2-(2-Pyridyl)-ethyltrimethylammonium iodide was recrystallized from water; m.p. 253–253.5°, yield 80%.

Anal. Calcd. for $C_{10}H_{17}IN_2$: C, 41.1; H, 5.9. Found: C, 41.4, H, 6.0.

2-(5-Ethyl-2-pyridyl)-ethylmethylpyrrolidinium iodide was recrystallized from methanol–ether to give a 97% yield of material of m.p. 128–129°.

Anal. Calcd. for $C_{14}H_{23}IN_2$: C, 48.6; H, 6.7. Found: C, 48.7; H, 6.9.

2-(2-Pyridyl)-ethylmethylmorpholinium iodide was recrystallized from acetone; m.p. 130°, yield 49%.

Anal. Calcd. for $C_{12}H_{19}IN_2O$: C, 43.1; H, 5.7. Found: C, 43.0, H, 5.5.

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16-Substituted Steroids. XVIII.[1] 6,16-Difunctional 3,5-Cyclo-5α-androstanes

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The preparation of eight cycloandrostane compounds with oxygen functions in 6 and 16-positions (III, IV, V, VI, XII, XIV, XV, and XVIII) is described. Only 3,5-cyclo-5α-androstan-6β,16α-diol (XII) produced transient lowerings in the mean systolic blood pressure of dogs under sodium pentobarbital anesthesia.

In the clinical study of androst-5-en-3β,16α-diol in acute alcoholism, an occasional pronounced lowering of blood pressure has been noted.[2] It was believed of importance to investigate this hypotensive effect further, and a series of related steroids bearing the cyclopropyl ring was prepared.

(1) XVII. M. N. Huffman, M. H. Lott, and A. Tillotson, *J. Biol. Chem.*, **222**, 447 (1956).
(2) C. H. Campbell and M. N. Huffman, *J. Okla. State Med. Assn.*, **48**, 295 (1955).

Using modifications of the method of Beynon and co-workers,[3] it was possible to synthesize the 3,5-cyclo-5α-androstanes with ring D functional position at C_{16}. Similar preparations, using 3β-hydroxyandrost-5-en-17-one had been accomplished by Butenandt and Surányi[4] and by Wallis and co-workers.[5]

The steroid 3,5-cyclo-5α-androstan-6β,16α-diol (XII) produced transient lowerings in the mean systolic blood pressure of dogs under sodium pentobarbital anesthesia, the pharmacological basis of which was not investigated. Thus, a first dog cautiously administered by femoral vein 2.5 mg./kg. steroid XII (in propylene glycol–isotonic saline solution) showed a reduction in blood pressure of 13 mm., with a return to normal in 20 minutes; another similar dose given 1 hour later rapidly lowered the blood pressure from 150 to 135 mm., the effect lasting 40 minutes. A second dog identically treated demonstrated a blood pressure fall of 10 mm. (return to normal in 16 minutes) upon the first injection and, after the second injection, a lowering from 172 to 114 mm., with return to normal in 25 minutes. It was believed that these results did not, in themselves, justify clinical investigation.

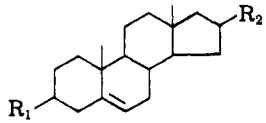
Experimental[6]

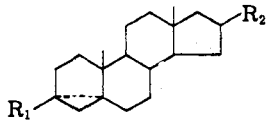
6β-Hydroxy-3,5-cyclo-5α-androstan-16-one (III).—A solution of 3β-hydroxyandrost-5-en-16-one[7] (I) (7.76 g.) in dry pyridine (150 ml.) was cooled to 0° and *p*-toluenesulfonyl chloride (16 g.) was added. After standing at room temperature for 24 hr., the tosylate II was precipitated with 4 l. of ice water, filtered, washed, dried at 40°, and dissolved in 400 ml. of acetone. This solution was mixed with a solution of 16 g. of potassium acetate in 400 ml. of water and 550 ml. of acetone, refluxed for 6 hr., concentrated *in vacuo*, and extracted with 750 ml. portions of ether. The ether solutions were washed with water containing a little pyridine, dried and evaporated. To saponify any unreacted tosylate II, the residue was dissolved in 500 ml. of a 5% ethanolic potassium hydroxide solution and refluxed for 1 hr. After addition of 3 l. of water, the suspension was extracted three times with 1-liter portions of ether. The combined ether solutions were washed twice with water, dried and evaporated. Half of the crystalline material thus obtained (3.62 g.) was dissolved in 180 ml. of 90% ethanol and mixed with a solution of 15.36 g. of digitonin in 1536 ml. of 90% ethanol. After standing for 4 days, the

