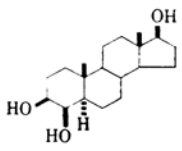
The Preparation of 5α-Androstane-3β,4α,17β-triol through a Hydroboration Reaction[1]

By Hisao NAKATA

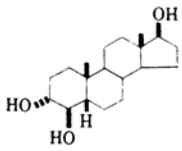
(Received June 29, 1964)

Although the syntheses of a number of androgenic steroids have been reported, only two androstane-3, 4, 17-triols have been described in the literature. Thus, 5α-androstane-3β, 4β, 17β-triol (I) was obtained by the catalytic reduction[2] of androst-5-ene-3β,4β,17β-triol, which, in turn, was prepared from androst-5-ene-3β, 17β-diol either by direct oxidation with selenium dioxide[2,3] or by the treatment of its dibromo derivatives with bases.[4,5] An isomeric 5β-androstane-3α, 4β, 17β-triol (II) was prepared[6] by the reduction of 4β, 5-epoxy-5β-androstan-17β-ol-3-one 17-acetate with lithium aluminum hydride.

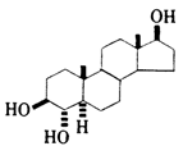
In connection with other steroid studies,[7] we have had occasion to synthesize another isomer of the triol from easily-available starting materials; this paper will deal with the preparation and configurational assignment of the previously unknown 5α-androstane-3β, 4α, 17β-triol (III).



(I)



(II)



(III)

When testosterone benzoate (IV) was treated with sodium borohydride in methanol, the reduction of the carbonyl group readily took place and androst-4-ene-3β, 17β-diol 17-benzoate (V) was obtained in a fairly good yield. The configuration of the 3-hydroxyl group is assigned as such on the basis of the steric course of similar reactions.[8-16] The assignment was confirmed by the fact that, after the benzoate group had been removed by saponification, the product was identical with the known androst-4-ene-3β, 17β-diol (VI).[17] A small amount of an isomeric alcohol was also isolated from the reaction mixture. This alcohol is probably androst-4-ene-3α, 17β-diol 17-benzoate (VII).

The introduction of an oxygen function at C_4 of the steroid nucleus has been accomplished in many ways,[18,19] but the application of the recently-reported hydroboration reaction[20-22] seems most promising because the reaction usually proceeds in a highly stereospecific manner and gives an excellent yield. Thus, the hydroboration of the allylic alcohol (V) yielded a triol monobenzoate as the sole product. Since it is well-established that the

1) This work was initiated at the Department of Medicine, C. Roswell Park Memorial Institute, Buffalo, N. Y., and completed at the Chemical Institute, Nagoya University.

2) L. Ruzicka and P. A. Plattner, *Helv. Chim. Acta*, **20**, 809 (1939).

3) R. E. Marker, H. M. Crooks, Jr., and E. L. Wittbecker, *J. Am. Chem. Soc.*, **63**, 777 (1941).

4) M. Hosoi, *J. Pharm. Soc. Japan*, **67**, 129 (1947).

5) M. Hosoi, Japanese Pat. 177658, (1949).

6) B. Camerino and D. Cattapan, *Farmaco (Pavia) Ed. Sci.*, **13**, 39 (1958); *Chem. Abstr.*, **52**, 13767 (1958).

7) H. Nakata, *Tetrahedron*, **19**, 1959 (1963).

8) W. G. Dauben, R. A. Micheli and J. F. Eastham, *J. Am. Chem. Soc.*, **74**, 3852 (1952).

9) W. W. Zorbach, ibid., **75**, 6344 (1953).

10) M. Gut, *J. Org. Chem.*, **21**, 1327 (1956).

11) F. Unger, M. Gut and R. I. Dorfman, *J. Biol. Chem.*, **224**, 191 (1957).

12) O. H. Wheeler and J. L. Mateos, *Can. J. Chem.*, **36**, 1049 (1958).

13) F. Sondheimer and Y. Klibansky, *Tetrahedron*, **5**, 15 (1959).

14) B. Pelc, *Coll. Czeck. Chem. Comm.*, **25**, 309 (1960).

15) D. Kupfer, *Tetrahedron*, **15**, 193 (1961).

