The Retropinacol Rearrangement of 17β-Hydroxyandrostanes

WILLIAM F. JOHNS AND GEORGE P. MUELLER

Division of Chemical Research, G. D. Searle and Company, Chicago 80, Illinois

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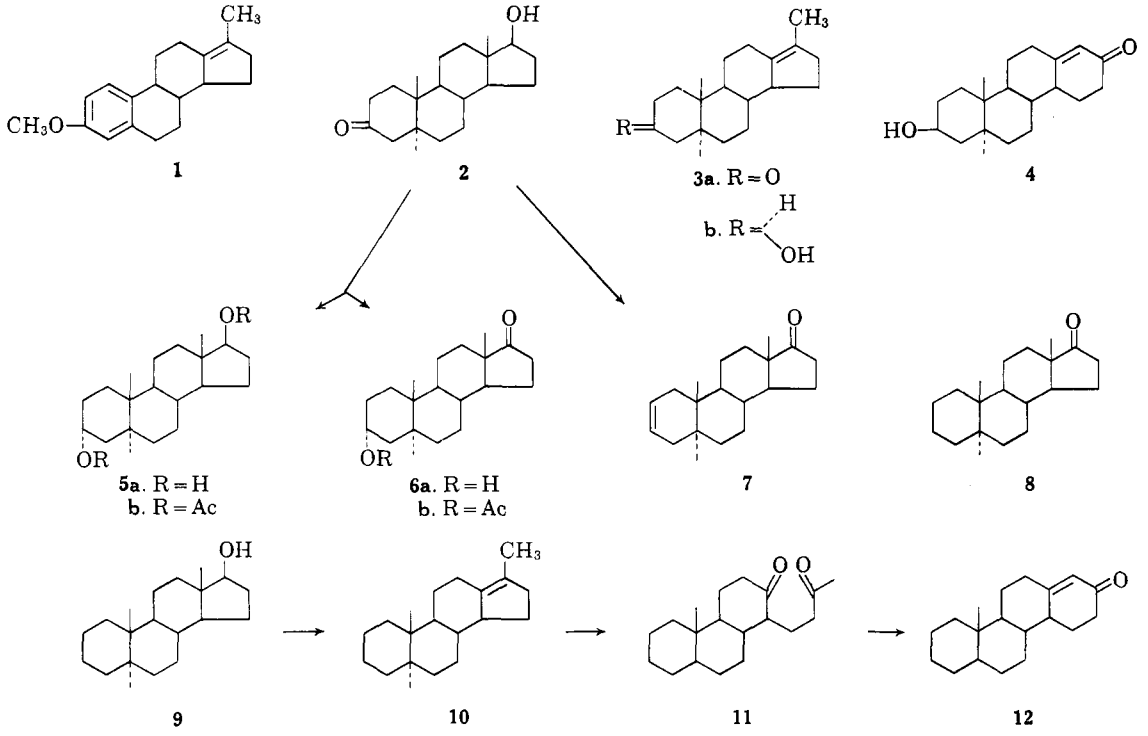
The reaction of 17β-hydroxyandrostan-3-one with boric acid at 380° leads to the formation of androst-2-en-17-one (**7**). Similar treatment of androstan-17β-ol produces 17-methyl-18-norandrost-13(17)-ene (**10**).

The successful conversion of estradiol 3-methyl ether to 17 - methyl - 3 - methoxy - 18 - norestra - 1,3,5(10),-13(17)-tetraene (**1**) by use of boric acid at elevated temperatures[1] prompted application of this reaction to the androstanes. The anticipated product, an analogous 17-methylandrost-13(17)-ene (such as **3**), could be used readily in the preparation of a variety of 18-nor steroids in direct analogy to the synthesis of 18,19-dinor steroids.[2] The sequence of reactions would proceed from olefin **3** through the derivative unsaturated ketone **4**. Although both compounds **3b** and **4** had been described previously by Miescher and Kagi,[3] the use of their synthesis was made unattractive by the relative difficulty in obtaining the starting material, androstane-3β,17α-diol. Since the inception of this project, preparation of 18-nor steroids has been accomplished by several methods.[4]

was 17β-hydroxyandrostan-3-one. When heated with boric acid to 380°, then distilled, and chromatographed, this steroid yielded a crystalline unsaturated ketone having the expected empirical formula, $C_{19}H_{28}O$. An alcohol, obtained by hydride reduction of this ketone, was treated with ozone or osmium tetroxide–periodic acid to oxidize the double bond. The resulting dicarbonyl compound failed to yield any of the desired unsaturated ketone **4** on treatment with base.

