cholesta-8,14-dien-7-one [3]) (yield 700 mg) which resisted all efforts at crystallization; $\lambda_{max.}$ (EtOH) 248 nm (log ε 4.1); δ 5.6 (1 H, m, 15-H), 4.65 (total 2 H, m, 3- and 7-H), 1.1 (3 H, s, 19-H_3), and 0.95 (3 H, s, 18-H_3); *m/z* 442 (M^+) (Found: C, 78.7; H, 10.55. $C_{29}H_{46}O_3$ requires C, 78.73; H, 10.40%).

3β-*Acetoxy*-8α,9α-*epoxy*-5α-*cholestan*-7β-*ol* (6a) (from 3β-acetoxy-8α,9α-epoxy-5α-cholestan-7-one [3]) (yield 550 mg), m.p. 177—180 °C (from methanol); $[\alpha]_D^{20}$ +1.8°; δ 4.70 (1 H, m, 3-H), 4.00 (1 H, m, 7-H), 2.00 (3 H, m, OAc), 1.18 (3 H, s, 19-H_3), and 0.73 (3 H, s, 18-H_3); *m/z* 460 (M^+) (Found: C, 75.6; H, 10.5. $C_{29}H_{48}O_4$ requires C, 75.65; H, 10.48%).

3β-*Acetoxy*-8α,14α-*epoxy*-5α-*cholestan*-7β-*ol* (8a) (from 3β-acetoxy-8α,14α-epoxy-5α-cholestan-7-one [3]) (yield 550 mg), m.p. 129—131 °C (from methanol); $[\alpha]_D^{20}$ +10°; δ 4.70 (1 H, m, 3-H), 3.95 (1 H, m, 7-H), 2.00 (3 H, s, OAc), and 0.95 [total 6 H, 2 × 5 (overlapping), 18- and 19-H_3]; *m/z* 460 (M^+) (Found: C, 75.5; H, 10.35. $C_{29}H_{48}O_4$ requires C, 75.65; H, 10.48%).

In all reductions minor amounts of the corresponding 7α-epimers were observed on t.l.c. analysis of the crude reaction mixtures.

3β-*Acetoxy*-8α,9α-*epoxy*-5α-*cholestan*-7α-*ol* (6c) *and* 3β-*Acetoxy*-8α,14α-*epoxy*-5α-*cholestan*-7α-*ol* (8c).—3β-Acetoxy-5α-cholest-7-ene (1.5 g) was added in portions to a stirred solution of *m*-chloroperbenzoic acid (1.7 g, 85%) in chloroform (35 ml) at 0 °C. After 8 d at 4 °C in the dark the mixture was filtered and the filtrate was washed in turn with 5% aqueous sodium hydrogen sulphite and 5% aqueous sodium hydrogen carbonate. The dried organic phase was evaporated to dryness and the residue was chromatographed on silica gel with hexane–ethyl acetate (7 : 3, v/v) as eluant to afford (i) 3β-*acetoxy*-8α,14α-*epoxy*-5-*cholestan*-7α-*ol* (8c) (500 mg), m.p. 121—122 °C (from methanol); $[\alpha]_D^{20}$ +1°; δ 4.75 (1 H, m, 3-H), 3.65 (1 H, m, 7-H), and 0.95 [total 6 H, 2 × s (overlapping), 18- and 19-H_3]; *m/z* 460 (M^+) (Found: C, 75.7; H, 10.5. $C_{29}H_{48}O_4$ requires C, 75.60; H, 10.48%) and (ii) 3β-*acetoxy*-8α,9α-*epoxy*-5α-*cholestan*-7α-*ol* (6c) (600 mg) m.p. 145—147 °C (from methanol); $[\alpha]_D^{20}$ +34°; δ 4.75 (1 H, m, 3-H), 4.10 (1 H, m, 7-H), 1.05 (3 H, s, 19-H_3), and 0.69 (3 H, s, 18-H_3); *m/z* 460 (M^+) (Found: C, 75.8; H, 10.55. $C_{29}H_{48}O_4$ requires C, 75.60; H, 10.48%).

Reaction with Hydrochloric Acid at Reflux.—General procedure. A solution of the steroid (300 mg) in ethanol (33 ml) and hydrochloric acid (2 ml; 36%) was refluxed under nitrogen for 1 h. The solution was concentrated under reduced pressure, diluted with water, and extracted with diethyl ether. The combined extracts were washed successively with 5% aqueous sodium hydrogen carbonate and water and were then dried and evaporated to dryness under reduced pressure to yield a residue which was chromatographed on silica (40—63 mesh) with hexane–ethyl acetate (4 : 1, v/v) as eluant to separate the aromatic fraction from ketonic compounds. The aromatic fraction was then rechromatographed on silica gel G–Celite–$AgNO_3$ (1 : 1 : 0.3, w/w) with hexane–ethyl acetate (100 : 5, v/v) as eluant to separate 12-methyl-18-nor-5α,17β(H)-cholesta-8,11,13-trien-3β-ol (4) and 12-methyl-18-nor-5α-cholesta-8,11,13-trien-3β-ol (5) [from compounds (3), (6a), and (8a)].