(3) J. S. Beynon, I. M. Heilbron, and F. S. Spring, *J. Chem. Soc.*, 1459 (1937).
(4) A. Butenandt and L. A. Surányi, *Chem. Ber.*, **75**, 591 (1942).
(5) A. F. Wagner, N. E. Wolff, and E. S. Wallis, *J. Org. Chem.*, **17**, 529 (1952).
(6) All melting points are uncorrected. The microanalyses and optical rotations were carried out by Huffman Microanalytical Laboratories, Wheatridge, Colorado.
(7) M. N. Huffman, M. H. Lott, and A. Tillotson, *J. Biol. Chem.*, **218**, 565 (1956).

cloudy solution was concentrated *in vacuo* to 500 ml., diluted with 3 l. of water, and extracted with ether. The ether solutions were washed with water, dried and evaporated to give 2.79 g. of crude product III. After recrystallizing once from aqueous methanol containing a little pyridine, twice from acetone–hexane, and finally from aqueous acetone, there were obtained 790 mg. of leaflets, m.p. 122–123°. Further recrystallization from aqueous methanol gave 600 mg. of pure III, m.p. 123–123.5°, $[\alpha]^{24}D$ −151° (*c*, 1.02 in $CHCl_3$).

Anal. Calcd. for $C_{19}H_{28}O_2$: C, 79.12; H, 9.79. Found: C, 79.24; H, 9.88.





I, R_1 = —OH, R_2 = O
II, R_1 = —OTs, R_2 = O
VII, R_1 = —OH, R_2 = —OH
VIII, R_1 = —OH, R_2 = —OAc
IX, R_1 = —OH, R_2 = —OTs
X, R_1 = —OTs, R_2 = —OAc
XVI, R_1 = —OH, R_2 = —OBz

Ts = —$SO_2C_6H_4$·CH_3
Ac = —$COCH_3$
Bz = —COC_6H_5

III, R_1 = —OH, R_2 = O
IV, R_1 = —OH, R_2 = —OH
V, R_1 = O, R_2 = O
VI, R_1 = —OH, R_2 = —OH
XI, R_1 = —OH, R_2 = —OAc
XII, R_1 = —OH, R_2 = —OH
XIII, R_1 = O, R_2 = —OAc
XIV, R_1 = O, R_2 = —OH
XV, R_1 = —OH, R_2 = —OH
XVII, R_1 = —OH, R_2 = —OBz
XVIII, R_1 = O, R_2 = —OH

3,5-Cyclo-5α-androstan-6β,16β-diol (IV).—A solution of 1.39 g. of the 16-ketone III in 65 ml. of methanol and 5 ml. of pyridine was cooled and mixed with a solution of 1.12 g. of sodium borohydride in 10 ml. of methanol and 4 ml. of pyridine. After 45 min., 400 ml. of ice water and 15 ml. of acetone were added. After an additional 15 min., the solution was diluted with 1200 ml. of ice water and refrigerated overnight. The crystals were filtered, washed with water and dried to give 1.12 g. of IV, which melted at 176–177°. Several recrystallizations from 80–85% methanol yielded 600 mg. of cotton-like needles, m.p. 197–198°, $[\alpha]^{24}D$ +27.5° (*c*, 1.0225 in $CHCl_3$).

Anal. Calcd. for $C_{19}H_{30}O_2$: C, 78.57; H, 10.41. Found: C, 78.64; H, 10.53.