16) W. G. Dauben and A. C. Ashcraft, *J. Am. Chem. Soc.*, **85**, 3673 (1963).

17) A. Butenandt and A. Heusner, *Ber.*, **71**, 198 (1938).

18) L. F. Fieser and M. Fieser, "Steroids," Reinhold, New York, N. Y. (1959).

19) C. Djerassi, ed., "Steroid Reactions," Holden-Day, San Francisco, California (1963).

20) H. C. Brown, *Tetrahedron*, **12**, 117 (1961).

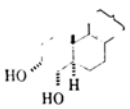
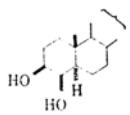
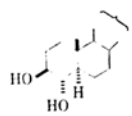
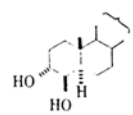
21) H. C. Brown, "Hydroboration," W. A. Benjamin, New York, N. Y. (1962).

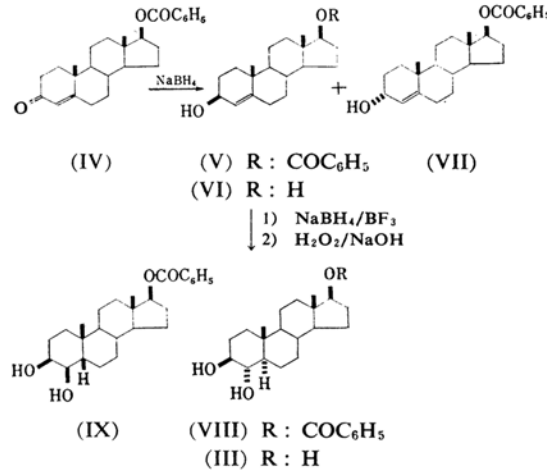
22) G. Zweifel and H. C. Brown, in A. C. Cope, ed., "Organic Reactions," Vol. 13, John Wiley & Sons, New York, N. Y. (1963), p. 1.

hydroboration reaction is anti-Markownikoff cis-addition and that the attack takes place from the less-hindered side of a given molecule,[20-22] the product may be formulated as 5α-androstane-3β, 4α, 17β-triol 17-benzoate (VIII). A less probable alternative is 5β-androstane-3β, 4β, 17β-triol 17-benzoate (IX).

To discriminate these two possibilities, the rate of lead tetraacetate consumption was measured. Unfortunately, the kinetic data for the 3β, 4α-glycol system have not been found in the literature and so no direct comparisons of the present experiment with references could be made. However, as may be seen from Table I, the observed rate constant, 7.43×10^{-3} l. mol^{-1} sec^{-1}, is quite compatible as a steroidal trans-glycol system when compared with the data so far available in the literature.[23,24] If the two hydroxyl groups were cis to each other, as in IX, the rate constant would be expected to be much larger than is actually observed. It is, therefore, safe to conclude that the product is 5α-androstane-3β, 4α, 17β-triol 17-benzoate (VIII).[25] The free triol (III) was obtained after removing the benzoate group by saponification.

TABLE I. RATES OF $Pb(OAc)_4$ CONSUMPTION OF 3,4-DIOLS AT 25°C

3,4-Diol	Configuration	10^3k (l. mol^{-1} sec^{-1})	Ref.
	3α, 4α-	112.6	23
	3β, 4β-	91.3	23
	3β, 4α-	7.43	Present study
	3α, 4β-	0.0357	23



The physiological properties of the new androstane-triol (III) are now being investigated; the results will be reported elsewhere.

Experimental

The melting points were determined on a micro hot stage and are uncorrected. The ultraviolet spectra have been measured with a Beckman DK-2 spectrophotometer, while the infrared spectra were taken on a Koken IR-S spectrometer.

The Reduction of Testosterone Benzoate (IV) with Sodium Borohydride.—About 5 g. of sodium borohydride was gradually added into a suspension of 5.00 g. of testosterone benzoate (m. p. 191—192°C) in 100 ml. of methanol. After it had been stirred for 2 hr., the mixture became a clear solution. The mixture was then neutralized with a methanolic solution of acetic acid and poured into 300 ml. of water. The precipitated white solid (4.95 g.) was collected. Five recrystallizations from aqueous acetone gave 2.94 g. of androst-4-ene-3β, 17β-diol 17-benzoate (V) as colorless needles, m. p. 173—174°C. λ_{max}^{EtOH} 230 mμ (ε 12050), ν_{max}^{KBr} 1718, 1660 cm^{-1}.

