Ring B Functionalization of the 10α-Estra-4-en-17β-hydroxy-3-one System

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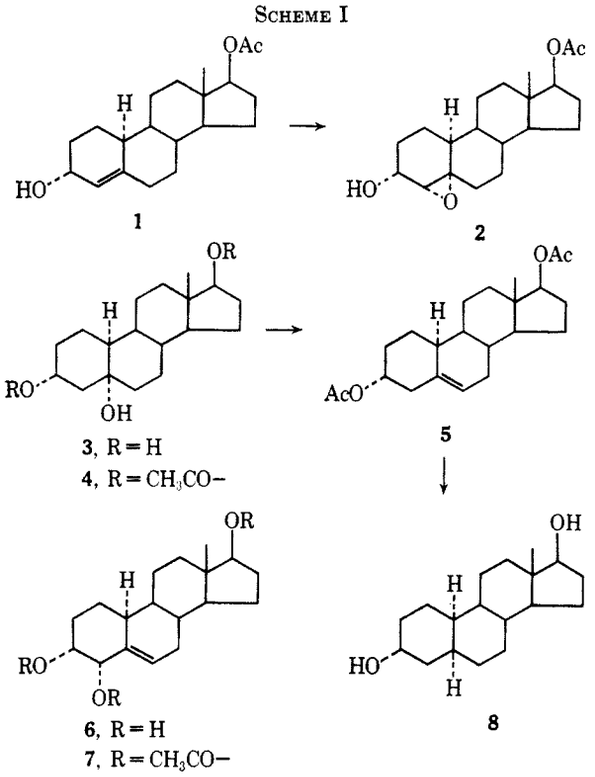
The syntheses and chemistry of ring-B functionalized members of the 10α-estrane series were studied. 10α-Estr-5(6)-en-3α,17β-dihydroxy diacetate (**5**) was synthesized from 10α-estr-4α,5α-oxido-3α,17β-diol 17-acetate **2** by lithium aluminum hydride reduction and subsequent dehydration of the resulting C-5 tertiary hydroxy group in **4**. The lithium aluminum hydride reduction of **2** also gave 3α,4α,17β-trihydroxy-10α-estr-5(6)-ene (**6**). The olefinic bond in **5** was used to introduce the $\Delta^{5(6)}$-7-one, 5α,6α-oxido, and 6-chloro-5-hydroxy groupings into the 10α-estrane system.

In the course of studies directed toward the preparation of steroids with modified (unnatural) stereochemistry, we have reported the properties of a new class of 19-nor steroids, the 10α-estrenes.[1] The present report is concerned with the synthesis and properties of some ring-B functionalized members of this series.

Functionalization of ring B in a variety of steroids has been accomplished using the $\Delta^{5(6)}$ double bond,[2] which can be introduced through dehydration of the corresponding C-5 hydroxy steroid. The synthesis of 10α-estr-5(6)-ene-3α,17β-diol was accomplished in a manner similar to that shown in Scheme I.

Scheme I



10α-Estr-4-ene-3α,17β-diol 17-acetate (**1**) was epoxidized with *m*-chloroperbenzoic acid to give the 4α,5α-epoxy alcohol (**2**).[1] The configuration of the oxirane ring was assigned on the basis of conformational considerations and its nmr spectrum. The unique conformation of the 10α-estrene system results in steric hindrance of the ring A β face due to the presence of the ring B boat.[1a] Reactions such as epoxidation and hydrogenation, therefore, are expected to occur preferentially on the less hindered α face.[3] In the nmr spectrum the signal for the proton at C-4 is a broadened doublet at δ 3.05 ppm (J = 2 Hz). Molecular models of **2** show that the dihedral angle between the 3β,4β protons is approximately 60°, leading to the predicted coupling constant of 2 Hz.[4] The corresponding dihedral angle for the 4β,5β-epoxide is 94° and would be expected to result in little or no coupling between the 4α,3β protons. The observed results, therefore, favor the 4α,5α configuration for the oxirane ring.