3,5-Cyclo-5α-androstan-6,16-dione (V).—A mixture of 2.81 g. of III in 100 ml. of glacial acetic acid and of 2.0 g. of chromium trioxide in 76 ml. of acetic acid and 20 ml. of water was allowed to stand at room temperature overnight. The oxidation product was isolated in the usual manner and recrystallized from 43% methanol. Clusters of oblong plates (1.28 g.) were obtained, m.p. 141.5–142°. Further recrystallization from 50% methanol did not raise this m.p., $[\alpha]^{26}D$ −145° (*c*, 1.050 in $CHCl_3$).

Anal. Calcd. for $C_{19}H_{26}O_2$: C, 79.68; H, 9.15. Found: C, 79.87; H, 9.08.

3,5-Cyclo-5α-androstan-6α,16β-diol (VI).—To a solution of 600 mg. of V in 50 ml. of ethanol, 600 mg. of sodium borohydride was added and the mixture kept at 15° for 1 hr. The reduction product was precipitated by addition of water, filtered and recrystallized from 30% aqueous methanol. The 6α,16β-diol (VI) thus obtained weighed 480 mg. and melted at 174.5–175.5°, $[\alpha]^{24.5}D$ +68° (*c*, 1.095 in $CHCl_3$).

Anal. Calcd. for $C_{19}H_{30}O_2$: C, 78.57; H, 10.41. Found: C, 78.64; H, 10.37.

Androst-5-en-3β,16α-diol 16-Acetate (VIII). (a) From Androst-5-en-3β,16α-diol (VII).[8]—A solution of 960 mg. of VII in 31.2 ml. of glacial acetic acid was refluxed for 2 hr. After addition of 300 ml. of water, the suspension was extracted with 500 ml. of benzene. The benzene solution was washed several times with water and evaporated *in vacuo*. For removal of any diacetate, the residue (1.10 g.) was dissolved in 80 ml. of 90% ethanol and a solution of 4.4 g. of digitonin in 440 ml. of 90% ethanol was added. After standing overnight at room temperature the digitonide was filtered, washed with ether and decomposed with 50 ml. of warm pyridine. Then 500 ml. of absolute ether was added and the mixture kept overnight at 5°. The digitonin was filtered off, washed with ether, and the filtrates were washed with 250 ml. of 10% hydrochloric acid and twice with water. Evaporation of the dried ether solution gave 530 mg. of crystals, m.p. 160–162°. Several recrystallizations from 60–70% methanol yielded 130 mg. of monoacetate VIII, m.p. 169.5-170°.

Anal. Calcd. for $C_{21}H_{32}O_3$: C, 75.86; H, 9.70. Found: C, 75.79; H, 9.75.

(b) **From Androst-5-en-3β,16β-diol 16-Tosylate (IX).**[8]—This derivative was prepared as previously described.[8] After several recrystallizations from 65–70% acetone, it was obtained in two new modifications, m.p. 139–139.5° and 149–150° (reported 91–96°). The material melting at 139° was analyzed.

Anal. Calcd. for $C_{26}H_{36}O_4S$: S, 7.21. Found: S, 7.25.

A solution of 1.88 g. of IX of m.p. 139° or 149–150° and 4.1 g. of freshly fused sodium acetate in 82 ml. of glacial acetic acid was refluxed for 1 hr., cooled, diluted with 1 l. of water, and kept in the refrigerator overnight. The crystals were filtered, washed with water and dried. The crude product (1.42 g.) was submitted to a digitonin precipitation as described under (a) to remove any diacetate which might have formed. The monoacetate thus obtained (645 mg.) was recrystallized twice from acetone-hexane and twice from aqueous methanol to give 370 mg. of VIII, m.p. 169–170°; no m.p. depression in mixture with material prepared according to method (a).

3,5-Cyclo-5α-androstan-6β,16α-diol 16-Acetate (XI).—To a solution of 5 g. of VIII in 200 ml. of pyridine, 9 g. of *p*-toluenesulfonyl chloride was added. After 24 hr., the tosylate X was precipitated with 5 l. of water, filtered, washed, and dried. It was then dissolved in 690 ml. of acetone and a solution of 10.5 g. of potassium acetate in 256 ml. of water was added. The mixture was refluxed for 6 hr. and subsequently concentrated to turbidity. Upon cooling overnight, a precipitate appeared which was filtered and recrystallized from 67% aqueous methanol to give 4.36 g. of the cycloandrostane compound XI, m.p. 130–131°. An analytical sample obtained by further recrystallization from aqueous methanol melted at 131–132°.