Found: C, 79.14; H, 8.67. Calcd. for $C_{26}H_{34}O_3$: C, 79.15; H, 8.69%.

From the mother liquor of the recrystallization, a small amount of the 3α-isomer was obtained. Recrystallization from aqueous methanol gave a pure specimen of androst-4-ene-3α, 17β-diol 17-benzoate (VII) as colorless needles, m. p. 153—154°C. λ_{max}^{EtOH} 230 mμ (ε 12000), ν_{max}^{KBr} 1722, 1658 cm^{-1}.

Found: C, 79.24; H, 8.81. Calcd. for $C_{26}H_{34}O_3$: C, 79.15; H, 8.69%.

The Saponification of Androst-4-ene-3β, 17β-diol 17-Benzoate (V).—A solution of 0.023 g. of the benzoate (V) (m. p. 173—174°C) in 5 ml. of methanol was refluxed for 5 hr. with a methanolic solution of potassium hydroxide (1 g./10 ml.). The mixture was then diluted with 10 ml. of water, and the product was extracted with chloroform. The evaporation of the solvent and the recrystallization of the residue from aqueous methanol gave 0.012 g. of androst-4-ene-3β, 17β-diol (VI) as

23) C. Djerassi and R. Ehrlich, *J. Org. Chem.*, **19**, 1351 (1954).
24) S. J. Angyal and R. J. Young, *J. Am. Chem. Soc.*, **81**, 5251, 5467 (1959).
25) The preparation of 5α-cholestane-3β,4α-diol by a similar route has recently been reported.[26,27]
26) L. Caglioti and G. Cainelli, *Atti Accad. Nazl. Lincei, Rend., Classe Sci. Fis., Mat. e Nat.*, **29**, 555 (1960); *Chem. Abstr.*, **56**, 7386 (1962).
27) M. Nussim, Y. Mazur and F. Sondheimer, *J. Org. Chem.*, **29**, 1120 (1964).

colorless plates, m. p. 153—154°C. The reported melting point[17] is 153—154°C.

Found: C, 78.39; H, 10.22. Calcd. for $C_{19}H_{30}O_2$: C, 78.57; H, 10.41%.

The Hydroboration Reaction of Androst-4-ene-3β, 17β-diol 17-Benzoate (V).—A solution of 2.488 g. (6.31 mmol.) of androst-4-ene-3β, 17β-diol 17-benzoate (V) (m. p. 172—174°C) in 50 ml. of diglyme and 0.823 g. of sodium borohydride (purity 82%, 17.83 mmol.) were placed in a three-necked flask equipped with a magnetic stirrer, a pressure-equilibrated dropping funnel, a nitrogen inlet and outlet, and a reflux condenser. The reaction flask was flushed out with nitrogen, and a solution of freshly-distilled boron trifluoride etherate (2 ml., 15.83 mmol.) in 20 ml. of diglyme was added drop by drop over a period of 30 min. After the addition was complete, the mixture was stirred for 18 hr. under nitrogen at 30—40°C.

The reaction mixture was then hydrolyzed with 30 ml. of water. When the evolution of hydrogen had ceased, 20 ml. of 3 N sodium hydroxide was added, and the oxidation reaction was carried out by adding 30 ml. of 30% hydrogen peroxide. The mixture was allowed to cool, 30 ml. of water was added, and then the mixture was extracted with five 100 ml.-portions of methylene chloride. The extracts were combined, washed with water, and dried over sodium sulfate. The removal of the solvent gave a crystalline solid. Recrystallization from aqueous acetone afforded 1.132 g. of colorless needles, m. p. 237—238°C (first crop), and 0.522 g., m. p. 229—231°C (second crop). Repeated recrystallizations gave a specimen with an m. p. of 239—240°C. λ_{max}^{EtOH} 230 mμ (ε 12100), ν_{max}^{KBr} 1710 cm^{-1}. The analytical figure shows that this specimen was a mono-hydrate of the desired 5α-androstane-3β, 4α, 17β-triol 17-benzoate (VIII).