The results of these two experiments showed clearly that the parent olefin was not **3a**. It then became important to know whether the product had the rearranged skeleton and was simply a double bond isomer of the expected material **3a**, or whether the dehydration had proceeded without effecting rearrangement, perhaps to yield an androst-16-ene. That both hypotheses were incorrect was determined by



Ideally the starting androstane chosen for the boric acid rearrangement would contain a C-3 grouping that would be stable under the acidic dehydrating conditions employed. Such stability is lacking in ordinary derivatives of the alcohol or ketone functions (such as esters or ketals). The compound thus selected for the reaction

hydrogenation of the unknown keto olefin. The dihydro derivative was clearly different from androstan-3-one but proved to be identical to androstan-17-one (**8**) by spectral comparison with an authentic sample. Identification of the parent olefin was then assisted by inspection of its n.m.r. spectrum, which showed both angular methyl groups undisturbed and the existence of two vinyl hydrogens. The unknown unsaturated ketone was then proved to be androst-2-en-17-one (**7**) by virtue of the identity of its infrared spectrum with that of an authentic sample.[5]

(1) W. F. Johns, *J. Org. Chem.*, **26**, 4583 (1961).

(2) W. F. Johns, *J. Am. Chem. Soc.*, **80**, 6456 (1958).

(3) K. Miescher and H. Kagi, *Helv. Chim. Acta*, **32**, 761 (1949); **22**, 683 (1939).

(4) R. Anliker, M. Muller, M. Perelman, J. Wohlfahrt, and H. Heusser, *ibid.* **42**, 1071 (1959); L. Velluz, G. Amiand, R. Heymes, and B. Goffinet, *Compt. rend.*, **250**, 371 (1960); W. S. Johnson and K. V. Yorka, *Tetrahedron Letters*, **8**, 11 (1960); R. Pappo, U. S. Patent 3,080,360; D. K. Fukushima and H. L. Bradlow, *Abstr. Endocrine Soc.*, 7 (June, 1962).

(5) R. E. Marker, O. Kamm, D. M. Jones, and L. W. Mixon, *J. Am. Chem Soc.*, **59**, 1363 (1937).

Formation of olefin **7** is reasonably explained by postulating first the formation of a borate ester at C-17.[6] Internal oxidation–reduction might follow, the borate ester acting as the reducing agent. This type of reduction of carbonyl groups by alkyl borates at elevated temperatures[7] employs a mechanism analogous to that found in Meerwein–Ponndorf reduction and Oppenauer oxidation.[8] The equilibrium in the present case could be driven to the formation of a C-17 carbonyl not only by the inherently greater stability of a cyclopentanone carbonyl over a cyclohexanone carbonyl,[9] but also by virtue of a much more facile elimination of the C-3 hydroxyl group as compared to the C-17β hydroxyl. This is particularly true since the Meerwein–Ponndorf reduction is expected to give more of the axial isomer than is obtained by other methods of reduction, especially as the size of the reducing agent is increased.[10] The axial hydroxyl would then be removed readily by a facile *trans* diaxial elimination.[11]

Experimental validation of the proposed mechanism of the oxidation–reduction step was initiated by running the boric acid reaction at a lower temperature, conditions which would avoid the final elimination step. The product, acetylated to facilitate separation of components, was carefully chromatographed, allowing isolation of two crystalline compounds, androstane-3α,-17β-diol diacetate (**5b**) and androsterone acetate (**6b**). Although several other constituents could be detected by paper chromatography, none could be isolated and crystallized. This multiplicity of products under preparative conditions would be expected to simplify itself as the reactants approached 380°; the products would undergo transformation to the more stable keto ester and elimination of ester or hydroxyl groups would occur.

To show the absence of an inherent barrier to the retropinacol rearrangement of androstan-17β-ols generally, the reaction sequence was performed on androstan-17β-ol (**9**). Lacking the alternate course of reaction described for the 3-keto analog, this steroid provided the expected olefin **10** as the major product. Its identity was suggested by the n.m.r. spectrum which shows a methyl group attached to a double bond. Ozonolysis of the olefin led to a diketone (**11**) (no spectral indication of aldehyde) which cyclized readily to the unsaturated ketone **12**. The n.m.r. spectrum of the diketone showed an acetyl methyl group and the ultraviolet spectrum of the unsaturated ketone showed the expected cyclohexenone absorption. These data preclude the possibility of the double bond in **10** being in any position besides $C_{13(17)}$ and thus established concretely the structure of compounds **10–12**.

