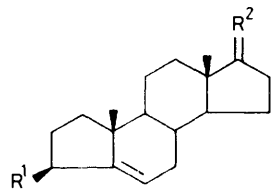
Stereochemistry of Epoxidation of some A-Norandrost-5-enes

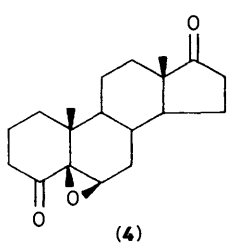
John F. Gordon, James R. Hanson,* Peter B. Hitchcock, Andrew G. Jarvis, and Harry J. Wadsworth
School of Molecular Sciences, University of Sussex, Brighton, Sussex, BN1 9QJ
Arnold H. Ratcliffe
I.C.I. Pharmaceuticals Division p.l.c., Alderley Park, Macclesfield, Cheshire, SK10 4TG

The epoxidation of 17β-hydroxy-3-hydroxymethyl-4-norandrost-5-ene and of 3-diacetoxymethyl-4-norandrost-5-en-17-one with *m*-chloroperbenzoic acid, has been shown to give the 5β,6β-epoxides.

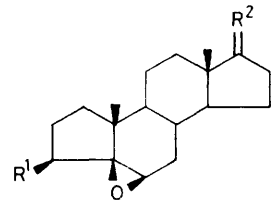
The epoxidation of Δ^5-steroids such as cholesterol with peracids has been thoroughly studied.[1,2] The major product is the 5α,6α-epoxide accompanied by variable, usually small, proportions of the 5β,6β-epoxide, the amounts of which are dependent upon the solvent, the peracid used, and the nature of the substituents at C-3.[3] The results are rationalized in terms of preferential attack of the reagent from the less-hindered α-face of the molecule. However, the stereochemistry of epoxidation of A-norsteroids is less clear-cut in view of the flattened nature of ring A and the preferred *cis* fusion of a hydrindane.[4] In this paper we present results which show that epoxidation can proceed predominantly from the β-face of the molecule in some A-nor steroids.



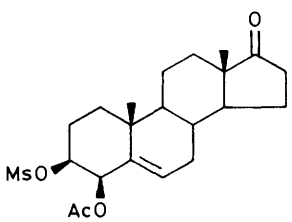
(**1**) $R^1 = CH_2OH$, R^2 = α-H, β-OH
(**2**) $R^1 = CH(OAc)_2$, $R^2 = O$
(**3**) $R^1 = CO_2H$, $R^2 = O$



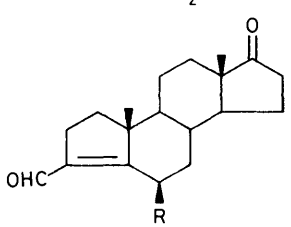
(**4**)



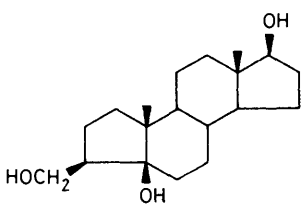
(**5**) $R^1 = CH_2OH$, R^2 = α-H, β-OH
(**6**) $R^1 = CH(OAc)_2$, $R^2 = O$



(**7**)



(**8**) R = OH
(**9**) R = H



(**10**)

The directing effect of an allylic alcohol on the stereochemistry of epoxidation of steroidal Δ^4- and Δ^5-double bonds has been well established and rationalized in terms of hydrogen bonding by the hydroxy group.[5] A similar possibly less-pronounced effect might be anticipated in the homoallylic system (**1**). We have examined the stereochemistry of epoxidation of the 3-hydroxymethyl derivative (**1**) and the diacetate (**2**) by *m*-chloroperbenzoic acid in this context. The hydroxymethyl compound (**1**) was prepared[6] by treatment of the epoxy dione (**4**) with potassium t-butoxide in t-butyl alcohol which gave 3-carboxy-4-norandrost-5-en-17-one (**3**) the methylester of which was reduced with lithium aluminium hydride to afford the diol (**1**). Epoxidation of the alcohol (**1**) with *m*-chloroperbenzoic acid in dichloromethane at 0 °C gave a single epoxide (**5**), the stereochemistry of which was established as follows. A ^1H n.m.r. selective-population transfer experiment based on the hydroxymethyl signals (δ 3.48 and 3.58) led to a modification in the one-proton multiplet at δ 2.29 which was therefore assigned to 3α-H. Irradiation of the signal at δ 3.15, assigned to 6-H, led to the collapse of the signal at δ 2.06 to a double doublet (*J* 3 and 13 Hz) and also affected a further resonance inside the methylene envelope at δ 1.19. These resonances were geminally coupled (*J* 13 Hz) and were assigned to 7β-H and 7α-H, respectively. Irradiation of the 19-H signal (δ 0.90) and the 6-H signal (δ 3.15) afforded the nuclear Overhauser enhancements shown in Figure 1 in terms of the β-epoxide. Whilst these enhancements were compatible with this stereochemistry, they do not uniquely establish it and more definitive evidence was obtained in the case of epoxidation of the diacetate (**2**) with which this epoxide was then linked.

