Base-catalysed Epoxidation and Reduction of 3-Formyl-A-norandrost-3(5)-en-17-one

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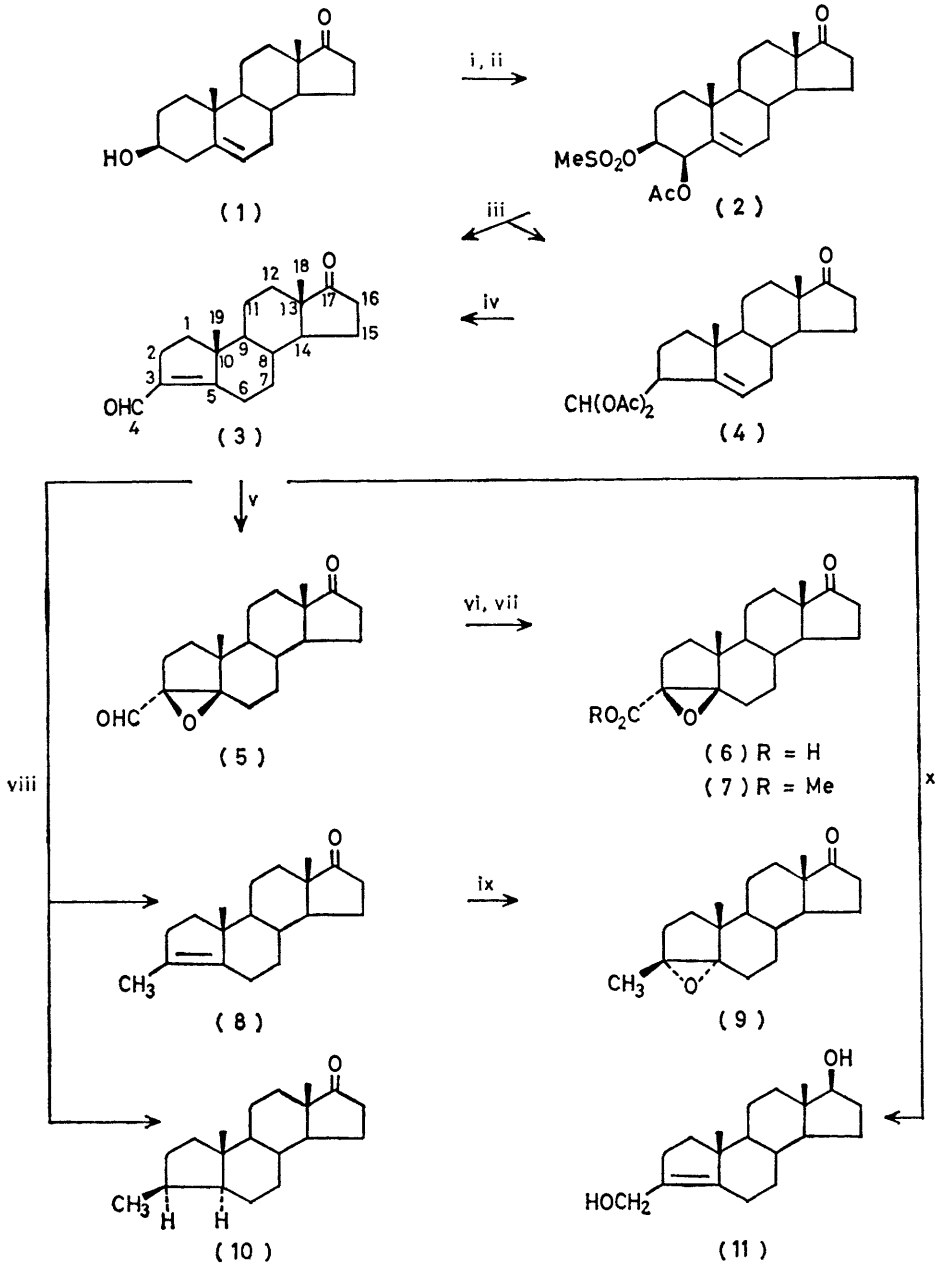
The base-catalysed epoxidation of 3-formyl-A-norandrost-3(5)-en-17-one has been shown by *X*-ray analysis to afford the β-epoxide. Catalytic reduction gave predominantly the 3-methyl-A-norandrost-3(5)-en-17-one whilst reduction with sodium borohydride gave the product of 1,2- rather than conjugate addition.

