# Unsaturated Steroids. Part 10.[1] The Mechanism of the Anthrasteroid Rearrangement: The Conformation of Anthrasteroids

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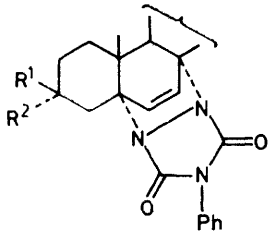
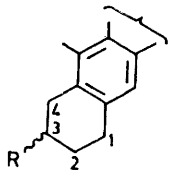
The mechanism previously suggested for the conversion of the adducts of steroidal 5,7-dienes with 4-phenyl-1,2,4-triazoline-3,5-dione into anthrasteroids has been substantiated. The conformation of the anthrasteroids has been clarified using c.d. and n.m.r. studies.

WE have previously[2] reported the conversion of the adduct of type (1; $R^1$ = OH, $R^2$ = H) from steroidal 5,7-dienes and 4-phenyl-1,2,4-triazoline-3,5-dione into the corresponding anthrasteroid (2; R = α-OH), by the action of boron trifluoride–diethyl ether. The stereospecificity of this rearrangement was interpreted in terms of preferential co-ordination of the reagent with the carbonyl adjacent to the asterisked amide residue in compound (1). We present further evidence for the correctness of this mechanism.

Thus, reduction with sodium borohydride of the ketone[3] (1; $R^1$, $R^2$ = O) gave the 3α-ol (1; $R^1$ = H, $R^2$ = OH) as the major product, together with minor amounts of the corresponding 3β-ol. This result is in accord with expectations since approach of the reducing agent to the β-face of the ketone (1; $R^1$, $R^2$ = O) would



(1)



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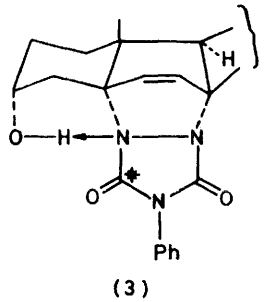

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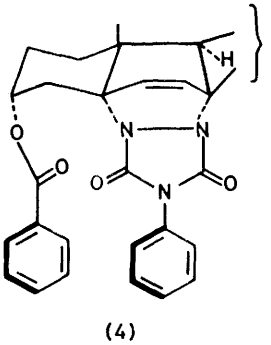

(4)

be less hindered than approach from the α-face. In accord with the formulation of (1; $R^1$ = H, $R^2$ = OH) the 3β (equatorial) proton exhibited a signal at τ 5.79 of $W_{\frac{1}{2}}$ 7 Hz.[4] Additionally the i.r. spectrum (chloroform) showed a broad absorption band at 3 380 $cm^{-1}$, which did not decrease in intensity upon dilution, in accordance with *intra*molecular hydrogen bonding as in (3); in contrast the 3β-ol (1; $R^1$ = OH, $R^2$ = H) shows a sharp i.r. band at 3 600 $cm^{-1}$ (free OH stretching) and a broad band at 3 400 $cm^{-1}$ (hydrogen-bonded OH). This latter band decreased in intensity upon dilution, showing that in (1; $R^1$ = OH, $R^2$ = H) hydrogen bonding was *inter*molecular

The rearrangement of (1; $R^1$ = H, $R^2$ = OH) to (2; R = β-OH) under the influence of boron trifluoride–diethyl ether occurred only very slowly (4½ h as opposed to 10 min) in accord with the more-hindered approach to the reagent, and perhaps the decreased availability of the lone pair of electrons on nitrogen.

Unequivocal evidence for the 3α-orientation of (1; $R^1$ = H, $R^2$ = OH) was provided by its oxidation to the ketone (1; $R^1$, $R^2$ = O).