Anal. Calcd. for $C_{21}H_{32}O_3$: C, 75.86; H, 9.70. Found: C, 75.61; H, 9.55.

3,5-Cyclo-5α-androstan-6β,16α-diol (XII).—Four grams of the 16-monoacetate XI was refluxed for 1 hr. in a solution of 10 g. of KOH in 200 ml. of 95% ethanol. The solution was concentrated *in vacuo* and the crystals which appeared were

(8) M. N. Huffman, M. H. Lott, and A. Tillotson, *J. Biol. Chem.*, **222**, 447 (1956).

filtered, washed with water and dried, m.p. 156–157°, $[\alpha]^{23.5}D$ +15° (*c*, 1.043 in $CHCl_3$).

Anal. Calcd. for $C_{19}H_{30}O_2$: C, 78.57; H, 10.41. Found: C, 78.43; H, 10.48.

Occasionally, the same diol was obtained in a crystalline modification, m.p. 152.5–153.5°.

16α-Hydroxy-3,5-cyclo-5α-androstan-6-one (XIV).—The oxidation mixture containing 180 mg. of XI, 140 mg. of chromium trioxide, 12 ml. of glacial acetic acid and 14 drops of water was allowed to stand overnight and was worked up in the usual manner to give the acetoxyketone XIII. This material was refluxed with 5% alcoholic potassium hydroxide solution for 1 hr., whereupon the hydroxyketone XIV was isolated by addition of water. Two recrystallizations from 42% aqueous methanol gave 60 mg. of long, fine needles, m.p. 133°, $[\alpha]^{22}D$ +30° (*c*, 1.004 in $CHCl_3$).

Anal. Calcd. for $C_{19}H_{28}O_2$: C, 79.12; H, 9.79. Found: C, 79.02; H, 9.91.

3,5-Cyclo-5α-androstan-6α,16α-diol (XV).—The reduction of 800 mg. of XIV with 600 mg. of sodium borohydride in absolute ethanol was carried out as described for the preparation of VI. The crude reaction product was recrystallized three times from 55% aqueous methanol and gave 610 mg. of crystals, m.p. 150–150.5°, $[\alpha]^{28}D$ +64.5° (*c*, 0.9505 in $CHCl_3$).

Anal. Calcd. for $C_{19}H_{30}O_2$: C, 78.57; H, 10.41. Found: C, 78.45; H, 10.43.

16β-Hydroxy-3,5-cyclo-5α-androstan-6-one (XVIII).—The starting material for this compound was androst-5-en-3β,16β-diol 16-benzoate[9] (XVI) (2 g.) which was treated with 4 g. of *p*-toluenesulfonyl chloride in 80 ml. of pyridine. The crude tosylate was isolated and cyclized as described for the preparation of III (276 ml. of acetone, 4.5 g. of potassium acetate, 102 ml. of water). There was obtained 1.99 g. of 3,5-cyclo-5α-androstan-6β,16β-diol 16-benzoate (XVII), m.p. 131–133°. This compound was dissolved in 78 ml. of glacial acetic acid and oxidized with a solution of 1.5 g. of CrO_3 in 56 ml. of acetic acid and 8 ml. of water (overnight at room temperature). Finally, the oxidation product was saponified with 5% alcoholic KOH solution as described for XII and gave 1.06 g. of the hydroxyketone XVIII. After one recrystallization from aqueous methanol, it melted at 155°, $[\alpha]^{30}D$ +25° (*c*, 1.040 in $CHCl_3$).

Anal. Calcd. for $C_{19}H_{28}O_2$: C, 79.12; H, 9.79. Found: C, 78.92; H, 9.79.

(9) F. Šorm and M. Horák, *Collection Czechoslov. Chem. Commun.*, **21**, 926 (1956).