Hydrogenation of the Unsaturated Oxetanone (17).—A solution of 477 mg (1.20 mmol) of **17** in 35 ml of ethyl acetate was hydrogenated in the presence of a Pd–C catalyst until uptake of the gas ceased. The catalyst was removed by suction filtration through magnesium sulfate and the filtrate was evaporated to dryness. Crystallization of the residue from acetone–methanol gave 309 mg of 5,7β-epoxy-5β-cholestan-6-one (**12**) as long white needles, mp 91–93.5°. The mixture melting point with starting material was 76–90°. A second recrystallization from the same solvents yielded 248 mg with mp 92.5–94°. The ir spectrum of this product was identical with that of **12** prepared from the bromo ketone **11b** and no depression in melting point was noted upon admixture of the two samples.

Dilution of the first mother liquor with water gave an additional 65 mg of **12**, mp 92–93°, softened at 87°, which brought the total yield to 78%.

Registry No.—**5a**, 16526-63-9; **5b**, 14956-13-9; **5c**, 6579-84-6; **6a**, 16526-66-2; **6b**, 16526-67-3; **6c**, 16525-96-5; **6d**, 16525-97-6; **7a**, 16525-98-7; **7b**, 16525-99-8; **7c**, 16526-00-4; **7d**, 16526-01-5; **8a**, 6580-08-1; **8b**, 6580-09-2; **8c**, 16564-29-7; **9b**, 16526-04-8; **9c**, 16526-05-9; **10a**, 16526-06-0; **10b**, 16526-07-1; **10c**, 16526-08-2; **11a**, 16526-09-3; **11b**, 16526-10-6; **12**, 16526-11-7; **14a**, 16526-12-8; **14b**, 16526-13-9; **15a**, 16526-14-0; **16**, 16526-15-1; **17** (2-ene), 16526-16-2; **17** (3-ene), 16526-17-3.

Acknowledgments.—We are indebted to Dr. Robert M. Moriarty and Mr. Steve J. Druck of The Catholic University of America for determining some nmr spectra during the early phases of this work and to Dr. Alex Nickon of the Johns Hopkins University for extremely helpful interpretations of the bromo ketone nmr spectra. Gratitude is expressed for the ORD spectra, which were determined at the Merck Sharp & Dohme Research Laboratories by Drs. James J. Wittick and George V. Downing, Jr. The competent technical assistance of Miss Doris Pickel and Messrs. Stephen Funk, George Heavner, and Larry Rinehart is gratefully acknowledged.

A New Type of Steroid Dimer

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The cyclic ethylene hemithioketals of saturated steroidal ketones react with *p*-toluenesulfonic acid and acetic anhydride to form enol ether dimers. The reaction proceeds through the monomer enol ether formed by preferential acylative cleavage of the carbon–sulfur bond. It is shown that 3,3-dialkyl ketals and Δ^2- and Δ^3-enol ethers form similar dimers in yields of 40–90%. Hydrolysis of the enol ether dimers gives dimer β,γ-monoketones of the type obtained from cholestanone and dihydrotestosterone acetate by aldol condensation in highly acidic media.

It might be expected that polymers of steroidal ketones (or ketone derivatives) would readily be formed in reaction media of high acidity or basicity. There seems, however, to be only two instances of an aldol type of product having been isolated in sufficient quantity and purity to have merited reporting in the literature. Corey and Young[1] found that cholestanone is converted by hydrogen bromide in acetic acid into 2α-(2′-cholesten-3′-yl)-3-cholestanone (IIIa). What is presumed to be the same dimer, in less pure form, has recently been isolated from the products of oxidation of cholestanol with chromium trioxide–acetic acid.[2]

This report describes a new type of steroid dimer: enol ethers related to the Corey–Young type of 2,3′-β,γ-unsaturated ketone. Each of the cyclic ethylene hemithioketals of 5α-cholestanone[3] reacted readily at 25° with *p*-toluenesulfonic acid in acetic anhydride (but *not* in benzene), yielding 85% of a crystalline product whose infrared spectrum displayed typical bands of an acetylthio group (5.88 and 8.79 μ) and an ultraviolet absorption maximum at 230 mμ. Mild acid hydrolysis converted this presumed diene into a ketone identical with the dimer of Corey and Young, which for comparison was resynthesized in 10% yield by heating cholestanone in a 5% solution of anhydrous *p*-toluenesulfonic acid in benzene. Clearly, the hemithioketals Ia and Ia′ had been acetylatively cleaved at the carbon–sulfur bond and dimerized to the acetylthioethyl enol ether of structure IIa, which was then hydrolyzed to dimer ketone IIIa.

For further study, the isomeric 3-ethylene hemithioketals (Ib and Ib′) of 5α-dihydrotestosterone acetate[4] were prepared. Each of these reacted with toluenesulfonic acid in acetic anhydride to yield 60% of an acetylthioethyl enol ether (IIb) which could not be crystallized nor adequately purified by chromatography. Acid hydrolysis afforded 40–50% (over-all from hemithioketals) of dimer keto diacetate IIIb. By-products of this reaction sequence were dihydrotestosterone acetate and probably Wagner–Meerwein rearrangement products of the D ring.[5]

The dimer IIIb was also formed in low yield on heating dihydrotestosterone acetate in toluenesulfonic acid–benzene solution, but was extremely difficult to purify. Its N-acetyloxime was shown to be identical with the same derivative of the dimer ketone from IIb.