The diacetate (**2**) was obtained by acetolysis of 4β-acetoxy-3β-methanesulphonyloxyandrost-5-en-17-one (**7**).[7] Epoxidation of this diacetate (**2**) with *m*-chloroperbenzoic acid gave only one major epoxide (**6**). Hydrolysis of the acetate with aqueous methanolic sodium hydroxide gave the γ-hydroxy-α,β-unsaturated aldehyde (**8**). The downfield shift of the 19-H resonance (Δδ 0.23) compared with the corresponding signal in (**9**)[7] suggested that the alcohol had the 6β-stereochemistry. However a C-6 alcohol could arise from either the α- or the β-epoxide (see the Scheme). Hence we sought additional evidence firstly from the ^1H n.m.r. spectrum of the epoxide.

The stereochemistry of steroidal 5,6-epoxides is reflected in

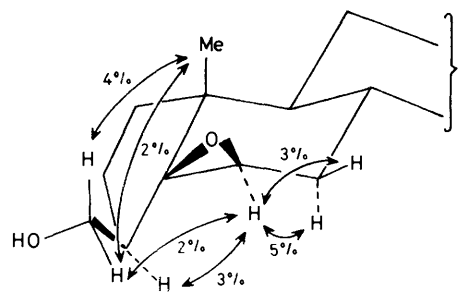
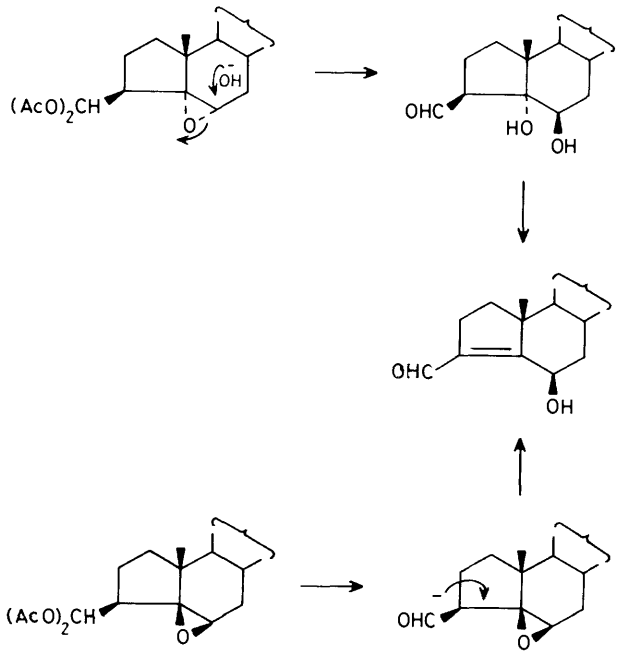


Figure 1.



Scheme.

the position of the 6-H resonance and in the 6-H,7-H coupling constants (6α-H, δ 3.05—3.10, *J* 2.1—2.7 Hz; 6β-H, δ 2.82—2.86, *J* 3.3—4.1 Hz).[8] The position of the corresponding signal in the epoxide (**2**) (δ 3.18 dd, *J* 1.6 and 2.0 Hz) suggested that the epoxide possessed the β-configuration. However the alteration to the size of ring A could easily modify the dihedral angles of ring B sufficiently to render this correlation, which is based on rather similar coupling constants, ambiguous. Consequently an attempt was also made to assign the stereochemistry using n.O.e. techniques. Spin-decoupling experiments based on the acetal signal (δ 6.66) led to the assignment of the 3-H signal (δ 2.65) whilst irradiation of the signal at δ 3.18 (6-H) removed a 2 Hz coupling from a signal at δ 1.32 (*J* 2.0, 10.5, and 14.5 Hz, 7α-H) and a 1.6 Hz coupling from an 8-line multiplet, δ 2.32 (*J* 1.6, 4.3, and 14.5 Hz, 7β-H). An n.O.e. difference experiment based on the irradiation of 19-H (δ 0.96) led to enhancements at δ 1.48 (16%, 8-H ?), 1.93 (10%, 2-H ?), and 6.66 [3%, $CH(OAc)_2$] thus establishing the β-configuration of the acetal. However, an n.O.e. experiment based on irradiation of the epoxide proton resonance (δ 3.18) gave enhancements at δ 1.32 (9%, 7α-H), 2.23 (4%, 7β-H), 2.65 (5%, 3-H), and 6.66 [6%, $CH(OAc)_2$]. There was no observed interaction with 19-H. Whilst these results are also compatible with a β-oriented 5,6-epoxide and a *cis* A/B ring junction, they did not provide a completely unambiguous assignment and could be accommmodated by an α-epoxide.