Reduction of the epoxy alcohol **2** with lithium aluminum hydride gave two triols. The predominant, more polar product **3** has two hydroxyl groups which were readily acetylated to give a diacetate to which structure **4** was assigned. Treatment of **4** with phosphorus oxychloride gave the desired C-5(6) olefin **5**. The nmr spectrum of **5** showed a single olefinic proton at δ 5.47 as a broadened doublet (J = 5–6 Hz), which represents a 0.1-ppm downfield shift from the corresponding signal of **4**.[1] Therefore, the double bond was assigned to the $\Delta^{5(6)}$ position.[5] Hydrogenation of **5** gave 5α,10α-estra-3α,17β-diol (**8**) which serves to establish that the 10α stereochemistry was retained during this reaction sequence.

The second triol **6** was shown by nmr spectrum to possess a new secondary alcohol function and a trisubstituted double bond. These observations were further verified by acetylation of **6** to a triacetate (**7**); the nmr spectrum of **7** retained the signal for the olefinic proton. The vicinal relationship of the newly introduced hydroxyl group to the hydroxyl group at C-3 was demonstrated by the facile periodic acid oxidation of **6** to an aldehyde.[6] Since Campion and Morrison observed that 3-methoxycholestanol 4α,5α-epoxide forms 3-methoxy-4α-hydroxycholesterol,[7] it is reasoned that the C-4 hydroxyl group of **6** also retains the 4α configuration. The exact mechanism for the formation of **6** remains obscure, although the intervention of aluminum salts as Lewis catalysts can not be discounted.

The chemical consequences of introducing a C-5(6) double bond into the 10α-estrane system were studied (see Scheme II). Epoxidation of **5** gave **9** in good yield. The configuration of epoxide **9** was deduced to be 5α,6α, using the nmr method described by Cross.[4]

(1) See M. Debono, E. Farkas, R. M. Molloy, and J. M. Owen, *J. Org. Chem.*, submitted for publication. Preliminary communication of the work appeared in E. Farkas, J. M. Owen, M. Debono, R. M. Molloy, and M. M. Marsh, *Tetrahedron Lett.*, 1023 (1966).

(2) (a) Pl. A. Plattner, H. Heusser, and M. Feurer, *Helv. Chim. Acta*, **32**, 587 (1949); (b) L. F. Fieser, *J. Amer. Chem. Soc.*, **75**, 4377 (1953); (c) A. J. Fudge, C. W. Shoppee, and G. H. R. Summers, *J. Chem. Soc.*, 958 (1954).

(3) H. B. Henbest and R. A. L. Wilson *ibid.*, 1958 (1957).

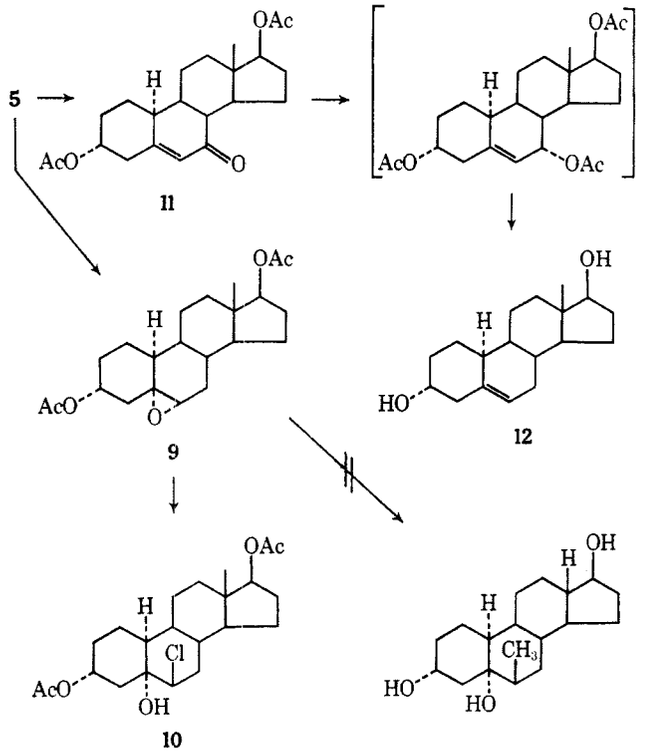
(4) A. D. Cross, *J. Amer. Chem. Soc.*, **84**, 3206 (1962).