Found: C, 72.80; H, 9.07. Calcd. for $C_{26}H_{36}O_4 \cdot H_2O$: C, 72.52; H, 8.90%.

The pure anhydrous sample of VIII, m. p. 239—240°C, was obtained after drying it over phosphorus pentoxide under a high vacuum at 110°C for 36 hr.

Found: C, 75.50; H, 8.72. Calcd. for $C_{26}H_{36}O_4$: C, 75.69; H, 8.80%.

5α-Androstane-3β, 4α, 17β-triol (III).—A solution of 0.037 g. of the benzoate (VIII) (m. p. 239—240°C) in 10 ml. of methanol was refluxed for 5 hr. with a methanolic solution of potassium hydroxide (1 g./10 ml.). The mixture was then concentrated to 5 ml. under reduced pressure and diluted with 20 ml. of water. The product was collected (0.029 g.) and recrystallized from aqueous methanol as colorless needles of 5α-androstane-3β, 4α, 17β-triol (III), m. p. 248—250°C.

Found: C, 73.98, H, 10.39. Calcd. for $C_{19}H_{32}O_3$: C, 73.98; H, 10.46%.

The Kinetic Measurement of Lead Tetraacetate Oxidation.—Essentially the same procedure as that reported in the literature[28] was used. The lead tetraacetate solution was prepared by dissolving 1.9 g. of lead tetraacetate in 50 ml. of glacial acetic acid. The sample of 5α-androstane-3β, 4α, 17β-triol 17-benzoate (VIII) (m. p. 239—240°C) (208.42 mg., 0.505 mmol.), dissolved in 20 ml. of acetic acid, was then mixed with 20 ml. of the lead tetraacetate solution (ca. 1.7 mmol.), and the volume was adjusted to 100 ml. with glacial acetic acid. Periodically an aliquot (10.0 ml.) was taken and added to 25 ml. of an aqueous solution of 0.5 g. of sodium iodide and 5 g. of sodium acetate, the liberated iodine being titrated with a 0.025 N sodium thiosulfate solution. The oxidation was carried out at 25°C, and the appropriate blank was used with each titration.

The rate constant for the oxidation was calculated in the following manner.[29] The $\log [a(b-x)/b(a-x)]$ was plotted against the time, t, where (a is the initial concentration of the sample (VIII) 0.00505$_2$ mol./l.), b is the initial concentration of lead tetraacetate (0.0168 mol./l.), and x is the amount reacted at time t. The slope of the resultant straight line was calculated and substituted into the equation: $k = (2.303 \times \text{slope})/(b-a)$ l. mol^{-1} sec^{-1} The numerical data are shown in Table II, from which one can obtain the rate constant as 7.43×10^{-3} l./mol^{-1} sec^{-1}.

Table II. Kinetic measurement of $Pb(OAc)_4$ consumption

Time sec.	Thiosulfate titre, ml. Sample	Blank	$Pb(OAc)_4$ consumption mol./l.	$\log \frac{a(b-x)}{b(a-x)}$
0	13.37	13.42	0.063×10^{-3}	0.0038
480	13.21	13.40	0.238	0.0148
1020	12.90	13.41	0.638	0.0418
1620	12.63	13.41	0.975	0.0671
2400	12.35	13.41	1.325	0.0964
3300	12.11	13.37	1.575	0.1195
4980	11.50	13.34	2.300	0.1861
8580	10.79	13.30	3.138	0.3317

The author is indebted to Professor Yoshimasa Hirata of Nagoya University for his encouragement during this work. The author is also grateful to Professor Michio Shiota of Ochanomizu University for his helpful discussion at the earlier stage of the present study.

Chemical Institute
Faculty of Science
Nagoya University
Chikusa-ku, Nagoya

28) R. C. Hockett, M. T. Dienes and H. E. Ramsden, *J. Am. Chem. Soc.*, 65, 1474 (1943).
29) J. P. Cordner and K. H. Pausacker, *J. Chem. Soc.*, 1953, 102.