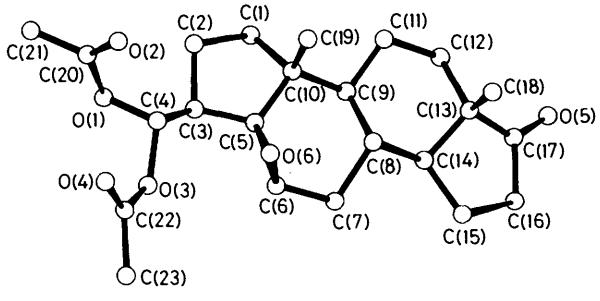


Figure 2. Molecular structure of 3β-diacetoxymethyl-5β,6β-epoxy-4-norandrostan-17-one (**6**)

Table. Fractional atomic co-ordinates (× 10^4) with estimated standard deviations in parentheses

	x	*y*	*z*
O(1)	4 750(11)	3 984(11)	1 694(2)
O(2)	2 612(14)	2 936(14)	1 617(2)
O(3)	4 524(11)	6 354(11)	1 773(2)
O(4)	2 947(14)	5 457(14)	2 065(2)
O(5)	4 597(13)	11 231(14)	−118(2)
O(6)	3 030(12)	7 509(13)	1 281(2)
C(1)	5 316(17)	5 150(17)	851(3)
C(2)	5 179(19)	4 356(18)	1 127(3)
C(3)	5 051(17)	5 660(16)	1 336(3)
C(4)	4 180(16)	5 286(16)	1 575(3)
C(5)	4 284(16)	6 815(16)	1 163(3)
C(6)	4 372(19)	8 316(18)	1 249(3)
C(7)	4 330(17)	9 517(17)	1 047(3)
C(8)	3 832(15)	9 004(16)	760(3)
C(9)	4 551(15)	7 597(15)	677(3)
C(10)	4 174(17)	6 401(17)	867(3)
C(11)	4 219(18)	7 221(17)	379(3)
C(12)	4 614(19)	8 429(18)	177(3)
C(13)	3 790(18)	9 824(17)	268(3)
C(14)	4 279(16)	10 140(17)	553(3)
C(15)	3 712(20)	11 680(20)	592(3)
C(16)	4 178(19)	12 326(18)	311(3)
C(17)	4 240(20)	11 111(19)	133(3)
C(18)	2 193(21)	9 668(21)	229(3)
C(19)	2 681(17)	5 780(17)	819(3)
C(20)	3 884(22)	2 883(22)	1 699(3)
C(21)	4 495(25)	1 556(26)	1 829(4)
C(22)	3 793(20)	6 380(20)	2 007(3)
C(23)	4 078(20)	7 711(19)	2 166(3)

Hence we obtained an *X*-ray crystal structure for the diacetate (**6**) which established the β-configuration of the epoxide (see Figure 2).

The two series of compounds were then inter-related by reduction of each epoxide to the same triol (**10**) with lithium aluminium hydride.

In conclusion we have shown that, unlike the normal steroid series, in this A-nor series epoxidation takes place from the 'β' face. Secondly, in the normal steroid series the directing effect of a neighbouring hydroxy group is lost on acetylation and epoxidation then occurs from the 'α' face,[5] in the A-nor series epoxidation still occurs from the 'β' face.

Experimental

Light petroleum refers to the fraction b.p. 60—80 °C. Silica for chromatography was Merck Kieselgel 60 type 9380. Infrared spectra were determined for Nujol mulls; ^{1}H n.m.r. spectra were determined at 360 MHz in deuteriochloroform on a Bruker WH 360 spectrometer.