(5) (a) J. N. Shoolery and M. T. Rogers, *ibid.*, **80**, 5121 (1958); (b) N. S. Bhacca and D. H. Williams, "Application of NMR Spectroscopy in Organic Chemistry," Holden-Day, Inc., San Francisco, Calif., 1964, p 87.

(6) E. L. Jackson, *Org. Reactions*, **2**, 341 (1944).

(7) T. H. Campion and G. A. Morrison, *Tetrahedron Lett.*, 1 (1968).

SCHEME II



The coupling between the 6–7β protons is 4 Hz at δ 3.0 ppm, which is in good agreement with the predicted values (3.7–4.8 Hz). This reaction appeared to occur with high preference for formation of the α-epoxide; no significant amount of the β-oxide could be detected. The epoxide function of **9** proved to be resistant to attack by Grignard and organolithium reagents during attempts to synthesize the corresponding 6-methyl analog.[8] No explanation can be readily advanced at this time to account for the unreactivity of the oxirane ring toward these reagents. The possibility exists that the conformation of **9** produces interference with axial approach of the 6 position by the Grignard reagent from the β side, thereby interfering with the *trans*-diaxial cleavage of the epoxide ring.[9]

Addition of hydrogen chloride to **9** gave a chlorohydrin (**10**) in quantitative yield.[10] Treatment of **9** with boron trifluoride etherate resulted in no isomerization to 6-keto steroids under conditions known to cause this transformation in other series.[11]

Functionalization of C-7 was, however, readily accomplished by oxidation of **5** with *t*-butyl chromate, according to conditions outlined by Heusler to give the corresponding $\Delta^{5(6)}$-7-keto steroid **11**.[12] In order to confirm the retention of the 10α stereochemistry, **11** was reduced with $LiAlH_4$ to a mixture of triols; these were acetylated and reduced with a lithium solution in anhydrous ethylamine to remove the sole allylic acetate.[13] This process resulted in the regeneration of the $\Delta^{5(6)}$ system **12**. A photooxygenation path to **11**, using conditions described by Nickon,[14] failed and resulted in quantitative recovery of starting material.

Experimental Section[15]

Epoxidation of 1.—To a solution of **1** (5.52 g) in $CHCl_3$ (150 ml) which was cooled to 0° in an Me_2CO–ice bath, a solution of *m*-chloroperbenzoic acid (3.96 g) in $CHCl_3$ (125 ml) was added dropwise. The resultant solution was allowed to stand at 0° for 16 hr. After the addition of an equal volume of H_2O, the mixture was extracted with three portions of $CHCl_3$. The organic extracts were washed with $Na_2S_2O_3$ solution, 10% $NaHCO_3$ solution, H_2O, and dried overnight ($MgSO_4$). The solvent was evaporated to give **2** as a white powder (2.19 g); this was crystallized from Me_2CO: mp 177–178°; nmr ($CDCl_3$) δ 0.74 (s, 3 H, 18-CH_3), 2.02 (s, 3 H, acetate), 3.02 (d, 1 H, J = 2 Hz, 4β-H), 2.92 (m, 1 H, $W_{1/2}$ = 15 Hz, 3β-H), 4.65 (t, 1 H, J = 7 Hz, 17-H). *Anal.* Calcd for $C_{20}H_{30}O_4$: C, 71.82; H, 9.04. Found: C, 71.73; H, 9.15.

