# An Improved Synthesis of 13-*epi*-Androstanes and of 13-*epi*-Oestranes

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Treatment of a 17-hydroxyimino-steroid with refluxing acetic anhydride and pyridine affords an equilibrium mixture of 13-*epi*-enimide and 13-*epi*-enamide. A free-radical mechanism is proposed. Acidic hydrolysis gives the 17-oxo-13-*epi*-steroid in high overall yield.

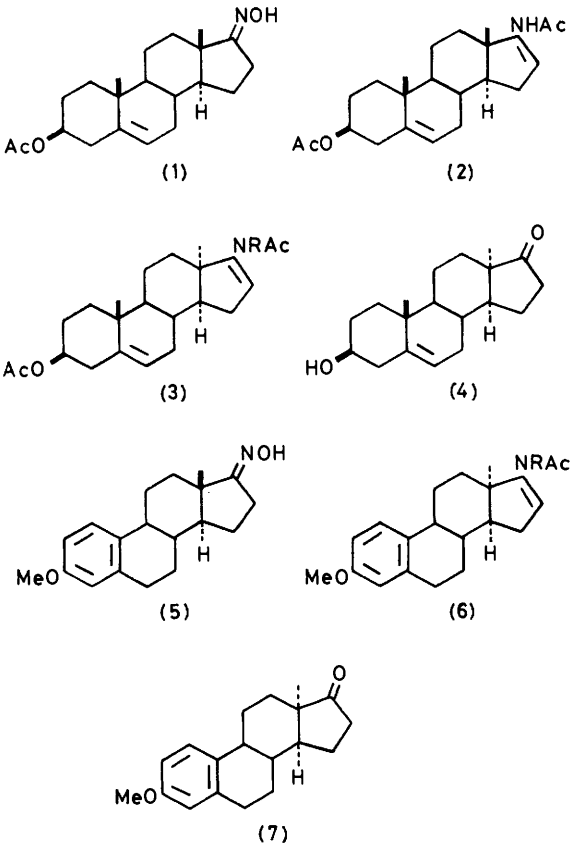
THE generally greater stability of steroids with CD *cis*- as opposed to *trans*-stereochemistry [1] permits the synthesis of 13-*epi*-derivatives by reactions which involve cleavage and subsequent re-formation of the 13,17 bond. Thus, u.v. irradiation of 17-oxo-steroids generates, *via* a 13,17-diradical, an equilibrium mixture of the normal and 13-*epi*-isomers.[2-4] Separation of this mixture then affords the 13-*epi*-compound in acceptable, if not high, yield. Alternatively, treatment of 20-oxo-pregnanes with antimony pentafluoride–hydrogen fluoride affords, *via* a 17-carbocation, a major amount of the 13α,17α-isomer.[5] We now report details [6] of our recently described enamide synthesis [7] as applied to the preparation in high yield of pure 17-*epi*-androstanes and -oestranes.

Reduction of 3β-acetoxy-17-hydroxyiminoandrost-5-ene [8] (1) in acetic anhydride with chromium(II) acetate gave the expected [7] enamide (2), m.p. 229—232°, $[\alpha]_D$ −15°. The structure of this product is well established.[9] When the oxime (1) was treated with refluxing acetic anhydride and pyridine, two products resulted. These were easily separated by chromatography on silica gel. Comparison of the n.m.r. spectrum and the molecular rotation of the more polar product, m.p. 160—163°, $[\alpha]_D$ −102°, with those of the enamide (2) strongly suggested that the former was the 13-*epi*-enamide (3; R = H). The less polar product, m.p. 118—121°, $[\alpha]_D$ −99°, was evidently the 13-*epi*-enimide (3; R = Ac), since it was converted into the more polar product by chromatography on an alumina column.[7] The enamide (3; R = H) and the enimide (3; R = Ac) are apparently in equilibrium in refluxing acetic anhydride and pyridine.