THE stereochemistry of alkaline epoxidation of unsaturated ketones has been the subject of a number of studies.[1] In previous work it has been suggested [2] that a determining feature for the stereochemistry of the base-catalysed epoxidation of an αβ-unsaturated ketone is the requirement that the intermediate hydroperoxide which is allylic to the enolate anion of the transition state possesses an axial configuration for maximum orbital over-

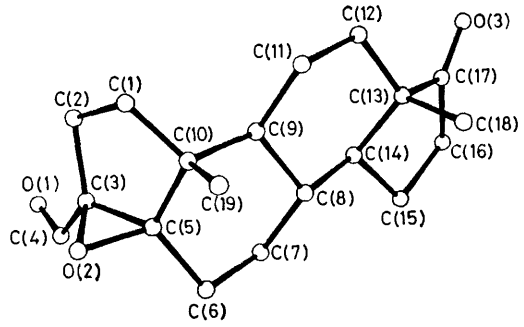


SCHEME *Reagents:* i, Br_2, AgOAc; ii, $MeSO_2Cl$, pyr.; iii, NaOAc, AcOH; iv, NaOH; v, H_2O_2, NaOH; vi, CrO_3; vii, CH_2N_2; viii, H_2, Pd–C; ix, *m*-$ClC_6H_4CO_3H$; x, $NaBH_4$

lap in the formation of the epoxide. In the light of this, we have examined the stereochemistry of epoxidation of the unsaturated aldehyde 3-formyl-A-norandrost-3(5)-en-17-one (3). 4β,5β-Epoxyketones are the predominant products from the alkaline epoxidation of Δ^4-3-ketones [3] and A-norcholest-3(5)-en-2-ones.[4] On the other hand epoxidation of 3-methyl-A-norandrost-3(5)-enes with *m*-chloroperbenzoic acid affords [5] almost entirely the α-epoxide. Consequently there is a possible dichotomy in the case of the unsaturated aldehyde (3) between steric approach control favouring the α-epoxide and product development control.

The substrate was readily prepared from dehydroisoandrosterone (1) by acetoxylation at C-4,[6] mesylation, and acetolysis of the resultant 4β-acetoxy-3β-methylsulphonyloxyandrost-5-en-17-one (2).[7] This afforded [8] both the required 3-formyl compound (3) and 3β-diacetoxymethyl-A-norandrost-5-en-17-one (4). Hydrolysis of the latter with base gave a further quantity of the 3-formyl-A-norandrost-3(5)-en-17-one. Treatment of the unsaturated aldehyde (3) with hydrogen peroxide and sodium hydroxide in methanol gave a single epoxy-aldehyde (5). In the ^{1}H n.m.r. spectrum the aldehyde C-H signal had shifted upfield to δ 9.51 whilst in the ^{13}C n.m.r. spectrum the tetrasubstituted olefinic carbon signals were replaced by signals typical of an epoxide. The epoxy-aldehyde (5), in contrast to the parent unsaturated aldehyde (3), was readily oxidized to the acid (6) by treatment with the 8N-chromium trioxide reagent. The acid was purified as its methyl ester (7).

The stereochemistry of the epoxy-aldehyde was determined by *X*-ray analysis. The molecular structure is shown in Fig. 1. This showed that the epoxide has taken up the β-configuration affording an A/B-*cis* ring junction.