Treatment of 3β-*acetoxy*-5α-*cholesta*-8,14-*dien*-7β-*ol* (3). Acid treatment of compound (3) gave, after chromatography, the *triene* (4) (145 mg) as an oil; $\lambda_{max.}$ (cyclohexane) 225 nm (log ε 4.07); $\nu_{max.}$ 3 500 and 3 330 cm^{-1}; δ 6.94 (1 H, s, 11-H), 3.67 (1 H, m, 3-H), 3.30 (1 H, m, 17-H), 2.26 (3 H, s, 18-H_3), 1.10 (3 H, m, 19-H_3), and 0.55 (3 H, d, *J* 6 Hz, 21-H_3); *m/z* 382 (M^+) (Found: C, 84.7; H, 11.1. $C_{27}H_{42}O$ requires C, 84.82; H, 11.14%) and the *triene* (5) (16 mg), m.p. 97—99 °C (from methanol); $\lambda_{max.}$ (cyclohexane) 225 nm; $\nu_{max.}$ 3 500 and 3 330 cm^{-1}; δ 6.93 (1 H, s, 11-H), 3.67 (1 H, m, 3-H), 3.15 (1 H, m, 17-H), 2.26 (3 H, s, 18-H_3), and 1.10 (3 H, s, 19-H_3); *m/z* 382 (M^+) (Found: C, 84.55; H, 11.1. $C_{27}H_{42}O$ requires C, 84.82; H, 11.14%).

Treatment of 3β-*acetoxy*-8α,9α-*epoxy*-5α-*cholestan*-7β-*ol* (6a). Acid treatment of compound (6a) gave after chromatography, (i) the aromatic compound (4) (110 mg), identical with that obtained from compound (3), (ii) the aromatic isomer (5) (12 mg), identical with that obtained from compound (3), and (iii) 3β-hydroxy-5α-cholest-8-ene-7-one (7a) (50 mg), m.p. 122—123 °C (from methanol); $\lambda_{max.}$ 253 nm; $\nu_{max.}$ 3 340, 1 655, and 1 586 cm^{-1}; identical with an authentic sample.[4]

Treatment of 3β-*acetoxy*-8α,14α-*epoxy*-5α-*cholestan*-7β-*ol* (8a). Similar treatment of compound (8a) gave, after chromatography, (i) the aromatic compound (4) (105 mg), identical with that obtained from compound (3); (ii) the aromatic isomer (5) (10 mg), identical with that obtained from compound (3), (iii) 3β-hydroxy-5α-cholest-8(14)-en-15-one (10a) (13 mg), m.p. 145—146 °C (from methanol); (lit.,[6] 145—146 °C), identical (n.m.r. and mass spectra) with an authentic sample, and (iv) 3β-hydroxy-5α-cholest-8(14)-en-7-one (9a) (30 mg), m.p. 129—130 °C (from methanol); $[\alpha]_D^{20}$ −54°, identical (n.m.r. and mass spectra) with an authentic sample.[4,5]

Treatment of 3β-*acetoxy*-8α,9α-*epoxy*-5α-*cholestan*-7α-*ol* (6c). Similarly, compound (6c) gave after chromatography, the ketone (7a) (120 mg), m.p. 122—123 °C, identical (n.m.r. and mass spectra) with an authentic sample.[4] No aromatic steroids were detected by g.l.c. analysis of the crude product.

Treatment of 3β-*acetoxy*-8α,14α-*epoxy*-5α-*cholestan*-7α-*ol*

(8c). In an identical manner, compound (8c) gave, after chromatography, the ketones (10a) (40 mg) and (9a) (100 mg), both identical with authentic samples. No aromatic steroids were observed by g.l.c. analysis of the crude product.

Isolation of 3β-*Acetoxy*-5α-*cholesta*-7,9(11),14-*triene* * (1b). —A solution of the alcohol (3) in ethanol (30 ml) and hydrochloric acid (2 ml; 36%) was kept at room temperature for 30 min and was then cooled. Under these conditions 3β-acetoxy-5α-cholesta-7,9(11),14-triene (1b) crystallized out as needles, m.p. 90—91 °C, identical (n.m.r. and mass spectra) with an authentic sample.[1] If the solution was kept for a longer time at room temperature the parent alcohol (1a) was obtained together with its acetate (1b).

Acknowledgements

We thank the Ministero della Pubblica Istruzione and the Consiglio Nazionale delle Ricerche for support.

* 5α-Cholesta-7,9(11),14-trien-3β-yl acetate.

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Received 7th July 1982; *Paper* 2/1147