$LiAlH_4$ Reduction of 2.—A solution containing 8.24 g of **2** in 400 ml of THF was added dropwise to a cooled and stirred suspension of 3.2 g of $LiAlH_4$ in 900 ml of THF. The reaction was judged to be essentially complete by tlc after 14 hr. The excess $LiAlH_4$ was destroyed by successive additions of EtOAc, aqueous EtOH, and finally H_2O. The ether layer was washed with H_2O, dried ($MgSO_4$), and evaporated to dryness. The residual oil was chromatographed over 300 g of Davison silica gel (60–200 mesh), using benzene–EtOAc mixtures. Elution with solvent up to 50% EtOH in benzene gave unidentified oily products. A crystalline product (**6**) (2.19 g) was eluted with 20% EtOAc–benzene and 30% EtOAc–benzene: mp 181–182°; nmr ($CDCl_3$) δ 0.71 (s, 3 H, 17-CH_3), 3.55 (m, 2 H, 3- and 17-H), 4.08 (d, 1 H, J = 3 Hz, 4βH), 5.60 (d, broad, 1 H, J = 5 Hz, 6-H). *Anal.* Calcd for $C_{18}H_{28}O_3$: C, 73.93; H, 9.65. Found: C, 73.77; H, 9.62.

A sample of **6** (100 mg) was oxidized rapidly by a molar quantity of periodic acid to an oily aldehyde which resisted purification. Ir (1685 cm^{-1}) and nmr data [δ 9.4 (s, 1 H, HCOC=), 6.7 ppm (m, 1 H, OC=CH–)] indicate the presence of the α,β-unsaturated aldehyde group expected from structure **6**.

Further elution with 20% Me_2CO in EtOAc gave 3.39 g of crystalline product **3**, mp 214–216° (Me_2CO). *Anal.* Calcd for $C_{18}H_{30}O_3$: C, 73.43; H, 10.27. Found: C, 73.41; H, 10.35.

Acetylation of 3.—A solution of **3** (100 mg) in pyridine (3 ml) containing acetic anhydride (1.5 ml) was allowed to stand at room temperature overnight. After evaporation of solvents crystalline diacetate **4** (106 mg) was obtained: mp 178–179° (Et_2O); nmr ($CDCl_3$) δ 0.78 (s, 3 H, 18-CH_3), 2.02 (s, 6 H, CH_3COO–), 4.6 (m, 2 H, 3- and 17-H). *Anal.* Calcd for $C_{22}H_{34}O_5$: C, 69.81; H, 9.05. Found: C, 70.00; H, 9.28.

Acetylation of 6.—Acetylation of **6** (100 mg) was accomplished by the above procedure. Colorless crystalline triacetate **7** (49 mg) was obtained: mp 151–152° (Et_2O); nmr ($CDCl_3$) δ 0.80 (s, 3 H, 18-CH_3), 2.0, 2.04, 2.10 (s, 3 H each acetate), 4.05 (m, 2 H, 3- and 17-H), 5.5 (d, 1 H, J = 2.5 Hz, 4α-H), 5.80 (d, broad, 1 H, J = 6 Hz, 6-H). *Anal.* Calcd for $C_{24}H_{34}O_6$: C, 68.87; H, 8.19. Found: C, 68.64; H, 8.15.

10α-Estra-5(6)-ene-3α,17β-diol Diacetate (5).—Compound **4** (2.9 g) was dissolved in pyridine (50 ml) to which was slowly added $POCl_3$ (15 ml) with external cooling. This mixture was allowed to stand for 64 hr at 10° and the poured slowly into 150 ml of ice water. The reaction product was isolated by extraction with three portions of Et_2O which were combined and washed successively with H_2O, saturated $NaHCO_3$ solution, and H_2O. After drying ($MgSO_4$) and evaporation of solvent, 2.2 g of **5** was obtained as a colorless crystalline product: mp 135–136° (Et_2O); nmr ($CDCl_3$) δ 0.79 (s, 3 H, 18-CH_3), 2.0 (s, 6 H, 2-acetates), 4.62 (m, 2 H, 3β- and 17α-H), 5.47 (d, 1 H, J = 6 Hz, 6-H).