Molecular structure of 3β,5β-epoxy-3α-formyl-A-norandrostan-17-one

A possible rationalization of the formation of the β-epoxide may lie in the following. Ring A of the formyl compound may adopt conformations such that both a 5α- and a 5β-hydroperoxide can attain an axial conformation. However the 5α-hydroperoxide is also an axial substituent on ring B whereas the 5β-hydroperoxide is an equatorial substituent. It has been concluded [3] that the reaction involves the addition of the hydroperoxide ion to the C–C double bond and that this step precedes a slower one in which the anionic adduct is transformed into the epoxide and hydroxide ion. If the rate-determining step requires an *anti*-geometry between the enolate anion and the departing hydroxide component of the hydroperoxide, steric interactions will be minimized in the trajectory of the latter case. The formation of the α-epoxide in the case of an androst-4-ene-3,11-dione [3] may also be rationalized in these terms since the departing hydroxide anion will have a trajectory on the α-face of the molecule favoured by the electropositive character of the C-11 carbonyl carbon atom.

Surprisingly catalytic reduction of the 3-formyl-A-norandrost-3(5)-en-17-one over 10% palladium–charcoal at atmospheric pressure proceeded predominantly with hydrogenolysis of the formyl group and the formation of the 3-methyl-A-norandrost-3(5)-en-17-one (8). Treatment of the mother-liquors with *m*-chloroperbenzoic acid and separation of the products by preparative t.l.c. afforded the 3α,5α-epoxide (9) and a small amount of the 3β-methyl-5α-A-norandrostan-17-one (10). Hydrogenolysis under these circumstances is typical of a highly hindered double bond. Reduction of the formyl compound with sodium borohydride gave the product (11) of 1,2-addition with, unlike a steroidal 4-en-3-one,[9] no indication of the reduction of the olefinic double bond. The ^{13}C n.m.r. data for these A-nor-steroids, which reveal the retention of the double bond, are given in Table 1.

TABLE 1

^{13}C N.m.r. signals of some A-nor-steroids (in $CDCl_3$, p.p.m. from Me_4Si)

Carbon atom	Compound (3)	(5)	(7)	(8)	(9)	(11)
1	37.2	31.2	31.3	38.1	31.2	36.0
2	23.0	23.4 [a]	22.7	25.8	22.0 [a]	23.5
3	134.6	78.9	77.1	130.6	68.2	129.6
4	188.3	199.1	169.5	13.6	15.3	59.1
5	170.6	72.6	67.8	140.9	75.2	146.2
6	27.3	29.0 [b]	26.1	31.6	31.4	31.6
7	31.3	29.6 [b]	28.9	30.9	27.6	30.4
8	35.4	34.9	34.9	35.6	34.9	36.1
9	54.6	47.5	47.6	55.1	49.4	55.1
10	52.2	45.5	44.7	49.8	43.2	50.2
11	21.8	21.7	21.7	22.0	21.8	22.2
12	30.6	29.6	30.5	29.7	32.8	38.0
13	47.8	47.9	47.8	48.0	48.1	43.2
14	50.6	50.8	50.8	51.2	50.5	50.5
15	21.8	23.7 [a]	21.7	22.5	22.8 [a]	22.8
16	35.6	35.7	35.7	35.4	35.7	31.2
17	220.2	220.3	220.2	221.3	220.8	81.8
18	13.7	13.8	13.8	13.6	13.8	11.1
19	18.0	15.8	15.8	18.0	16.9	13.0

[a,b] These assignments may be reversed

As anticipated the ring A carbon resonances reflect the different geometry and substitution pattern whilst those of rings C and D are typical of other steroids.

EXPERIMENTAL

^{1}H N.m.r. spectra were determined in deuteriochloroform at 90 MHz on a Perkin-Elmer R 32 spectrometer; ^{13}C n.m.r. spectra were determined at 25 MHz on a JEOL PS 100 spectrometer in deuteriochloroform.

3-*Formyl*-A-*norandrost*-3(5)-*en*-17-*one*.—4β-Acetoxy-3β-methylsulphonyloxyandrost-5-en-17-one (2), prepared from 4β-acetoxy-3β-hydroxyandrost-5-en-17-one [6] with methane-