The n.m.r. spectrum of the 3α-benzoate (1; $R^1$ = H, $R^2$ = $PhCO_2$) showed signals at τ 5.94 ($J_{4\alpha,4\beta}$ 16 Hz and $J_{3\beta,4\alpha}$ 1.5 Hz, 4α-H), 4.48 (3β-H) and τ 3.71 (t, C-6, C-7 protons). Thus either the C-6 or C-7 proton is deshielded in comparison with the epimeric 3β-benzoate which has τ 3.71 (d, $J_{6,7}$ 7.5 Hz, C-6 or C-7 proton, H) and 3.54 (d, $J_{6,7}$ 7.5 Hz, C-6 or C-7 proton, H). It would seem most likely that the C-6 proton is deshielded due to the proximity of the carbonyl group of the 3α-benzoyl residue. In the n.m.r. spectrum of (1; $R^1$ = H, $R^2$ = $PhCO_2$) the region from τ 1.80—3.44 is assigned to the ten aryl protons. Five of these are deshielded relative to those in the 3β-benzoate (1; $R^1$ = $PhCO_2$, $R^2$ = H). It thus appears that the aromatic rings in the adduct (1; $R^1$ = H, $R^2$ = $PhCO_2$) are oriented parallel to each other as in (4) so that three protons of the benzoyl residue and two from the *N*-phenyl moiety are mutually deshielded.

In accord with the absence of hydrogen bonding in (4), treatment of (4) with boron trifluoride–diethyl ether rapidly (10 min) gave the 1(10→6)*abeo*-ergosta-5,7,9,22-tetraen-3β-yl benzoate (2; R = β$PhCO_2$).

These observations clearly indicate that the boron trifluoride co-ordinates more easily with the asterisked carbonyl than with the (presumably) more-hindered second amide carbonyl residue of these adducts, in agreement with our original postulate.[2]

In accord with the presence of an aromatic ring the c.d. spectrum of our anthrasteroids (see Table 1 for a selection of data) exhibits three principal bands corresponding to the three principal transitions in the u.v.

spectra. In these steroids the dominant chromophore is the benzenoid ring B, which is responsible for the c.d. band in the range of 276—280 nm. The small numerical values of $\Delta\varepsilon$ (Table 1) reflect the relatively symmetrical environment of ring B. The variation in wavelength of the c.d. bands at λ 245 and 225 nm arises from the overlap of the c.d. due to ring B with that of the ester groups (where present) at C-3. With the C-3 benzoates, overlap of the c.d. of this residue with that of ring B inverts the sign of the shortest-wavelength band relative to that of the corresponding alcohol and acetate (Table 1).

The results of *X*-ray analysis [2] shows that the rigid cyclohexene ring C has a negative helicity [5] (as a sofa) [2] (Figure 1). The cyclohexene ring A must be a half-chair [2] (or sofa) of helicity similar to that of ring C, since the 3α-substituent is equatorial in the crystalline state,[2] and this conformation apparently persists in solution since the n.m.r. signals for the appropriate 3β protons (Table 2) have $W_{\frac{1}{2}}$ 16—18 Hz in accord with axial orientation.[4] In the absence of pseudo-axial substitution on the benzylic carbon atoms, negative helicity leads to a negative, long wavelength c.d. band and conversely.[5] The negative c.d. bands at 285 and 245 nm exhibited by the 3α-anthrasteroidal alcohols and their acetates are thus in agreement with the conclusions from *X*-ray crystallography and n.m.r. spectroscopy.