Epoxidation of 17β-Hydroxy-3β-hydroxymethyl-4-nor-androst-5-ene (**1**).—The steroid (**1**)[6] (500 mg) in dichloromethane (30 ml) was treated with *m*-chloroperbenzoic acid (400 mg) at 0 °C for 1 h. Aqueous sodium sulphite (20 ml) was added and the two layers were then separated. The organic phase was extracted consecutively with aqueous sodium hydrogen carbonate and sodium chloride solution and then dried. The solvent was evaporated and the residue was crystallized from ethyl acetate to give 5β,6β-*epoxy*-17β-*hydroxy*-3β-*hydroxy-methyl*-4-*norandrostane* (**5**) (420 mg) as needles, m.p. 154—156 °C (Found: C, 74.7; H, 9.6. $C_{20}H_{30}O_3$ requires C, 74.5; H, 9.9%); $\nu_{max.}$ 3 320 and 1 020 cm^{-1}; δ 0.67 (3 H, s, 18-H_3), 0.90 (3 H, s, 19-H_3), 2.29 (1 H, m, 3-H), 3.15 (1 H, m, 6-H), 3.48 and 3.58

(2 H, ABX multiplet, *J* 4.8 and 11.6 Hz, CH_2OH), and 3.57 (1 H, t, *J* 7.5 Hz, 17-H).

Epoxidation of 3β-*Diacetoxymethyl*-4-*norandrost*-5-*en*-17-*one* (**2**).—The steroid (**2**)[7] (250 mg) in chloroform (10 ml) was treated with *m*-chloroperbenzoic acid (250 mg) for 12 h at room temperature. The solution was washed consecutively with aqueous sodium sulphite containing a trace of sodium iodide as an indicator and aqueous sodium hydrogen carbonate, and was then dried. The solvent was evaporated to afford 3β-*diacetoxymethyl*-5β,6β-*epoxy*-4-*norandrostan*-17-*one* (**6**) (240 mg) which crystallized as needles from methanol, m.p. 188—189 °C, $[\alpha]_D$ + 32° (*c* 0.6) (Found: C, 68.0; H, 8.0. $C_{23}H_{32}O_6$ requires C, 68.3; H, 8.0%); $\nu_{max.}$ 1 750 cm^{-1}; δ 0.83 (3 H, s, 18-H_3), 0.96 (3 H, s, 19-H_3), 2.07 and 2.13 (each 3 H, s, OAc), 3.18 (1 H, t, *J* 1.6 Hz, 6-H), 6.66 (1 H, d, *J* 4.8 Hz, $CHAc_2$).

Hydrolysis of 3β-*Diacetoxymethyl*-5β,6β-*epoxy*-4-*norandrostan*-17-*one* (**6**).—The steroid (**6**) (200 mg) in methanol (10 ml) was treated with saturated aqueous sodium hydroxide (1 ml) for 20 min at room temperature. The solution was neutralized with acetic acid, concentrated under reduced pressure and poured into aqueous sodium hydrogen carbonate. The steroids were recovered in ethyl acetate and dried, and the solvent was evaporated to afford 3-*formyl*-6β-*hydroxy*-4-*norandrost*-3-*en*-17-*one* (**8**) (70 mg) which crystallized from ether as needles, m.p. 182—184 °C, $[\alpha]_D$ +78° (*c* 0.6) (Found: C, 75.4; H, 8.9. $C_{19}H_{26}O_3$ requires C, 75.5; H, 8.7%); $\nu_{max.}$ 3 440, 1 720, and 1 660 cm^{-1}; δ 0.97 (3 H, s, 18-H_3), 1.3 (3 H, s, 19-H_3), 5.37 (1 H, m, 6-H), and 10.07 (1 H, s, 3-H).