sulphonyl chloride in pyridine, had m.p. 120—125 °C, $[\alpha]_D$ −56° (lit.,[7] m.p. 113 °C, $[\alpha]_D$ −54.6°) (Found: C, 65.4; H, 8.0. Calc. for $C_{22}H_{32}O_6S$: C, 65.3; H, 7.9%), $\nu_{max.}$ 1 753 cm^{-1}, δ 0.90 (3 H, s, 18-H_3), 1.17 (3 H, s, 19-H_3), 2.10 (3 H, s, OAc), 3.03 (3 H, s, OSO_2Me), 4.60 (1 H, m, 3-H), 5.57 (1 H, d, *J* 3 Hz, 4-H), and 5.90 (1 H, d, *J* 4 Hz, 6-H). The methanesulphonate (1 g) and anhydrous sodium acetate (1 g) in acetic acid (20 ml) were heated under reflux for 4 h. The solvent was removed *in vacuo* and the steroids were recovered in ethyl acetate, washed with water and aqueous sodium hydrogencarbonate, dried, and the solvent was evaporated off. The residue was purified by preparative t.l.c. on silica in light petroleum–ether (3 : 2 v/v) to afford 3β-diacetoxymethyl-A-norandrost-3(5)-en-17-one (150 mg) and 3-formyl-A-nornadrost-3(5)-en-17-one (500 mg) (3) which were identified by their n.m.r. spectra.[8]

Epoxidation of 3-*Formyl-A-norandrost*-3(5)-*en*-17-*one*.—The unsaturated aldehyde (3) (1 g) in methanol (50 ml) was treated with 30% aqueous hydrogen peroxide (5 ml) and saturated sodium hydroxide (1 ml) for 3 h at room temperature. The reaction was quenched with glacial acetic acid and aqueous sodium sulphite and the steroid recovered in ethyl acetate. The extract was washed with aqueous sodium hydrogencarbonate and dried and the solvent was evaporated off to afford 3β5β,-*epoxy*-3α-*formyl-A-norandrostan*-17-*one* (5) which crystallized from ethyl acetate–ether as needles, m.p. 171—172 °C, $[\alpha]_D$ +60° (*c*, 0.6) (Found: C, 71.5; H, 9.2. $C_{19}H_{26}O_3 \cdot H_2O$ requires C, 71.2; H, 8.8%), $\nu_{max.}$ 3 450 and 1 720 cm^{-1}, δ 0.90 (3 H, s, 18-H_3), 1.06 (3 H, s, 19-H_3), and 9.51 (1 H, s, CHO).

Oxidation of 3β,5β-*Epoxy*-3-*formyl*-A-*norandrostan*-17-*one*.—The epoxyaldehyde (250 mg) in acetone (50 ml) was treated with the 8N-chromium trioxide reagent (0.5 ml) for 30 min at room temperature. Aqueous sodium sulphite (10 ml) and dilute hydrochloric acid (5 ml) were added and the solution was concentrated. Water (50 ml) was added and the steroid was recovered in ethyl acetate. The extract was dried and evaporated to afford a gum which was taken up in ether and treated with an excess of diazomethane in ether. The solvent was evaporated off to afford 3β,5β-*epoxy*-3α-*methoxycarbonyl*-A-*norandrostan*-17-*one* (230 mg) which crystallized from ether as needles, m.p. 140—142 °C, $[\alpha]_D$ +161° (*c*, 0.6) (Found: C, 72.0; H, 8.4. $C_{20}H_{28}O_4$ requires C, 72.3; H, 8.5%), $\nu_{max.}$ 1 740 and 1 710 cm^{-1}, δ 0.90 (3 H, s, 18-H_3), 0.99 (3 H, s, 19-H_3), and 3.72 (3 H, s, OMe).