TABLE 1

| Compound | | | |
|---|---|---|---|
| 1(10→6)*abeo*-Stigmasta-5,7,9,22-tetraen-3α-yl benzoate | $\Delta\varepsilon_{276}$ −0.26 | $\Delta\varepsilon_{245}$ −0.19 | $\Delta\varepsilon_{227}$ +3.15 |
| 1(10→6)*abeo*-Stigmasta-5,7,9,22-tetraen-3α-yl acetate | $\Delta\varepsilon_{277}$ −0.21 | | $\Delta\varepsilon_{215}$ −1.83 |
| 1(10→6)*abeo*-Stigmasta-5,7,9,22-tetraen-3α-ol | $\Delta\varepsilon_{278}$ −0.23 | $\Delta\varepsilon_{238}$ −0.06 | $\Delta\varepsilon_{225}$ −1.21 |
| 1(10→6)*abeo*-Cholest-5,7,9-trien-3α-yl benzoate | $\Delta\varepsilon_{279}$ −0.18 | $\Delta\varepsilon_{235}$ −0.06 | $\Delta\varepsilon_{228}$ +4.15 |
| 1(10→6)*abeo*-Cholest-5,7,9-trien-3α-yl acetate | $\Delta\varepsilon_{278}$ −0.17 | $\Delta\varepsilon_{249}$ −0.05 | $\Delta\varepsilon_{214}$ −2.11 |
| 1(10→6)*abeo*-Ergosta-5,7,9,22-tetraen-3α-yl benzoate | $\Delta\varepsilon_{279}$ −0.28 | $\Delta\varepsilon_{247}$ −0.19 | $\Delta\varepsilon_{228}$ +3.20 |
| 1(10→6)*abeo*-Ergosta-5,7,9,22-tetraen-3α-ol | $\Delta\varepsilon_{277}$ −0.24 | $\Delta\varepsilon_{237}$ −0.08 | $\Delta\varepsilon_{226}$ −0.88 |
| 1(10→6)*abeo*-Ergosta-5,7,9,22-tetraen-3β-yl benzoate | $\Delta\varepsilon_{280}$ −0.22 | $\Delta\varepsilon_{242}$ +0.09 | $\Delta\varepsilon_{226}$ −3.76 |
| 1(10→6)*abeo*-Ergosta-5,7,9,22-tetraen-3β-ol | $\Delta\varepsilon_{280}$ −0.10 | | $\Delta\varepsilon_{274}$ +1.50 |

TABLE 2

| Compound | τ (H-3) | $W_{\frac{1}{2}}$/Hz |
|---|---|---|
| (1; $R^1$ = OH, $R^2$ = H) | 5.55 | 15 |
| (1; $R^1$ = H, $R^2$ = OH) | 5.80 | 7 |
| (2; R = β-OH) | 5.82 | 16 |
| (2; R = α-OH) | 5.88 | 17 |
| (2; R = α-$PhCO_2$) | 4.50 | 16 |
| (2; R = β-$PhCO_2$) | 4.52 | 18 |

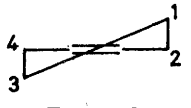


FIGURE 1

The 3β-anthrasteroids (Table 1) exhibit a negative c.d. band at 280 nm but of a value smaller than that of the 3α-analogues, whilst the 215-nm band is positive, *i.e.* of sign opposite to that of the 3α-derivatives. Since the rigid ring C will retain its negative helicity in the 3α-derivatives, it follows from the c.d. data that ring A must adopt a positive helicity [5] (Figure 2) in the 3α-series, *i.e.* a conformation in which the 3β-substituent is equatorial, in agreement with conformational principles. The n.m.r. data relating to the 3α- and 3β-protons in appropriate anthrasteroids confirm this conclusion. Thus *inter alia* (*a*) the signal for the axial C-3α proton in (1; $R^1$ = OH, $R^2$ = H) is at τ 5.55 and that for the equatorial C-3β proton in (1; $R^1$ = H, $R^2$ = OH) is at τ 5.80, but (*b*) the chemical shift at τ 5.82 for the axial C-3α proton in (2; R = β-OH) is very similar to that (τ 5.88) for the 3β-proton in (2; R = α-OH) and (*c*) similarly the signals at τ 4.50 and 4.52 for the axial C-3β proton in (2; R = α-$PhCO_2$), and the C-3α proton in (2; R = β-$PhCO_2$) respectively are also almost identical. Hence it may be concluded that the C-3 proton is axial in the 3β-series of anthrasteroids. This is substantiated by the $W_{\frac{1}{2}}$ values for the relevant signals (Table 2); the n.m.r. data therefore indicate that the substituent in *e.g.* (2; R = β-$PhCO_2$) is equatorial and thus the cyclohexene ring A must have a positive helicity.[5] The

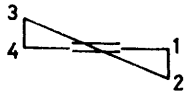


FIGURE 2

conclusions from the c.d. and n.m.r. studies are thus satisfyingly congruent.