Reduction of the Epoxides (**5**) *and* (**6**).—(*a*) The epoxide (**5**) (380 mg) in tetrahydrofuran (25 ml) containing lithium aluminium hydride (80 mg) was heated under reflux for 2 h. The mixture was cooled, poured into dilute hydrochloric acid, and the products were recovered in ethyl acetate. The extract was washed with aqueous sodium hydrogen carbonate and aqueous sodium chloride, and then dried. The solvent was evaporated and the residue was chromatographed on silica eluting with ethyl acetate–light petroleum (1:1) to afford 5β,17β-*dihydroxy*-3β-*hydroxymethyl*-4-*norandrostane* (**10**) (300 mg) which crystallized from methanol as needles, m.p. 189—191 °C (Found: C, 73.7; H, 10.4. $C_{19}H_{32}O_3$ requires C, 74.0; H, 10.5%); $\nu_{max.}$ 3 380 cm^{-1}; δ(90 MHz) 1.0 (3 H, s, 18-H_3), 1.2 (3 H, s, 19-H_3), 3.9 (1 H, t, *J* 7 Hz. 17-H), and 4.2 (2 H, d, *J* 5 Hz, CH_2OH).

(*b*) The steroid (**6**) (325 mg) was added to a stirred suspension of lithium aluminium hydride (500 mg) in tetrahydrofuran (30 ml) and the mixture was heated under reflux for 5 h. The excess of reagent was destroyed with wet ethyl acetate, the solution was then acidified with dilute hydrochloric acid, and the products were recovered in ethyl acetate. The extract was washed with aqueous sodium hydrogen carbonate and aqueous sodium chloride and then dried. The solvent was evaporated and the residue was crystallized from methanol to give 5β,17β-dihydroxy-3β-hydroxymethyl-4-norandrostane (**10**) (255 mg), m.p. 183—185 °C, identical (i.r. and n.m.r.) to the sample describe above.

X-*Ray Structure Determination*.—*Crystal data*. $C_{23}H_{32}O_6$, *M*, 404.5, tetragonal, space group $P4_32_12$ (no. 96), a = 9.432(4), c = 49.296(49) Å, U = 4 385.4 $Å^3$, Z = 8, D_{calc} = 1.22 g cm^{-3}. Monochromated Mo-K_α radiation λ = 0.710 69 Å, μ = 0.8 cm^{-1}.

The crystals of this compound were hollow and it was necessary to cut a solid fragment *ca.* 0.4 × 0.2 × 0.25 mm from the corner of a larger crystal. Data were collected on an Enraf–Nonius CAD 4 diffractometer using ω scans of width (0.6 + 0.35 tanθ)° and a maximum scan time of 1 min. A total of 2 358 unique reflections were measured for $2 < \theta < 25°$ but the higher angle data were very weak and only 1 111 reflections with $|F^2| > \sigma(F^2)$ were used in the refinement, where $\sigma(F^2) = [\sigma^2(I) + (0.04I)^2]^{\frac{1}{2}}/Lp$. There was no crystal decay and no absorption correction was applied. The structure was solved by routine direct methods (MULTAN). Owing to the limited data refinement by full-matrix least-squares was of isotropic C and O atoms only. Hydrogen atoms were omitted. The weighting scheme was $w = 1/\sigma^2(F)$ and the final residuals were R = 0.125 and R' = 0.151. Final atom co-ordinates are given in the Table whilst the intramolecular distances, torsional angles, and isotropic temperature factors have been deposited at the Cambridge Crystallographic Data Centre* and are available on request.

Acknowledgements

We thank I.C.I. Pharmaceuticals Division p.l.c. for CASE studentships.

* For details of the data deposition scheme, see 'Instructions for Authors (1988),' *J. Chem. Soc., Perkin Trans. 1*, 1988, issue 1, paragraph 5.6.3.

References

1 L. F. Fieser and M. Fieser, 'Steroids,' Reinhold, New York, 1959, p. 193.
2 D. N. Kirk and M. P. Hartshorn, 'Steroid Reaction Mechanisms,' Elsevier, Amsterdam, 1968, p. 71.
3 K. D. Bingham, T. M. Blaiklock, R. C. B. Coleman, and G. D. Meakins, *J. Chem. Soc.* (*C*), 1970, 2330.
4 N. L. Allinger, R. B. Hermann, and C. Djerassi, *J. Org. Chem.*, 1960, **25**, 922.
5 H. B. Henbest and R. A. L. Wilson, *J. Chem. Soc.*, 1957, 1958.
6 J. R. Hanson, D. Raines, and H. Wadsworth, *J. Chem. Soc., Perkin Trans. 1*, 1978, 743.
7 J. R. Hanson and H. J. Wadsworth, *J. Chem. Soc., Perkin Trans. 1*, 1980, 933.
8 A. D. Cross, *J. Am. Chem. Soc.*, 1962, **84**, 3206.

Received 3*rd July* 1987; *Paper* 7/1187