Hydrogenation of 3-*Formyl*-A-*norandrost*-3(5)-*en*-17-*one*.—The aldehyde (1 g) in ethyl acetate (100 ml) was hydrogenated at atmospheric pressure in the presence of 10% palladium–charcoal catalyst (0.4 g). When the hydrogen uptake had ceased (2 h), the solution was filtered and the solvent was evaporated off. The residue was purified by preparative t.l.c. on silica in ether–light petroleum (1 : 1 v/v) to afford 3-*methyl*-A-*norandrost*-3(5)-*en*-17-*one* (8) (600 mg) which crystallized from aqueous methanol as needles, m.p. 106—108 °C, $[\alpha]_D$ +115° (*c*, 0.6) (Found: C, 83.8; H, 10.2. $C_{19}H_{28}O$ requires C, 83.8; H, 10.4%), $\nu_{max.}$ 1 740 cm^{-1}, δ 0.93 (3 H, s, 18-H_3), 0.96 (3 H, s, 19-H_3), and 1.6 (3 H, s, 3-Me), *m/e* 272 (M^+). The mother-liquors were evaporated, redissolved in chloroform (10 ml), and treated with *m*-chloroperbenzoic acid (200 mg) at room temperature for 5 h. The solution was washed with aqueous sodium sulphite and aqueous sodium hydrogen carbonate, dried over sodium sulphate, and the solvent evaporated to afford a gum. Preparative t.l.c. on silica in ether–light petroleum (1 : 1 v/v) afforded two bands. The upper band gave 3β-*methyl*-5α-A-*norandrostan*(17-*one* (10) (55 mg) which crystallized from aqueous methanol as needles, m.p. 102—104 °C, $[\alpha]_D$ +99° (*c*, 0.6) (Found: C, 82.6; H, 11.7. $C_{19}H_{30}O$ requires C, 83.1; H, 11.0%), $\nu_{max.}$ 1 740 cm^{-1}, δ 0.87 (3 H, s, 18-H_3) and 1.00 (3 H, s, 19-H_3). The lower band afforded 3α,5α-epoxy-3β-methyl-A-norandrostan-17-one (100 mg) which crystallized from methanol as needles, m.p. 183—185 °C, identical (n.m.r.) to the material described below.

Epoxidation of 3-*methyl*-A-*norandrost*-3(5)-*en*-17-*one*.—The olefin (500 mg) in chloroform (10 ml) was treated with *m*-chloroperbenzoic acid (500 mg) at room temperature for 30 min. The solution was washed with aqueous sodium sulphite and aqueous sodium hydrogencarbonate and dried, and the solvent was evaporated off to afford 3α,5α-*epoxy*-3β-*methyl*-A-*norandrostan*-17-*one* (9) (350 mg) which crystallized from methanol as needles, m.p. 183—185 °C, $[\alpha]_D$ +105° (*c*, 0.6) (Found: C, 79.4; H, 9.7. $C_{19}H_{28}O_2$ requires C, 79.1; H, 9.8%), $\nu_{max.}$ 1 735 cm^{-1}, δ 0.90 (6 H, s, 18-H_3 and 19-H_3) and 1.37 (3 H, s, 3-Me).

Sodium Borohydride Reduction of 3-*Formyl*-A-*norandrost*-3(5)-*en*-17-*one*.—The aldehyde (1 g) in methanol (50 ml) was treated with sodium borohydride (0.5 g) at room temperature for 2 h. Acetic acid (1 ml) was added and the solution concentrated *in vacuo*. The steroid was recovered in ethyl acetate and the extract was washed with aqueous sodium hydrogencarbonate, dried, and evaporated. 17β-*Hydroxy*-3-*hydroxymethyl*-A-*norandrost*-3(5)-*ene* (11) crystallized from ethyl acetate as needles, m.p. 176—177 °C, $[\alpha]_D$ +56° (*c*, 0.6) (Found: C, 78.9; H, 10.2. $C_{19}H_{30}O_2$ requires C, 78.5; H, 10.4%, $\nu_{max.}$ 3 250 (br) cm^{-1}, δ 0.78 (3 H, s, 18-H_3), 0.95 (3 H, s, 19-H_3), 3.65 (1 H, t, *J* 9 Hz, 17-H), 4.17 (2 H, ABq, *J* 12 Hz, 3-CH_2OH).

X-Ray Structure Determination.—*Crystal data*. $C_{19}H_{26}O_3$, M = 302.42, orthorhombic, a = 6.226(2), b = 9.460(2), c = 27.957(6) Å, U = 1 646.6 Å^3, Z = 4, D_c = 1.22 g cm^{-3}, $F(000)$ = Mo-K_α radiation, λ = 0.710 73 Å, μ = 0.87 cm^{-1}. Space group $P2_12_12_1$ from systematic absences of $0k0$ for k odd, $h00$ for h odd, and $00l$ for l odd.