The Corey and Young structure for dimers of type III was supported by the nmr spectrum of IIIb, in which a one-proton quartet centered at δ 2.90 ppm is

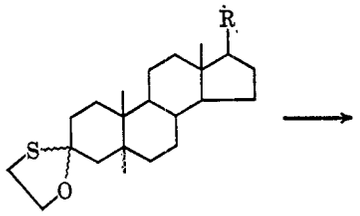
(1) E. J. Corey and R. L. Young, *J. Amer. Chem. Soc.*, **77**, 1672 (1955).

(2) C. W. Shoppee, R. E. Lack, S. C. Sharma, and L. R. Smith, *J. Chem. Soc.*, 1155 (1967).

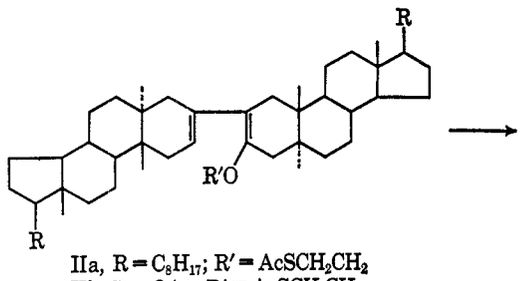
(3) (a) E. L. Eliel, L. A. Pilato, and V. G. Badding, *J. Amer. Chem. Soc.*, **84**, 2377 (1962); (b) E. L. Eliel and S. Krishnamurthy, *J. Org. Chem.*, **30**, 848 (1965), describe the stereoisomeric hemithioketals **Ia** and **Ia′**. (c) Also, for isomer **Ia**, see C. Djerassi and M. Gorman, *J. Amer. Chem. Soc.*, **75**, 3704 (1953); (d) L. F. Fieser, *ibid.*, **76**, 1945 (1954); (e) C. Djerassi, M. Shamma, and T. Y. Kan, *ibid.*, **80**, 4723 (1958).

(4) For mixture of hemithioketals **Ib** and **Ib**, see (a) J. Romo, G. Rosenkranz, and C. Djerassi, *ibid.*, **73**, 4961 (1951); (b) R. T. Blickenstaff and E. L. Foster, *J. Org. Chem.*, **26**, 5029 (1961). See Experimental Section for the individual isomers. The trivial name, 5α-dihydrotestosterone, is used throughout this report in referring to 5α-androstan-17β-ol-3-one.

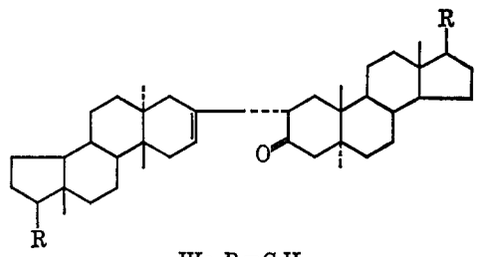
(5) (a) A. Cohen, J. W. Cook, and C. L. Hewett, *J. Chem. Soc.*, 445 (1935); (b) A. D. Cross, H. Carpio, and H. J. Ringold, *J. Med. Chem.*, **6**, 198 (1963).



Ia, R = C_8H_{17}; α-O-β-S
Ia′, R = C_8H_{17}; β-O-α-S
Ib, R = OAc; α-O-β-S
Ib′, R = OAc; β-O-α-S

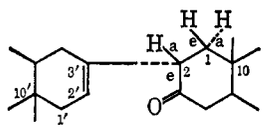


IIa, R = C_8H_{17}; R′ = $AcSCH_2CH_2$
IIb, R = OAc; R′ = $AcSCH_2CH_2$



IIIa, R = C_8H_{17}
IIIb, R = OAc

observed. This can be assigned to a 2 axial H coupled to the 1 equatorial H (J_1 = 6 cps) and also to the 1 axial H (J_2 = 12 cps), with α (equatorial) attachment of carbon 2 to carbon 3′.



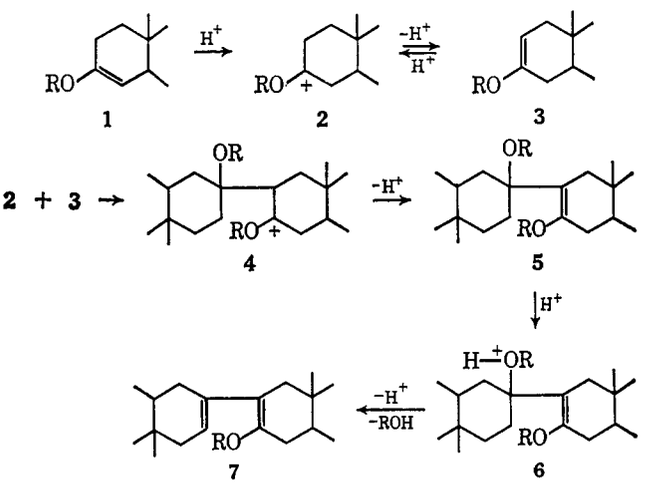
The α attachment at carbon 2 is also supported by the chemical shift (δ 1.07) of the 10-CH_3 of IIIa and b, which is precisely the value observed by Miller for the (2α,2′α-methylene)-bridged dimer of dihydrotestosterone acetate.[6] The previously discussed[1,2] preferences for a $\Delta^{2'}$-5α structure, rather than $\Delta^{3'}$-5α, seem most reasonable even though not yet unequivocally proved.