To confirm the formulation of the above products as 13-*epi*-androstanes, the enamide (3; R = H) was subjected to acidic hydrolysis. The ketone thus obtained was identical with authentic 3β-hydroxy-13α-androst-5-en-17-one (4).[3]

By the above method an overall yield of *ca.* 65% is readily obtained for the conversion of 17-oxo-steroid into 17-oxo-13-*epi*-steroid.

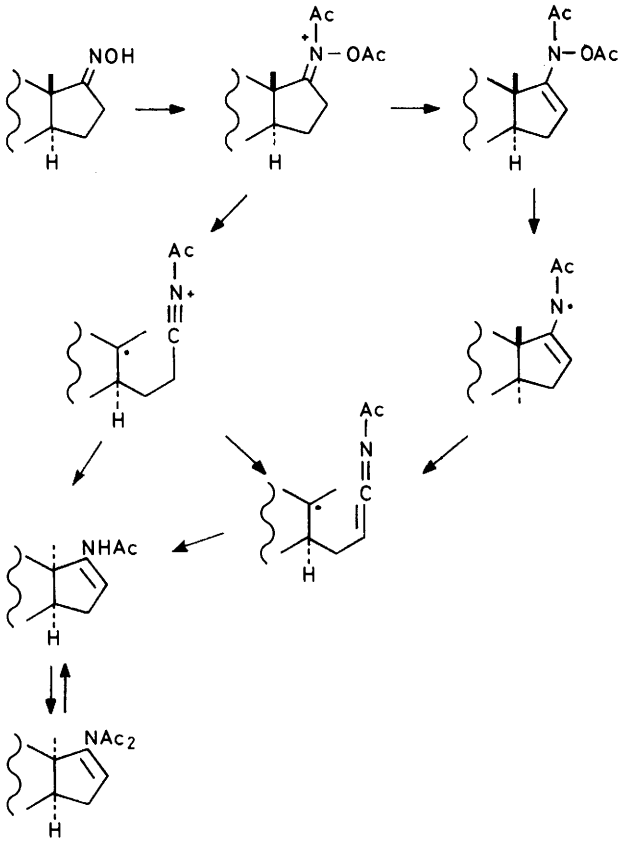
In an analogous series of experiments, 17-hydroxyimino-3-methoxyoestra-1,3,5(10)-triene [10] (5) was converted with similar efficiency into the 13-*epi*-enimide (6; R = Ac) and the 13-*epi*-enamide (6; R = H). Hydrolysis of the enamide gave 3-methoxy-13α-oestra-1,3,5(10)-trien-17-one (lumioestrone methyl ether) (7), m.p. 130—133°, $[\alpha]_D$ −27.5° (lit.,[11] m.p. 129—130°, $[\alpha]_D$ −28°).




In addition to providing an efficient, non-photochemical route to 13-*epi*-steroids, the reaction of 17-oximes with refluxing acetic anhydride and pyridine

[1] M. Hanack, 'Conformation Theory,' Academic Press, New York, 1965, pp. 176 *et seq.*
[2] A. Butenandt and L. Poschmann, *Ber.*, 1944, **77**, 394, and references therein.
[3] J. P. L. Bots, *Rec. Trav. chim.*, 1958, **77**, 1010.
[4] H. Wehrli and K. Schaffner, *Helv. Chim. Acta*, 1962, **45**, 385.
[5] J.-C. Jacquesy, R. Jacquesy, and J.-F. Patoiseau, *Bull. Soc. chim. France*, 1974, 1959.
[6] R. B. Boar, F. K. Jetuah, J. F. McGhie, M. S. Robinson, and D. H. R. Barton, *J.C.S. Chem. Comm.*, 1975, 748.
[7] R. B. Boar, J. F. McGhie, M. Robinson, D. H. R. Barton, D. C. Horwell, and R. V. Stick, *J.C.S. Perkin I*, 1975, 1237.
[8] R. Anliker, M. Müller, J. Wohlfahrt, and H. Heusser, *Helv. Chim. Acta*, 1955, **38**, 1404.
[9] G. Rosenkranz, O. Mancera, F. Sondheimer, and C. Djerassi, *J. Org. Chem.*, 1956, **21**, 520.
[10] B. M. Regan and F. N. Hayes, *J. Amer. Chem. Soc.*, 1956, **78**, 639.
[11] A. Butenandt, A. Wolff, and P. Karlson, *Ber.*, 1941, **74**, 1308.