(8) (a) For leading references to the addition of Grignard reagents to epoxides see J. G. Phillips and U. D. Parker, "Steroid Reactions," C. Djerassi Ed., Holden-Day, Inc., San Francisco, Calif., 1963, p 631; (b) R. Villotti C. Djerassi, and H. J. Ringold, *J. Amer. Chem. Soc.*, **81**, 4566 (1959); (c) L. F. Feiser and J. Rigaudy, *ibid.*, **73**, 4660 (1951).

(9) For leading references see E. L. Eliel, N. L. Allinger, S. J. Angyal, and G. A. Morrison, "Conformational Analysis," Interscience Publishers, Inc., New York, N. Y., 1965, p 296.

(10) R. A. Baxter and F. S. Spring, *J. Chem. Soc.*, 613 (1943).

(11) H. B. Henbest and T. I. Wrigley, *ibid.*, 4596 (1957).

(12) (a) K. Heusler and A. Wettstein, *Helv. Chim. Acta*, **35**, 284 (1952); (b) K. Block, *ibid.*, **36**, 1611 (1953).

(13) A. S. Hallsworth, H. B. Henbest, and T. I. Wrigley, *J. Chem. Soc.*, 1969 (1957).

(14) A. Nickon, N. Schwartz, J. B. DiGiorgio, and D. A. Widdowson, *J. Org. Chem.*, **30**, 1711 (1965).

(15) All melting points are uncorrected. Nmr data were obtained from a Varian HR-60 instrument; uv determinations were performed on a Cary-15 spectrophotometer; ir measurements were made on a Beckman IR-7 instrument.

Anal. Calcd for $C_{22}H_{32}O_4$: C, 73.30; H, 8.95. Found: C, 73.26; H, 9.01.

Epoxidation of 5.—The epoxidation procedure utilized above was employed to convert 500 mg of **5** into epoxide **9** (392 mg): mp 138.5–139.5° (Et_2O); nmr ($CDCl_3$) δ 0.77 (s, 3 H, 18-H, 18-CH_3), 2.02 (s, 6 H, CH_3COO–), 3.0 (d, 1 H, J = 4 Hz, 6β-H), 4.68 (m, 2 H, 3β-, 17α-H). *Anal.* Calcd for $C_{22}H_{32}O_5$: C, 70.18; H, 8.57. Found: C, 70.24; H, 8.47.

Hydrogenation of 5.—A sample of **5** (50 mg) was hydrogenated for 18 hr at atmospheric pressure using 75 mg of PtO_2 in 15 ml CH_3OH containing 3 drops of 48% HBr solution. The usual work-up gave 31 mg of fine, amorphous solid **8**, mp 219–222° (Me_2CO–petroleum ether (bp 30–60°)); melting point and X-ray differaction pattern were identical with those of authentic 5α,10α-estrane-3α,17β-diol. No depression was observed in the mixture melting point determination.

HCl Addition to 9.—Hydrogen chloride gas was bubbled into a solution containing 100 mg of **9** in 8 ml of $CHCl_3$ for 30 min.[10] Evaporation of solvent gave a residue which was recrystallized twice from Et_2O to give chlorohydrin **10** (67 mg), mp 197–198°. *Anal.* Calcd for $C_{22}H_{33}O_5Cl$: C, 63.98; H, 8.05. Found: C, 63.97; H, 7.92.