Dimers of type II must have been formed through the intermediacy of monomeric enol ethers. This dimerization is somewhat surprising in view of the preparation of monocyclic enol ethers from dialkyl ketals with small amounts of *p*-toluenesulfonic acid[7] and of cholestanone ethyl enol ether from the ketone and ethyl orthoformate–sulfuric acid.[3b] However, the validity of the assumption was demonstrated by treating the Δ^2- and Δ^3-methyl, or -ethyl, enol ethers of cholestanone and dihydrotestosterone acetate with 3–7% solutions of anhydrous *p*-toluenesulfonic acid in either acetic anhydride or benzene. The crystalline dimer methyl (IIa′, IIb′) and ethyl (IIb″) enol ethers (and an oily IIa″) analogous to IIa and IIb were formed in 40–60% yields. The formation of the same dimer enol ether from Δ^3-5α monomer as from Δ^2-5α monomer requires a double-bond shift to the thermodynamically favored Δ^2-enol ether prior to dimerization. Evidence for such a transformation in steroids has been elusive, having been only indirectly observed in the bromination of Δ^3-enol ethers.[8]

Acid hydrolysis of dimer enol ethers IIa′, a″, b′, and b″ afforded the same dimer ketones as derived from the cyclic ethylene hemithioketals.

The generality of the dimerization was apparent when it was observed that the dimethyl and diethyl ketals of 5α-dihydrotestosterone acetate and the dimethyl ketal of cholestanone were also converted by 3–4% anhydrous toluenesulfonic acid in acetic anhydride or benzene into 20–70% of dimer enol ethers IIa′, b′, and b″. In benzene, either heating or prolonged reaction times are necessary to yield significant amounts of dimer, although the reaction proceeds readily in acetic anhydride. Again, it is apparent that monomer Δ^2-enol ether is the intermediate for dimerization.

Mechanistically, these dimerizations obviously require only a high proton concentration, except that in the case of ethylene hemithioketals acetic anhydride is needed to provide acylium cation which effects preferential scisson of the carbon–sulfur bond, prior to dimerization. This is analogous to the acylative cleavage of cyclic ethylene dithioketals.[9] The enol ether **3** can dimerize to **4** by attack on its protonated form **2**. Subsequent loss, addition, and loss of a proton, followed by loss of alcohol then leads to the dimeric enol ether **7**, which is stable to anhydrous acid in the benzene or acetic anhydride medium. Other types of carbonium ion intermediates and other reaction paths may be postulated, but the proposed sequence invokes a minimum number of proton transfers and avoids multiply charged ions.



Experimental Section

Melting points are corrected (Fisher-Johns apparatus), with stage preheated to 10° below reported values. Ultraviolet spectra were taken in 95% ethanol with a Cary Model 11 spectrophotometer and infrared spectra were obtained with a Beckman

(6) T. C. Miller, *J. Org. Chem.*, **30**, 2922 (1965).
(7) U. Schmidt and P. Grafen, *Ann.*, **656**, 97 (1962).
(8) R. Gardi, P. P. Castelli, and A. Ercoli, *Tetrahedron Lett.*, 497 (1962).
(9) G. Karmas, *ibid.*, 1093 (1964).

IR-5 spectrophotometer, neat for oils, pressed KBr wafers for solids. Optical rotations were taken in chloroform (trace of pyridine) on a Rudolph Model 70 polarimeter. Nmr spectra were obtained on a Varian A-60 spectrophotometer in deuteriochloroform solution (*ca.* 1% pyridine). Chemical shifts are recorded as δ values (tetramethylsilane as internal standard), center of signal, and d = doublet, t = triplet, q = quartet, m = multiplet, with singlets not specified by abbreviation. Organic solutions were routinely dried with potassium carbonate prior to evaporation under vacuum. Elemental analyses were performed by Midwest Microlab, Inc., of Indianapolis, Ind.

5α-Dihydrotestosterone Acetate 3,3-Dimethyl Ketal.[10]—A solution of 1.5 g of dihydrotestosterone acetate and 50 mg of toluenesulfonic acid[11] in 20 ml of anhydrous methanol was boiled for 5 min, then made alkaline with solid sodium methylate, diluted with 500 ml of water, and twice extracted with ether. After being washed twice with water and dried, the ether solution was evaporated, and the residue was recrystallized from methanol (pyr) to give 1.35 g of the ketal: mp 144–146° (lit.[10] mp 143–147°); λ_{max} 5.74, 8.00, 9.07, 9.48, 9.68 μ.

5α-Dihydrotestosterone Acetate 3,3-Diethyl Ketal.[12]—A solution of 6 g of dihydrotestosterone acetate and 250 mg of toluenesulfonic acid in 100 ml of anhydrous ethanol was refluxed for 30 min and then made alkaline with sodium ethoxide (in ethanol). Work-up and recrystallization as for the dimethy ketal (above) gave 2.5 g of diethyl ketal: white prisms; mp 133–135°; λ_{max} 5.77, 7.97, 9.42, 9.63 μ.