Experimental[12,13]

Boric Acid Treatment of 17β-Hydroxyandrostan-3-one (2). A. At 310–380°.—The hydroxy ketone **2** (40 g.) and boric acid (10 g.) were ground together and heated at 320° for 1 hr. under nitrogen. The temperature was lowered to 220° and the pressure carefully reduced to 22 mm. at a slow rate to control foaming. The product was then distilled between 310° and 380° at 20 mm. The distillate, dissolved in ether, was washed with aqueous sodium bicarbonate and dried. Removal of solvent and distillation of the products afforded 14.77 g. of an oil of which 5.1 g. was chromatographed on 150 g. of silica. Elution of the column with 5% ethyl acetate in benzene yielded 2.31 g. of crystalline material which was recrystallized from aqueous ethanol to yield 1.75 g. of product, m.p. 80–86°. An infrared comparison of this material to authentic androst-2-en-17-one (**7**)[5] showed a very close similarity. The n.m.r. spectrum, $\Delta\nu$ 334 (C_2–C_3) and 319 (C_3–C_4) c.p.s., indicated a minor impurity to be androst-3-en-17-one.

Another sample was chromatographed and recrystallized twice from methanol, yielding plates, m.p. 100–108°, identical by mixture melting point and infrared absorption to an authentic sample of androst-2-en-17-one (**7**).

Hydrogenation[14] of 0.18 g. of the olefin **7**, m.p. 80–86°, in 30 ml. of ethanol containing 30 mg. of 5% palladium on charcoal, was complete in 1 hr. The product was purified by crystallization from methanol; 0.090 g., m.p. 121–123°, and 0.070 g., m.p. 117–121°, both crops being identical in infrared characteristics to an authentic sample of androstan-17-one (**8**).

B. At 250°.—17β-Hydroxyandrostan-3-one, 20 g., was ground with 5 g. of boric acid and heated under nitrogen in a short-necked distilling apparatus. Application of a metal bath, preheated to 185°, caused the mixture to melt and bubble vigorously as water was evolved. In 20 min. the bath was at 250°; bubbling was very slow; and the mixture had become a clear, heavy glass. Heating was discontinued. The main bulk of the glass, excepting samples removed at time intervals, was treated with repeated changes of water and benzene on the steam bath until the glassy residue had dissolved. The total benzene solution, 250 ml., was filtered and distilled to dryness, leaving 12 g. of clear glass as residue.

In order to assist fractionation, 11.5 g. of the residue was acetylated during 20 hr. in 50 ml. of pyridine and 50 ml. of acetic anhydride. The residue from the usual work-up with water, ether, dilute acid, and sodium bicarbonate was also a glass, 11.65 g.

The acetylated mixture, 2.71 g., was chromatographed on silica. Three poorly resolved bands were eluted in very close succession by 2% ethyl acetate in benzene. A fraction from the first peak, recrystallized three times from dilute acetone, melted at 157–165°, and was shown to be androstane-3α,17β-diol diacetate (**5b**), m.p. 163–166° (sweating at 160°), through similar R_f values in paper chromatography, identical infrared absorption spectra, and undepressed mixture melting point.

Repetition of the chromatogram on silica using a slower elution scheme gave crystalline fractions with 0.5% and 1% ethyl acetate in benzene, as well as an oily material upon elution with 5% ethyl acetate in benzene. The first peak consisted mainly of androstane-3α,17β-diol diacetate. The second peak was mainly androstanolone acetate (acetate of **2**) although the leading edge of the band contained a keto acetate, m.p. 161–166°, shown by infrared to be androsterone acetate (**6b**). A sample on a mixture with authentic androsterone acetate, m.p. 167.5–169.0°, melted at 163–168°. Paper chromatography showed the third band to be a mixture of about six compounds, a main component being perhaps a diketone. This band was not examined further.

Androst-2-en-17β-ol.—The olefin mixture (5.7 g.), obtained directly from the 380° boric acid treatment, in 100 ml. of ether was added to a stirred solution of 2.1 g. of lithium aluminum hydride in 180 ml. of ether. After the mixture was heated at reflux for 1 hr., the excess hydride was decomposed by addition of ethyl acetate followed by addition of dilute hydrochloric acid. The ether layer was separated, washed with water and with aqueous sodium bicarbonate, was dried, and concentrated. The resulting residue, 5.4 g. of semicrystalline material, was chromatographed on 300 g. of silica. Elution with benzene afforded 2.02 g. of crystalline material, which on sublimation yielded pure androst-2-en-17β-ol, m.p. 167–168°, having the same infrared spectrum as an authentic sample.[5]

(6) G. L. O'Connor and H. R. Nace, *J. Am. Chem. Soc.*, **77**, 1578 (1955).