also provides compelling evidence that, as proposed in our original publication,[7] enamide formation involves a free-radical pathway (Scheme). The alternative of




SCHEME

ring opening and re-closure *via* a carbocation species is not feasible under these (basic) reaction conditions.

## EXPERIMENTAL

N.m.r. data (90 MHz) are for solutions in deuteriochloroform with tetramethylsilane as internal reference. Acetic anhydride and pyridine were of AnalaR or equivalent grade. T.l.c. plates were prepared using Merck silica gel $GF_{254}$. Laporte type 0 alumina and Merck 60 silica gel were employed.

*17-Acetamidoandrosta-5,16-dien-3β-yl Acetate* (2).—17-Hydroxyiminoandrost-5-en-3β-yl acetate [8] (1 g) in dry *NN*-dimethylformamide (20 ml) was stirred under nitrogen, and acetic anhydride (25 ml) was added. After 1 h freshly prepared anhydrous chromium(II) acetate [12] (8 g) was added. The mixture was stirred overnight at 40 °C. The solvent was removed under reduced pressure, N-sodium carbonate solution (100 ml) was added, and the mixture was extracted with ethyl acetate. The combined extracts were washed with water, dried, and evaporated. The residue was chromatographed on a silica gel column to afford the 13β-enamide (2) (65%), m.p. 229—232°, $[\alpha]_D$ −15° (*c* 1.2 in ethanol) (lit.,[9] m.p. 237—240°, $[\alpha]_D$ −18°), τ 3.5br (1 H, exchanged with deuterium oxide, –NH–), 4.0br (1 H, 16-H), 4.60br (1 H, d, 6-H), 5.4 (1 H, m, 3α-H), 7.93 and 7.99 (each 3 H, s, Ac), and 8.95 and 9.11 (each 3 H, s, 18- and 19-$H_3$).

*Action of Acetic Anhydride–Pyridine on 17-Hydroxyimino-compounds.*—17-Hydroxyiminoandrost-5-en-3β-yl acetate [8] (1 g) in pyridine (50 ml) and acetic anhydride (30 ml) was stirred under nitrogen and heated on an oil-bath so that *gentle* refluxing occurred. The mixture rapidly developed a dark colour. Overheating afforded excessive amounts of a black deposit and lower yields of the required products. When no oxime or oxime acetate remained (t.l.c. control; *ca.* 12 h), the mixture was evaporated to dryness. The black, oily residue was treated with ether (80 ml), and N-sodium carbonate solution (80 ml) was added. The mixture was triturated thoroughly for several minutes, and then filtered through a thin pad of Celite. The granular black residue was washed thoroughly with several portions of ether. The combined ethereal extracts were washed with water, dried, and evaporated. T.l.c. of the resultant, pale brown oil indicated the presence of two products, one slightly less polar and one more polar than the original oxime.