Anal. Calcd for $C_{25}H_{42}O_4$: C, 73.85; H, 10.41. Found: C, 73.61; H, 10.50.

17β-Acetoxy-3-methoxy-2-(5α-androstene). A.—A solution of 1.2 g of dihydrotestosterone acetate 3,3-dimethyl ketal in 20 ml of xylene was refluxed under nitrogen for 6 hr. Chromatography of the xylene residue on neutral alumina (20 g Woelm grade I; 20-mm-i.d. column; eluted with 150 ml of methylene chloride) gave crude enol ether which was recrystallized from methanol and from acetone (pyr) to give 0.15 g of the Δ^2-enol ether: mp 127–129°; λ_{max} 5.72, 5.93, 7.97, 8.14, 9.60, 12.67 μ.

B.—When 680 mg of the dimethyl ketal was heated with 100 mg of powdered Pyrex glass at 220°[13] for 1 hr and the pyrolysis product purified as in A, there was obtained 70 mg of the Δ^2-enol ether, mp 126–129°.

Anal. Calcd for $C_{22}H_{34}O_3$: C, 76.26; H, 9.89. Found: C, 76.11; H, 9.98.

Cholestanone 3-ethylene hemithioketal, α-O–β-S (mp 135–136°, Ia) and cholestanone 3-ethylene hemithioketal, β-O–α-S (mp 112–113°, Ia′) were prepared essentially as described in ref 3a. These tentative configurations were based on nmr studies,[3a,b] but the chemical-shift values have not been noted in the publications. We have observed for Ia δ 3.02 (t, CH_2S), 4.15 (*split* t, CH_2O); for Ia′ 3.01 (t, CH_2S), 4.17 (*clean* t, CH_2O). The splitting of the CH_2O triplet of the α-O–β-S isomer is the most striking difference in the nmr spectra. This was also observed for the isomeric dihydrotestosterone 3-ethylene hemithioketals and their 17-acetates (below), and is the basis for their stereochemical assignments, following Eliel, Pilato, and Badding.[3a]

5α-Dihydrotestosterone Acetate 3-Ethylene Hemithioketal, β-O–α-S (Ib′).—A mixture of 10 g of β-mercaptoethanol, 10 g of dihydrotestosterone acetate, 500 mg of toluenesulfonic acid, and 500 ml of benzene was refluxed for 3 hr with separation of water (Dean–Stark trap). After several washings with water the benzene solution was evaporated to a crystalline residue of mixed hemithioketals. Fractional crystallization from ether and from ethyl acetate gave numerous small portions with roughly 10° melting point ranges, covering 140–185° over-all. All portions of melting point above 160° were combined and recrystallized successively from ethyl acetate, methanol, and ethyl acetate to give 1.1 g of white prisms of isomer Ib′: mp 185–186°; $[\alpha]_D$ +3.5°; λ_{max} 5.73, 7.97, 9.34, 9.65, 10.96, 11.41, 11.66 μ; nmr δ 0.79 (18-H_3), 0.82 (19-H_3), 2.01 (17β-OAc), 3.03 (t, CH_2S), 4.12 (t, CH_2O).

Anal. Calcd for $C_{23}H_{36}O_3S$: C, 70.40; H, 9.24. Found: C, 70.64; H, 9.30.

5α-Dihydrotestosterone 3-ethylene hemithioketal, β-O–α-S, by saponification of Ib′ (2% KOH–methanol, 10-min reflux), was obtained as white prisms from ethyl acetate: mp 207–209°; $[\alpha]_D$ +10.6°; λ_{max} 2.83, 9.29, 9.65, 10.90, 11.40, 11.69, 11.78 μ; nmr δ 0.74 (18-H_3), 0.83 (19-H_3), 3.04 (t, CH_2S), 4.12 (t, CH_2O).

Anal. Calcd for $C_{21}H_{34}O_2S$: C, 72.00; H, 9.77. Found: C, 71.78; H, 9.92.

5α-Dihydrotestosterone 3-Ethylene Hemithioketal, α-O–β-S.—The hemithioketal portions of melting point below 160° were combined and recrystallized from methanol to give 5 g of prisms, mp 143–150°, which was then saponified (200 ml of 2% KOH–methanol, 10-min reflux). The **17β-ol** obtained by dilution with water and removal of methanol under vacuum was recrystallized twice from ethyl acetate (few drops of water) to afford 3.2 g of white prisms: mp 152–153°; $[\alpha]_D$ +16°; λ_{max} 2.90, 9.28, 9.69, 10.40, 11.60, 11.80 μ; nmr δ 0.75 (18-H_3), 0.84 (19-H_3), 3.03 (t, CH_2S), 4.16 (*split* t, CH_2O).

Anal. Calcd for $C_{21}H_{34}O_2S$: C, 72.00; H, 9.77. Found: C, 71.58; H, 9.90.