## EXPERIMENTAL

Circular dichroism curves were determined using a Cary-61 dicrograph, with methanol as solvent. N.m.r. spectra were determined at 60 MHz in solution in deuteriochloroform, with $SiMe_4$ as internal standard.

Rotations were determined in solution in chloroform.

1(10→6)abeo-*Ergosta*-5,7,9,22-*tetraen*-3β-*ol*.—The adduct (3 g) of ergosta-5,7,22-trien-3-one with 4-phenyl-1,2,4-triazoline-3,5-dione, dissolved in methanol (35 ml) and chloroform (20 ml) was treated at room temperature with sodium borohydride (3 g) added during 0.5 h. After stirring during 2 h, ether (300 ml) was added to the reaction mixture. The product thus isolated was purified by chromatography on silica gel from ether–light petroleum (b.p. 60—80 °C) to yield the 3α-*ol* (1.1 g) which formed needles, m.p. 198—199 °C (decomp.) from dichloromethane–methanol: $[\alpha]_D^{21}$ −141° (*c*, 0.9) (Found: C, 75.9; H, 8.7; N, 7.4. $C_{36}H_{49}N_3O_3$ requires C, 75.6; H, 8.6; N, 7.4%).

The *benzoate* formed prisms, m.p. 176—179 °C (decomp.) from acetone–methanol: $[\alpha]_D^{24}$ −35° (*c*, 1.0) (Found: C, 76.2; H, 7.8; N, 6.3. $C_{43}H_{53}N_3O_4$ requires C, 76.4; H, 7.9; N, 6.2%).

Treatment of a solution of this 3α-ol (0.35 g) in benzene (14 ml) with boron trifluoride–ether (1.2 ml) at room temperature during 4½ h gave 1(10→6)abeo-*ergosta*-5,7,9,22-*tetraen*-3β-*ol* (0.17 g) as needles, m.p. 87 °C from dichloromethane–methanol: $[\alpha]_D^{24}$ +35° (*c*, 0.8) (Found: C, 84.9; H, 10.7%; $M^+$ 394. $C_{28}H_{42}O$ requires C, 85.2; H, 10.7%, *M* 394).

Oxidation of this 3β-ol with the Moffatt reagent gave 1(10→6)*abeo*-ergosta-5,7,9,22-tetraen-3-one,[3] m.p. 97—99 °C.

1(10→6)abeo-*Ergosta*-5,7,9,22-*tetraen*-3β-*yl Benzoate*.—Treatment of the benzoate (0.13 g) of the adduct of 4-phenyl-1,2,4-triazoline-3,5-dione and ergosta-5,7,22-trien-3α-ol with boron trifluoride–ether (0.55 ml) in benzene (6 ml) during 10 min, gave 1(10→6)abeo-*ergosta*-5,7,9,22-*tetraen*-3β-*yl benzoate* (0.85 g) as needles, m.p. 142—144 °C, from acetone–ethanol; $[\alpha]_D^{28}$ +57° (*c*, 0.8) (Found: C, 84.4; H, 9.5. $C_{35}H_{46}O_2$ requires C, 84.3; H, 9.3%).

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REFERENCES

[1] Part 9, R. Edmunds, J. M. Midgley, L. G. Tagg, B. J. Wilkins, and W. B. Whalley, *J.C.S. Perkin I*, 1978, 76.

[2] N. Bosworth, A. Emke, J. M. Midgley, C. J. Moore, W. B. Whalley, G. Ferguson, and W. C. Marsh, *J.C.S. Perkin I*, 1977, 805.

[3] A. Emke, D. Hands, J. M. Midgley, W. B. Whalley, and (in part) R. Ahmad, *J.C.S. Perkin I*, 1977, 820.

[4] N. S. Bhacca and D. H. Williams, 'Applications of Nuclear Magnetic Resonance Spectroscopy in Organic Chemistry,' Holden-Day, San Francisco, 1964, p. 79.

[5] G. Snatzke, M. Kajtár, and F. Snatzke in ' Fundamental Aspects and Recent Developments in Optical Rotatory Dispersion and Circular Dichroism,' eds. F. Ciardelli and P. Salvadori, Heyden and Son Ltd., London, 1973, pp. 148—172.