(7) H. G. Kuivila, S. C. Slack, and P. K. Siiteri, *ibid.*, **73**, 123 (1951).

(8) A. L. Wilds, *Org. Reactions*, **2**, 178 (1944); C. Djerassi, *ibid.*, **6**, 207 (1951).

(9) H. C. Brown, *J. Chem. Soc.*, 1248 (1956); *J. Org. Chem.*, **22**, 439 (1957). See also R. B. Turner and R. H. Garner, *J. Am. Chem. Soc.*, **80**, 1428 (1958).

(10) H. R. Nace and G. L. O'Connor, *ibid.*, **73**, 5824 (1951).

(11) D. H. R. Barton, *J. Chem. Soc.*, 1027 (1953).

(12) The authors wish to acknowledge the assistance of E. G. Daskalakis and his staff with chromatography and R. T. Dillon and his staff in providing the analyses and spectra reported.

(13) Infrared spectra were determined in chloroform. Rotations were recorded at 1% in chloroform. The n.m.r. spectra were determined in deuteriochloroform by use of an A-60 spectrometer, Varian Associates, Inc., at 60 Mc., using tetramethylsilane as an internal standard ($\Delta\nu$ 0 c.p.s.). The petroleum ether used boils at 63–68°.

(14) We wish to thank W. Selby for conducting the hydrogenation.

This material was cleaved with ozone in methylene chloride at −70° (same procedure as given later) or with osmium tetroxide-catalyzed hydroxylation followed by periodate cleavage (see ref. 1 for procedure), yielding in each instance the same noncrystalline product. Treatment of this material with refluxing methanolic potassium hydroxide failed to produce a pure material. None of the fractions from chromatographic analysis showed appreciable absorption at 240 mμ, indicating the absence of a conjugated cyclohexenone system.

18-Nor-17-methylandrost-13(17)-ene (10).—Androstan-17β-ol (9) was prepared by heating a stirred solution of 40 g. of 17β-hydroxyandrostan-3-one (2) in 0.4 l. of diethylene glycol containing 40 g. of potassium hydroxide and 50 ml. of 85% aqueous hydrazine in a slow stream of nitrogen at 140° for 30 min. and then at 190° for an additional hour. Dilution of the cooled solution with water, followed by filtration of the resulting crystalline mass and recrystallization of the product from methylene chloride–methanol, yielded 38.7 g. of material, m.p. 171–172°, identical in infrared absorption to an authentic sample.

Androstan-17β-ol (38 g.) and boric acid (20 g.) were mixed thoroughly and heated at 200° for 30 min. The mixture was then distilled at 400° and 10 mm. The distillate (18 g.) was dissolved in benzene and washed with aqueous potassium bicarbonate. A portion (3.1 g.) was purified from polar contaminants by chromatography over 150 g. of silica. Elution with petroleum ether gave 2.85 g. of a mobile oil, 18-nor-17-methyl-androst-13-(17)-ene (10); $[\alpha]_D$ −15°; $\Delta\nu$ 42 (C_{19}—CH_3), 95 (C=CCH_3) c.p.s.

Anal. Calcd. for $C_{19}H_{30}$: C, 88.30; H, 11.70. Found: C, 88.08; H, 11.72.

The distillation residue was dissolved in hot benzene and dilute aqueous potassium hydroxide. The washed and dried benzene solution was concentrated, affording 13 g. of semicrystalline material. Chromatography of 4.0 g. of this material on 50 g. of silica yielded 1.72 g. of the desired olefin **10**. Later eluates produced 1.95 g. of crystalline starting material (**9**), identified by melting point and infrared spectrum.