***t*-Butyl Chromate Oxidation of 4.**—A solution of **4** (150 mg) in CCl_4 (1.5 ml) was refluxed and then treated with *t*-butyl chromate (1.2 ml) containing Ac_2O (0.15 ml) according to the method described by Heusler and Wettstein.[12a] This procedure gave an oily product which was chromatographed on 15 g of Florisil (100–200 mesh). Solvent mixtures of pentane–benzene eluted 50 mg of intractable oils, but further elution with 20% Et_2O in benzene gave colorless prisms (23 mg) of **11**: mp 166–167°; ir ($CHCl_3$) 1675 cm^{-1}; uv (EtOH) 236 mμ (ε 11,000); nmr ($CDCl_3$) δ 0.76 (s, 3 H, 18-Me), 3.68 (m, 1 H, 17α-H), 5.68 (s, 1 H, 6-H). *Anal.* Calcd for $C_{22}H_{30}O_5$: C, 70.56; H, 8.08. Found: C, 70.55; H, 8.32.

Conversion of 11 to 12.—A solution of **11** (60 mg) was exhaustively reduced with $LiAlH_4$ in THF, and the resulting mixture was acetylated by the usual procedures to give a crystalline mixture of acetates. This broad-melting mixture was dissolved in anhydrous $EtNH_2$ (10 ml), added to a solution of Li (60 mg) in $EtNH_2$ (50 ml), and allowed to stand for 5 min at room temperature.[13] The blue color was then removed by slow addition of solid NH_4Cl, and the solvent was allowed to slowly evaporate to near dryness. Addition of H_2O was followed by extraction with ether; evaporation of the dried ($MgSO_4$) extract gave an oil (41 mg) which was chromatographed on 4 g of silica gel (Davison 60–200 mesh). Benzene eluted 9 mg of an oily substance; further elution with Et_2O gave a oil which crystallized from Me_2CO–petroleum ether, mp 172–174°, and gave no depression in melting point when mixed with **12**. Mass spectral fragmentation, R_f on tlc, and nmr spectra of this product and **12** were also identical with data obtained from the hydrolysis product of **5**.

Hydrolysis of 5 to 12.—A solution of **5** (500 mg) in CH_3OH (25 ml) and H_2O (2.5 ml) containing $KHCO_3$ (370 mg) was refluxed for 2 hr, evaporated to half-volume, and treated with 0.25 ml of AcOH. After extraction with three portions of CH_2Cl_2 (100 ml each) and washing with H_2O, the organic layer was dried ($MgSO_4$). Evaporation of solvent gave a white powder (**12**), mp 174–175° (Me_2CO–petroleum ether). *Anal.* Calcd for $C_{18}H_{28}O_2$: C, 78.21; H, 10.21. Found: C, 77.97; H, 10.09.

Attempted Photooxygenation of 4.—A solution of **4** (300 mg) in pyridine (40 ml) containing 10 mg of eosin bluish was agitated in a slow stream of oxygen for 4.5 days while being irradiated by a fluorescent desk lamp according to the method outlined by Nickon.[14] Only unreacted starting material was isolated under these conditions.

Attempted Methylation of 9.—A solution of **9** (150 mg) in THF (12 ml) was treated with 1.7 *N* CH_3MgI (4 ml) for 32 hr under reflux.[8] After the residual Grignard reagent was destroyed with NH_4Cl, H_2O was added; the solution was extracted with ether. The extracts were washed with H_2O and dried ($MgSO_4$). Evaporation of solvent gave 123 mg of a colorless gum which was chromatographed on silica gel to give only desacetyl **9**, mp 140–141° (Me_2CO), nmr ($CDCl_3$) δ 2.97 ppm (d, J = 4 Hz, 1 H, C-6 proton). *Anal.* Calcd for $C_{18}H_{28}O_3$: C, 73.93; H, 9.65. Found: C, 73.91; H, 9.73.

Registry No.—**2**, 19684-86-7; **3**, 19684-87-8; **4**, 19684-88-9; **5**, 19684-89-0; **6**, 19684-90-3; **7**, 19684-91-4; **9**, 19684-92-5; desacetyl **9**, 19684-93-6; **10**, 19684-94-7; **11**, 19684-95-8; **12**, 19684-96-9.