Acetylation of the **17β-ol** with pyridine–acetic anhydride gave **5α-dihydrotestosterone acetate 3-ethylene hemithioketal, α-O–β-S (Ib):** mp 145–146°; $[\alpha]_D$ +12°; λ_{max} 5.73, 7.97, 9.62, 11.72 μ; nmr δ 0.79 (18-H_3), 0.83 (19-H_3), 2.01 (17β-OAc), 3.20 (t, CH_2S), 4.16 (*split* t, CH_2O).

Anal. Calcd for $C_{23}H_{36}O_3S$: C, 70.40; H, 9.24. Found: C, 70.53; H, 9.41.

2-(2′-Cholesten-3′-yl)-3-(β-acetylthioethoxy)-2-cholestene (IIa). A.—To a stirred solution of 1.0 g of the α-O–β-S hemithioketal Ia[3a] in 4 ml of methylene chloride was added a solution of 1.0 g of toluenesulfonic acid in 11 ml of acetic anhydride. After 45 min, the suspension was cooled to 0°, further diluted with 20 ml of acetic anhydride containing 2 ml of pyridine and filtered. Washing on the filter with methanol (pyr) and air drying gave 0.9 g of pale yellow microgranules, mp 138–141°. Recrystallization from acetone gave the analytical sample: mp 140–143°; $[\alpha]_D$ +59°; λ_{max} 230 mμ (ε 8940); λ_{max} 5.88, 8.51, 8.79, 9.00 μ; nmr δ 2.31 (AcS), 3.05 (t, CH_2S), 3.72 (t, CH_2O), 5.31 (m, 2′-H).

Anal. Calcd for $C_{58}H_{96}O_2S$: C, 81.23; H, 11.28; S, 3.74. Found: C, 81.46; H, 11.38; S, 3.64.

B.—The process of A, applied on a one-tenth scale to the β-O–α-S hemithioketal Ia′ afforded 85 mg of dimer enol ether with infrared spectrum identical with the IIa obtained from Ia.

2-(2′-Cholesten-3′-yl)-3-methoxy-2-cholestene (IIa′). A.—To a stirred solution of 1.0 g of cholestanone dimethyl ketal[14] in 6 ml of methylene chloride was added 0.5 g of toluenesulfonic acid in 7 ml of acetic anhydride. After 20 min at 25° and 20 min at 0° the crystalline solid was filtered off, washing with small amounts of acetic anhyride and ether (pyr) to give 0.75 g of the dimer methyl enol ether. Recrystallization from ether (pyr) afforded 0.6 g of IIa′: white flakes; mp 163–165°; λ_{max} 230 mμ (ε 12,200); λ_{max} 8.10, 8.25, 8.73, 12.34 μ; nmr δ 3.42 (3-MeO), 5.30 (m, 2′-H).

Anal. Calcd for $C_{55}H_{92}O$: C, 85.84; H, 12.05. Found: C, 86.09; H, 11.87.

When cholestanone dimethyl ketal was kept at 25° in a 4% solution of anhydrous toluenesulfonic acid in benzene for 20 min, no significant amount of dimerization occurred. Conventional work-up, with constant excess of pyridine, gave only recovered ketal.

2-(2′-Cholesten-3′-yl)-3-ethoxy-2-cholestene (IIa″).—When 1.0 g of 3-ethoxy-3-cholestene[8] was reacted with toluenesulfonic acid in acetic anhydride plus methylene chloride as described above for IIa, a viscous oil separated from the mixture. After addition of 2 ml of pyridine, the mixture was hydrolyzed in ice and water containing 20 ml of pyridine and the oily product was extracted with methylene chloride. Evaporation gave the crude dimer ethyl enol ether IIa″, λ_{max} 229 mμ, which could not be induced to crystallize. Acid hydrolysis as described below afforded 0.4 g of the dimer ketone IIIa.

2α-(2′-Cholesten-3′-yl)-3-cholestanone (IIIa). A.—A solu-

(10) P. E. Shaw, F. W. Gubitz, K. F. Jennings, G. O. Potts, A. L. Beyler, and R. C. Clarke, *J. Med. Chem.*, **7**, 555 (1964), isolated this compound from a complex reaction mixture. The direct preparation seems not to have been described.

(11) In this section, toluenesulfonic acid as a reagent means *p*-toluenesulfonic acid monohydrate. However, it obviously becomes anhydrous acid in the presence of acetic anhydride and in those experiments where the monohydrate in benzene is boiled down to a small final volume.

(12) A. Ercoli and P. Ruggieri, *J. Amer. Chem. Soc.*, **75**, 650 (1953), describe this compound as an oil.

(13) Pyrolysis process of J. H. Fried, A. N. Nutile, and G. E. Arth, *ibid.*, **82**, 5704 (1960).

(14) R. M. Evans, G. F. H. Green, J. S. Hunt, A. G. Long, B. Mooney, and G. H. Phillipps, *J. Chem. Soc.*, 1529 (1958).

tion of 1.0 g of IIa and 0.3 ml of concentrated HCl in 20 ml of tetrahydrofuran and 10 ml of acetone was kept at 25° for 1 hr and then slowly diluted with 100 ml of water. The cream solid was filtered off, dried, and recrystallized from methylene chloride–ethyl acetate to give 0.75 g of IIIa: mp 206–208°; $[\alpha]_D$ +40° (reported[1] mp 209–211°, $[\alpha]_D$ +41°); λ_{max} 5.82, 8.40, 8.50, 10.40, 12.40 μ; nmr δ 1.06 (19-H_3), 2.92 (m, 2-H), 5.30 (m, 2′-H).