13,17-Secoandrostane-13,17-dione (11).—A solution of 10 g. of the olefin **10** in 100 ml. of methylene chloride and 2 ml. of pyridine were treated at −70° with a stream of oxygen containing ozone until the solution turned blue. Zinc dust, 10 g., and 10 ml. of acetic acid in 10 ml. of methylene chloride were added and the mixture was stirred in an ice bath for 30 min. The mixture was filtered and the filtrate was washed with water and aqueous potassium bicarbonate. Concentration of the dried extract afforded 12.5 g. of mobile oil, 4.0 g. of which was chromatographed on 150 g. of silica. The major portion was eluted with 2% ethyl acetate in benzene, yielding 1.98 g. of 13,17-secoandrostane-13,17-dione (11); $[\alpha]_D$ +3°; λ_{max} 5.82 μ; $\Delta\nu$ 44 (C_{10}–CH_3), 127 (–$COCH_3$) c.p.s. Despite a repeated chromatographic fractionation of this material and the use of a variety of solvents on the components, no crystalline material was obtained.

Anal. Calcd. for $C_{19}H_{30}O_2$: C, 78.57; H, 10.41. Found: C, 78.73; H, 10.29.

18-Nor-D-homoandrost-13(17a)-en-17-one (12).—A solution of 0.80 g. of the diketone 11 (purified by chromatography) in 30 ml. of methanol containing 5 ml. of 15% aqueous potassium hydroxide was heated at reflux for 1 hr. The cooled solution was diluted with water, and the resulting precipitate was separated by filtration. The product was washed with water, air-dried, and dissolved in petroleum ether. The solution, after treatment with charcoal, was concentrated, yielding 0.30 g. of the pure unsaturated ketone 12, m.p. 158–160°; $[\alpha]_D$ −39°; λ_{max} 5.98, 6.15 μ; λ_{max} 240 (16,800) mμ.

Anal. Calcd. for $C_{19}H_{28}O$: C, 83.77; H, 10.36. Found: C, 83.62; H, 10.44.

Synthesis of 3-Methoxy-17-acetyl-18-norestra-1,3,5(10),16-tetraene

WILLIAM F. JOHNS

Division of Chemical Research, G. D. Searle and Company, Chicago 80, Illinois

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Conversion of the D-homo unsaturated ketone **5** to the title compound has been accomplished by a sequence of five reactions: reduction (to **2b**), Grignard addition (**11**), dehydration (**13**), ozonolysis (**18**), and cyclization (**20**). Formation of the dienedione **10**, a by-product of the reduction step, is also discussed.

The facile production of the unsaturated ketone **5** from estradiol 3-methyl ether in three steps[1] allowed continuation of a projected synthesis of 18-norestrone and 18,19-dinor steroids.[2] The potential physiological interest of such materials was clear from the enhanced activities of several 19-nor steroids as compared to their methylated analogs.[3]

Proper introduction of a single asymmetric center into the D-homo ketone **5** is necessary to produce a molecule having the desired, naturally occurring *trans–anti–trans* ring junctures of rings B, C, and D. None of the remaining reactions in the planned sequence would labilize these bridgehead carbon atoms; thus the stereochemistry of these centers would remain unchanged. Ample literature precedent exists for the reduction of systems such as $\Delta^{1(9)}$-decalone-2 to *trans*-2-decalone by means of metal–ammonia systems.[4] Application of this reaction to the planar molecule **5** was complicated only by the possible concommitant reduction of the A-ring. In practice this problem was circumvented by use of lithium–ammonia in the absence of alcohol[5] which allowed conversion in good yield of the unsaturated ketone **5** to the saturated ketone **2b**.

An alternate method was to use a metal–ammonia reaction in the presence of alcohol, effecting reduction of both the A-ring and the unsaturated ketone moieties to produce the enol ether **4a**. With this method of preparation the C-17 hydroxyl is expected to be in the more stable α-configuration.[4] Whereas Oppenauer oxidation of this compound afforded the corresponding C-17 ketone **4b**, pyridine–chromium trioxide caused oxidation of both the A-ring and the alcohol producing the ketone **2b**.

The enol ether **4a** was readily transformed into the unsaturated ketone **1a** and, in turn, into the diketone **1b**. If purification of the enol ether **4a** was omitted and instead the entire metal–ammonia reduction product was hydrolyzed, a new component was isolable. In addition to the major product, the unsaturated ketone **1a**, there was obtained 7% of a compound having an ultraviolet maximum at 242 mμ (ε 35,600) with twice the intensity of a steroidal cyclohexenone. All additional information about this material confirmed the fact that it had two unsaturated ketone groups. Only

(1) W. F. Johns, *J. Org. Chem.*, **26**, 4583 (1961).
(2) W. F. Johns, *J. Am. Chem. Soc.*, **80**, 6456 (1958).
(3) See, *e.g.*, H. P. Schedl, C. Delea, and F. C. Bartter, *J. Clin. Endocrinol. Metab.*, **19**, 921 (1959).
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