Chromatography on a dry silica gel column, eluted with 30% ethyl acetate in light petroleum gave *17-diacetylamino-13α-androsta-5,16-dien-3β-yl acetate* (3; R = Ac), m.p. (from hexane) 118—121°, $[\alpha]_D$ −99° (*c* 0.7 in chloroform), $\nu_{max.}$ (Nujol) 1 730, 1 705, 1 240, and 1 020 $cm^{-1}$, τ 4.35br (1 H, t, 16-H), 4.60br (1 H, d, 6-H), 5.4 (1 H, m, 3α-H), 7.62 (6 H, s, $NAc_2$), 7.98 (3 H, s, OAc), and 8.90 and 9.04 (each 3 H, s) (Found: C, 72.65; H, 8.7; N, 3.4. $C_{25}H_{35}NO_4$ requires C, 72.6; H, 8.6; N, 3.4%). Further elution with 50% ethyl acetate in light petroleum afforded *17-acetamido-13α-androsta-5,16-dien-3β-yl acetate* (3; R = H), m.p. (from acetonitrile) 160—163°, $[\alpha]_D$ −102° (*c* 1.8 in chloroform), $\nu_{max.}$ (Nujol) 3 370, 1 725, 1 690, 1 540, 1 370, 1 240, and 1 030 $cm^{-1}$, τ 3.15br (1 H, s, exchanged with deuterium oxide, –NH–), 4.00br (1 H, s, 16-H), 4.6br (1 H, d, 16-H), 5.4 (1 H, m, 3α-H), 7.91 and 7.99 (each 3 H, s, Ac), and 9.01 and 9.12 (each 3 H, s) (Found: C, 74.3; H, 8.9; N, 3.75. $C_{23}H_{33}NO_3$ requires C, 74.4; H, 8.95; N, 3.8%).

Alternatively, chromatography of the total product on an alumina column yielded the enamide (3; R = H) (85%) as the sole product.

Identical treatment of 17-hydroxyimino-3-methoxyoestra-1,3,5(10)-triene [10] (5) with refluxing acetic anhydride and pyridine afforded *17-diacetylamino-3-methoxy-13α-oestra-1,3,5(10),16-tetraene* (6; R = Ac), m.p. (from methanol) 114—116°, $[\alpha]_D$ +32° (*c* 0.5 in chloroform), τ 2.86 (1 H, d, *J* 9 Hz, 1-H), 3.2—3.45 (2 H, m, 2- and 4-H), 4.31 (1 H, m, 16-H), 6.26 (3 H, s, OMe), 7.63 (6 H, s, $NAc_2$), and 8.85 (3 H, s, 18-$H_3$) (Found: C, 75.3; H, 8.0; N, 3.7. $C_{23}H_{29}NO_3$ requires C, 75.2; H, 7.95; N, 3.8%) and 17-acetamido-3-methoxy-13α-oestra-1,3,5(10),16-tetraene (6; R = H), a gum, $[\alpha]_D$ +11° (*c* 1.2 in chloroform), τ 2.86 (1 H, d, *J* 9 Hz, 1-H), 3.12br (1 H, s, exchanged with deuterium oxide, –NH–), 3.2—3.45 (2 H, m, 2- and 4-H), 4.0br (1 H, s, 16-H), 6.27 (3 H, s, OMe), 7.93 (3 H, s, Ac), and 8.93 (3 H, s, 18-$H_3$). Alternatively, chromatography of this mixture on a column of alumina gave solely the enamide (6; R = H) (80%).

*Hydrolysis of the 13α-Enamides* (3; R = H) *and* (6; R = H).—The enamide (3; R = H) (200 mg) in methanol (20 ml) containing 2N-hydrochloric acid (6 ml) was heated under reflux for 1 h. The mixture was evaporated to half

[12] J. R. Hanson, *Synthesis*, 1974, 1.

volume, poured into water, and extracted with ether. Crystallisation from hexane gave 3β-hydroxy-13α-androst-5-en-17-one (4), m.p. 180—184°, $[\alpha]_D$ −162° (*c* 0.6 in ethanol) (lit.,[3] m.p. 187—189°, $[\alpha]_D$ −162.9°). The acetate had m.p. 135—139°, $[\alpha]_D$ −152° (*c* 0.5 in ethanol) (lit.,[3] m.p. 143—144°, $[\alpha]_D$ −149°).

Similarly, the enamide (6; R = H) afforded 3-methoxy-13α-oestra-1,3,5(10)-trien-17-one (7), m.p. 130—133°, $[\alpha]_D$ −27.5° (*c* 0.5 in chloroform) (lit.,[11] m.p. 129—130°, $[\alpha]_D$ −28°).

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