B.—Acid hydrolysis of the crystalline dimer methyl enol ether IIa′, as in A, gave a high yield of the same dimer ketone IIIa.

C. From Cholestanone, through Crude Hemithioketal.—A mixture of 2 g of cholestanone, 2 ml of β-mercaptoethanol, 0.2 g of oxalic acid, and 150 ml of benzene was refluxed for 5 hr with water separation. Washing with water, drying, and evaporation of the benzene solution gave the mixed hemithioketals **Ia** + Ia′. This crystalline mass was dissolved in 8 ml of methylene chloride, 2 g of toluenesulfonic acid in 22 ml of acetic anhydride was added, and all was stirred at 25° for 3 hr and then hydrolyzed in ice and water containing 40 ml of pyridine. Methylene chloride extraction and evaporation, followed by acid hydrolysis and recrystallization as in A, afforded 1.4 g of IIIa, mp 204–208°.

D. From Cholestanone, by Aldol Condensation.—A suspension of 0.8 g of toluenesulfonic acid in 50 ml of benzene was boiled down to 10 ml to obtain a yellow solution of the anhydrous acid. Then 1.5 g of cholestanone and 10 ml of benzene was added, and the solution was refluxed for 3 hr. The water-washed benzene solution gave a glassy residue on evaporation, and from this there was obtained, after several recrystallizations from ethyl acetate, 0.15 g of IIIa: mp 200–204°; $[\alpha]_D$ +37°; ir and nmr spectra identical with those of the dimer ketone obtained in A. Cholestanone (0.7 g) was recovered during the recrystallization. There undoubtedly were other dimer isomers present in the remaining 0.5 g of high-melting (185–200°) material, but only IIIa could be isolated relatively pure through seeding with the material from A.

2-[17′β-Acetoxy-2′-(5′α-androsten)-3′-yl]-17β-acetoxy-3-methoxy-2-(5α-androstene) (IIb′). A.—To a solution of 0.75 g of toluenesulfonic acid in 25 ml of acetic anhydride was added 3.1 g of dihydrotestosterone acetate 3,3-dimethyl ketal. The mixture was stirred at 25° for 20 min; 8 ml of pyridine was added, and then it was hydrolyzed in ice and water containing 70 ml of pyridine. The white solid was filtered off, stirred well with 50 ml of methanol, and refiltered to give 2.5 g of the dimer methyl enol ether. This was recrystallized from acetone (pyr) to afford 2.0 g of IIb′: mp 192–199°; $[\alpha]_D$ +46°; λ_{max} 228 mμ (ϵ 6270); λ_{max} 5.75, 8.00, 9.53, 9.64 μ; nmr δ 0.80 (18-H_3, 18′-H_3, 19-H_3, 19′-H_3), 2.01 (17β-OAc), 3.41 (3-MeO), 5.30 (m, 2′-H).

Anal. Calcd for $C_{43}H_{64}O_5$: C, 78.14; H, 9.76. Found: C, 78.34; H, 9.90.

The methanol wash liquor from the crude dimer was acidified and worked up in conventional fashion to give 0.3 g of dihydrotestosterone acetate (identified by ir).

B.—On an appropriately smaller scale, 100 mg of 17β-acetoxy-3-methoxy-2-(5α-androstene) was treated with toluenesulfonic acid as in A to give 50 mg of dimer methyl enol ether, ir identical with that of IIb′ obtained in A.

C.—When dihydrotestosterone acetate 3,3-dimethyl ketal was kept for 1.5 hr at 25° in a 4% solution of anhydrous toluenesulfonic acid in benzene the yield of IIb′ was 30%. Boiling of a similar reaction mixture for 10 min raised the yield to 45%, apparently as a result of more monomeric enol ether first being formed.

Dimer 3-Ethyl Enol Ether (IIb″). A.—When 4.0 g of 17β-acetoxy-3-ethoxy-3-(5α-androstene)[8] was treated with toluenesulfonic acid and acetic anhydride as described for IIb′, there was obtained 3.5 g of crude dimer enol ether, mp 145–160°. Recrystallization from ether (pyr) gave 3.1 g of cream prisms of IIb″: mp 167–171°; $[\alpha]_D$ +49°; λ_{max} 230 mμ (ϵ 5700); λ_{max} 5.73, 8.01, 8.92, 9.63 μ; nmr δ 0.80 (18-H_3, 18′-H_3, 19-H_3, 19′-H_3), 1.09 and 3.53 (t, q, 3-EtO), 2.02 (17β-OAc), 5.29 (m, 2′-H).

Anal. Calcd for $C_{44}H_{66}O_5$: C, 78.29; H, 9.86. Found: C, 77.86; H, 9.98.

The same starting material, kept at 25° for 1.5 hr in 3% anhydrous toluenesulfonic acid in benzene, gave a 60% yield of dimer IIb″.

B.—When 1.0 g of 17β-acetoxy-3-ethoxy-2-(5α-androstene)[8] was treated with toluenesulfonic acid in acetic anhydride as in A, there was obtained 0.8 g of dimer whose ir and nmr spectrum were identical with those of IIb″ obtained in A.