A crystal *ca.* 0.25 × 0.20 × 0.15 mm was used for data collection on an Enraf–Nonius CAD4 diffractometer. Cell dimensions were derived from the setting angles for 25 reflections. Intensities for unique reflections with $2 < \theta < 22°$ were measured by a θ—2θ scan with a scan width of $(1.0 + 0.35 \tan\theta)°$ and monochromated Mo-K_α radiation. The scan rate for each reflection was determined by a rapid pre-scan at 10 deg min^{-1} in θ at which point reflections with $I < \sigma(I)$ were coded as unobserved. The remaining data were scanned at such a rate as to give $I/\sigma(I)$ of 20, subject to a maximum scan time of 2 min. The intensities of two standard reflections monitored every 30 min showed no significant variation. After correction for Lorentz and polarization effects but not for absorption, 737 reflections with $|F^2| > \sigma(F^2)$ were used in the structure refinement. The values of $\sigma(F^2)$ were taken as $[\sigma^2(I) + (0.06I)^2]^{\frac{1}{2}}/Lp$.

The structure was solved by direct methods using the MULTAN program.[11] The non-hydrogen atoms were refined with anisotropic temperature factors by full matrix least squares. Hydrogen atoms were included at idealised positions (C–H 1.08 Å) with a common isotropic temperature factor of B = 5.0 Å^2. Continued refinement with hydrogen atom parameters held fixed converged at R = 0.066, R' = 0.90, where the weighting scheme was $w = 1/\sigma^2(F)$, and the maximum shift to error ratio was 0.01. A final difference map was everywhere <0.25 e Å^{-3}.

The structure solution and refinement was done on a PDP11/34 computer using the Enraf–Nonius structure determination package. Scattering factors for neutral atoms were taken from ref. 10. Final atom co-ordinates, lists of temperature factors, hydrogen atom positions, and final structure factors have been deposited as Supplementary Publication No. SUP 23139 (11 pp.).*

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* For details see Notice to Authors No. 7 in *J. Chem. Soc., Perkin Trans. 1*, 1980, Index issue.

REFERENCES

[1] For reviews see: D. N. Kirk and M. P. Hartshorn, 'Steroid Reaction Mechanisms,' Elsevier, Amsterdam, 1968; G. J. Matthews and A. Hassner, in 'Organic Reactions in Steroid Chemistry,' ed. J. Fried and J. A. Edwards, Van Nostrand-Reinhold, New York, 1971, vol. 2, p. 10.

[2] D. Baldwin and J. R. Hanson, *J. Chem. Soc., Perkin Trans. 1*, 1972, 2051; J. R. Hanson, D. Raines and H. J. Wadsworth, *ibid.*, 1978, 743.

[3] H. B. Henbest and W. R. Jackson, *J. Chem. Soc. C*, 1967, 59.

[4] R. Heckendorn and Ch. Tamm, *Helv. Chim. Acta*, 1967, **50**, 1964.

[5] J. Bascoul, C. Reliaud, A. Guinot and A. Crastes de Paulet, *Bull. Soc. Chim. Fr.*, 1968, 4074.

[6] V. Petrov, O. Rosenheim and W. W. Starling, *J. Chem. Soc.*, 1943, 135.

[7] B. Ellis, V. Petrov and D. N. Stanway, *B.P.*, 1 134,071/1968.

[8] J. R. Hanson and H. J. Wadsworth, *J. Chem. Soc., Perkin Trans. 1*, 1980, 933.

[9] D. M. S. Wheeler and M. M. Wheeler in 'Organic Reactions in Steroid Chemistry,' eds. J. Fried and J. A. Edwards, Van Nostrand-Reinhold, New York, 1971, vol. 1, p. 73.

[10] 'International Tables for X-ray Crystallography,' Kynoch Press, Birmingham, 1974, vol. 4.

[11] G. Germian, P. Main, and M. M. Woolfson, *Acta Cryst., Sect. A*, 1971, 27, 368.