C.—Reaction as in A, performed on 0.5 g of dihydrotestosterone acetate 3,3-diethyl ketal, gave 0.3 g of dimer ethyl enol ether **IIb″**.

2α-[17′β-Acetoxy-2′-(5α-androsten)-3′-yl]-17β-acetoxy-5α-androstan-3-one (IIIb). A.—When 0.5 g of dihydrotestosterone acetate 3-ethylene hemithioketal α-O-β-S (**Ib**) was treated with toluenesulfonic acid in acetic anhydride as in process A for IIb″ (above), the product was a viscous oil which could not be crystallized. Chromatography on acidic alumina (20 g, Woelm grade I; 20-mm i.d. column; eluted with 300 ml of 1:1 benzene–hexane) gave 0.32 g of pale yellow oil whose ir spectrum was appropriate for the dimer β-acetylthioethyl enol ether IIb: λ_{max} 5.74, 5.88, 7.99, 8.77, 9.51, 9.63 μ. The 0.32 g of IIb, in 10 ml of acetone and 0.3 ml of concentrated HCl, was kept at 5° for 30 min and filtered to give 0.25 g of cream prisms. Recrystallization from acetone afforded 0.2 g of white prisms of IIIb: mp 258–261° dec; $[\alpha]_D$ +21°; λ_{max} 5.74, 5.80, 8.00, 9.66 μ; nmr δ *ca.* 0.80 (18-H_3, 18′-H_3, 19′-H_3), 1.07 (19-H_3), 2.01 (17β-OAc), 2.90 (q, J_1 = 6, J_2 = 12, 2-H), 5.23 (m, 2′-H).

Anal. Calcd for $C_{42}H_{62}O_5$: C, 77.97; H, 9.66. Found: C, 78.06; H, 9.62.

The N-acetyloxime of IIIb (standard oximation in pyridine followed by pyridine–acetic anhydride acetylation) was white flakes: mp 190–192°; $[\alpha]_D$ +41°; λ_{max} 5.73, 8.00, 9.52, 9.63, 10.80 μ; nmr δ 0.81 (18-H_3, 18′H_3, 19′-H_3), 0.97 (19-H_3), 2.02 (17β-OAc), 2.16 (3-AcON=), 2.98 (q, 2-H), 5.37 (m, 2′-H).

Anal. Calcd for $C_{44}H_{65}O_6N$: C, 75.07; H, 9.31; N, 1.99. Found: C, 75.24; H, 9.49; N, 1.86.

B.—The reaction described in A, performed on the β-O-α-S hemithioketal Ib′, gave intermediate oily dimer enol ether IIb and final dimer ketone IIIb exactly as isolated in A.

C and D.—Acid hydrolysis, as in A, of the dimer methyl enol ether IIb′ and dimer ethyl enol ether IIb″ gave high yields of the dimer ketone IIIb, with physical properties exactly as described in A.

E.—A solution of 3.0 g of dihydrotestosterone acetate and 1.4 g of anhydrous toluenesulfonic acid in 20 ml of benzene was refluxed for 4 hr. After washing with water and evaporation of the benzene solution, the glassy residue was recrystallized from methanol and three times from acetone, seeding with IIIb, to afford 0.5 g of white prisms, mp 250–260° dec, ir similar to that of IIIb. Conversion of the 0.5 g to N-acetyloxime and two recrystallizations from methanol gave 0.25 g of white flakes: mp 192–192°; ir spectrum identical with that of the acetyloxime described in A.

Chemical Shifts of Starting Materials.—Interpretations of dimer nmr spectra were based on the spectra of steroid ketone, ketal, and enol ether starting materials. Some of these have not been reported and so all of the meaningful shifts (in $CDCl_3$ with *ca.* 1% pyridine) are here appended: **cholestanone**, 0.70 (18-H_3), 1.03 (19-H_3); **dihydrotestosterone acetate**, 0.82 (18-H_3), 1.02 (19-H_3), 2.02 (17β-OAc); **cholestanone dimethyl ketal**, 0.68 (18-H_3), 0.82 (19-H_3 + other), 3.11 and 3.16 (3-MeO, 3-MeO); **dihydrotestosterone acetate dimethyl ketal**, 0.82 (18-H_3, 19-H_3), 2.04 (17β-OAc), 3.18 and 3.22 (3-MeO, 3-MeO); **17β-acetoxy-3-ethoxy-2-(5α-androstene)**, 0.80 (18-H_3, 19-H_3), 1.28 and 3.71 (t, q, 3-EtO), 2.03 (17β-OAc), 4.54 (m, 2-H); **3-ethoxy-3-cholestene**, 0.70 (18-H_3), 1.29 and 3.70 (t, q, 3-EtO), 4.51 (m, 4-H); **17β-acetoxy-3-ethoxy-3-(5α-androstene)**, 0.82 (18-H_3, 19-H_3), 1.28 and 3.71 (t, q, 3-EtO), 2.05 (17β-OAc), 4.52 (m, 4-H).

Registry No.—Ia, 2760-91-0; Ia′, 2760-93-2; Ib, 16158-92-2; Ib′, 16158-93-3; IIa, 16159-07-2; IIa′, 16158-94-4; IIb′, 16203-49-9; IIb″, 16203-48-8; IIIa, 16203-50-2; IIIb, 16158-95-5; N-acetyl oxime of IIIb, 16158-96-6; 5α-dihydrotestosterone acetate 3,3-diethyl-ketal, 16158-97-7; 17β-acetoxy-3-methoxy-2-(5α-androstene), 16158-98-8; 5α-dihydrotestosterone 3-ethylenehemithioketal β-O-α-S, 16158-99-9; 5α-dihydrotestosterone 3-ethylenehemithioketal, α-O-β-S, 16159-00-5; 5α-dihydrotestosterone acetate 3,3-dimethyl ketal, 16159-01-6; cholestanone, 566-88-1; dihydrotestoster-

one acetate, 1164-91-6; cholestanone dimethyl ketal, 16159-03-8; 17β-acetoxy-3-ethoxy-2-(5α-androstene), 16159-04-9; 17β-acetoxy-3-ethoxy-3-(5α-androstene), 16159-05-0; 3-ethoxy-3-cholestene, 16159-06-1.

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Steroids. VIII. The Beckmann Rearrangement of 2-Oximinocholesta-4,6-dien-3-one. The Synthesis of Some 2,3-Secocholesta-4,6-dienes[1a]

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The structure of an unusual dimeric Beckmann rearrangement product (III) derived from 2-oximinocholesta-4,6-dien-3-one (I) has been elucidated. A number of 2,3-secocholesta-4,6-dienes have been synthesized from I, making use of the Beckmann rearrangement as the ring-cleavage step.

The Beckmann rearrangement has been employed in the synthesis of a wide variety of aza steroids from various simple saturated and unsaturated steroidal ketoximines.[2] The Beckmann rearrangement of steroidal α-oximino ketones has been much less thoroughly investigated. This reaction appears to have been examined only with 16-oximino 17-ketones[3] and with 2,4-bisoximino 3-ketones;[4] it serves as a useful route to 16,17-seco steroids[3] and 2,3-seco-A-nor steroids,[4] respectively. We now report the behavior of the conjugated α-oximino ketone, 2-oximinocholesta-4,6-dien-3-one,[1a] (I) under Beckmann rearrangement conditions.

As reported previously, oximino ketone I reacts with acetic anhydride in pyridine to give an acetate (II) which can be hydrolyzed back to I without rearrangement or ring cleavage.[1a] On the other hand, the reaction of I with tosyl chloride in pyridine afforded a crystalline product, mp 197–198°, which was not the tosylate of I. It was assigned the unusual dimeric structure III on the basis of the spectral and chemical evidence discussed below.

The dimeric formula $C_{54}H_{82}O_3N_2$ fitted well with the results of both elemental analysis and molecular weight determinations. The infrared spectrum of III showed carbonyl bands at both 5.70 and 5.97 μ, as well as a series of bands at 6.17, 6.23, and 6.33 μ attributable to conjugated olefinic and imine functions; significantly, no nitrile absorption in the 4.4–4.5-μ region was observed.

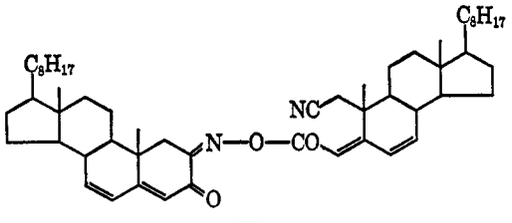
In the course of determining whether or not the dimer contained a readily reduced carbonyl group, it was allowed to react with sodium borohydride in methanol solution. Two crystalline products, mp 167 and 235°, were isolated in 41 and 37% yield, respectively, after preparative thin layer chromatography. It was soon shown that the reagent in this reaction was acting not as a reducing agent, but simply as a source of methoxide ion. The same products were obtained in approximately the same yields when dimer III was treated with a solution of sodium methoxide in methanol.

The product, mp 235°, was identified readily as the original oximino ketone I. The second product, mp 167°, analyzed for $C_{28}H_{43}O_3N$; it was assigned structure IV on the basis of its spectral and chemical properties. The infrared spectrum of IV showed an ester carbonyl at 5.78, a cyano group at 4.40, and conjugated olefin bands at 6.14 and 6.25 μ; no hydroxyl absorption in the 3-μ region was observed. The nmr spectrum of IV showed the methoxyl of the ester function as a singlet at τ 6.27, as well as a multiplet at 3.29–4.31 corresponding to three olefinic protons. Reaction of dimer III with sodium hydroxide yielded a mixture of oximino ketone I and the cyano acid V, mp 218°. Acid V was converted by diazomethane into the cyano ester IV.

The proposed mechanism for the conversion of oximino ketone I into the oxime imidate ester III, and fragmentation of III into I and IV by methoxide ion, is shown in Scheme I.

The interception of imino derivatives in the course of Beckmann rearrangements is well known.[5] An example of a Beckmann rearrangement in which an equivalent of unrearranged oxime is incorporated into the isolated product has been provided by Hill, who described the conversion of A into B shown in Scheme II.[6]

A rather analogous process can be envisaged for the Beckmann rearrangement of oximino ketone I to give a dimeric product of structure IIIa. The latter struc-



IIIa

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