Acknowledgment. We are grateful to Dr. W. G. Anderson and Mrs. D. N. Davis for the NMR spectra and to Dr. S. K. Dasgupta for the preparation of some of the starting material. We are indebted to Dr. M. N. Cayen of Ayerst Research Laboratories, Montreal, P.Q., for the cholesterol biosynthesis inhibition sassays. This study was supported by U.S. Public Health Service Grant AM-03419 from the Institute of Arthritis and Metabolic Diseases and by a grant from the National Science Foundation, GB-38612.

Registry No.—**1**, 25819-77-6; **2**, 58958-20-6; **3**, 58958-21-7; **4**, 58958-22-8; **5**, 58958-23-9; **6a**, 58958-24-0; **6b**, 58958-25-1; **6c**, 58958-26-2; **6d**, 58958-27-3; **7**, 58958-28-4; **8a**, 58958-29-5; **8b**, 58958-30-8; **9**, 26622-97-9; **10a**, 3092-00-0; **10b**, 58958-31-9; **10c**, 58958-32-0; **10d**, 58958-33-1; **11a**, 58958-34-2; **11b**, 58958-35-3; **11c**, 58958-36-4; **12a**, 58966-79-3; **12b**, 58958-37-5; methyl iodide, 74-88-4; 1-bromo-4-methylpentane, 626-88-0; isoamyltriphenylphosphonium iodide, 52710-37-9; cholesterol, 57-88-5.

References and Notes

(1) Taken, in part, from a dissertation by Y. Letourneux in partial fulfillment of the requirements for the Ph.D. degree in organic chemistry, University of Paris-Sud, Centre d'Orsay, 1975.
(2) For reviews see S. Burstein and M. Gut, *Adv. Lipid Res.*, **9**, 291 (1971); *Recent Prog. Horm. Res.*, **27**, 303 (1971).
(3) Q. Khuong-Huu, Y. Letourneux, M. Gut, and R. Goutarel, *J. Org. Chem.*, **39**, 1065 (1974); M. Gut, Y. Letourneux, J. A. Story, S. A. Teppor, and D. Kritchevsky, *Experientia*, **30**, 1325 (1974).
(4) G. R. Pettit, B. Green, G. L. Dunn, and P. Sunder-Plassman, *J. Org. Chem.*, **35**, 1387 (1970).
(5) R. F. N. Hutchins, M. J. Thompson, and J. A. Svoboda, *Steroids*, **5**, 113 (1970).
(6) R. Greenwald, M. Chaykovsky, and E. J. Corey, *J. Org. Chem.*, **28**, 1128 (1963).
(7) G. Drefahl, K. Ponsold, and H. Schick, *Chem. Ber.*, **98**, 604 (1965); A. M. Krubiner and E. P. Oliveto, *J. Org. Chem.*, **31**, 24 (1966); S. G. Wyllie and C. Djerassi, *Ibid.*, **33**, 305 (1968).
(8) N. K. Chaudhuri, R. Nickolson, H. Kimball, and M. Gut, *Steroids*, **15**, 525 (1970).
(9) Compare M. J. Weiss, R. E. Schaub, G. R. Allen, J. F. Poletto, C. Pidacks, R. B. Conrow, and C. J. Coscia, *Tetrahedron*, **20**, 357 (1964); L. E. Hightower, L. R. Glasgow, K. M. Stone, D. A. Albertson, and H. A. Smith, *J. Org. Chem.*, **35**, 1881 (1970).
(10) G. A. Smith and D. H. Williams, *J. Chem. Soc. A*, 2811 (1972).
(11) T. A. Narwid, K. E. Cooney, and M. R. Uskoković, *Helv. Chim. Acta*, **54**, 771 (1974).
(12) F. Sondheimer and R. Mechoulam, *J. Am. Chem. Soc.*, **80**, 3087 (1958).
(13) N. K. Chaudhuri and M. Gut, *J. Am. Chem. Soc.*, **87**, 3737 (1965).
(14) H. M. Walborsky and L. E. Allen, *Tetrahedron Lett.*, 823 (1970); *J. Am. Chem. Soc.*, **93**, 5465 (1971).
(15) The cholesterol synthesis was tested in vitro by a rat liver homogenate preparation. A pooled liver homogenate was incubated simultaneously with acetate-^{14}C and mevalonate-^{3}H in the presence of different concentrations of 20-methylcholesterol and the incorporation into nonsaponifiable lipids and cholesterol was measured. For methodology see M. N. Cayen and D. Dvornik, *Can. J. Biochem.*, **46**, 179 (1968).
(16) S. Burstein, H. L. Kimball, N. K. Chaudhuri, and M. Gut, *J. Biol. Chem.*, **243**, 4417 (1968).

Synthesis and Cyclization of 21-Hydroxyethylthioprogesterone Derivatives

Bhaskar R. Samant and Frederick Sweet*

Department of Obstetrics and Gynecology, Washington University School of Medicine, St. Louis, Missouri 63110

Received December 29, 1975

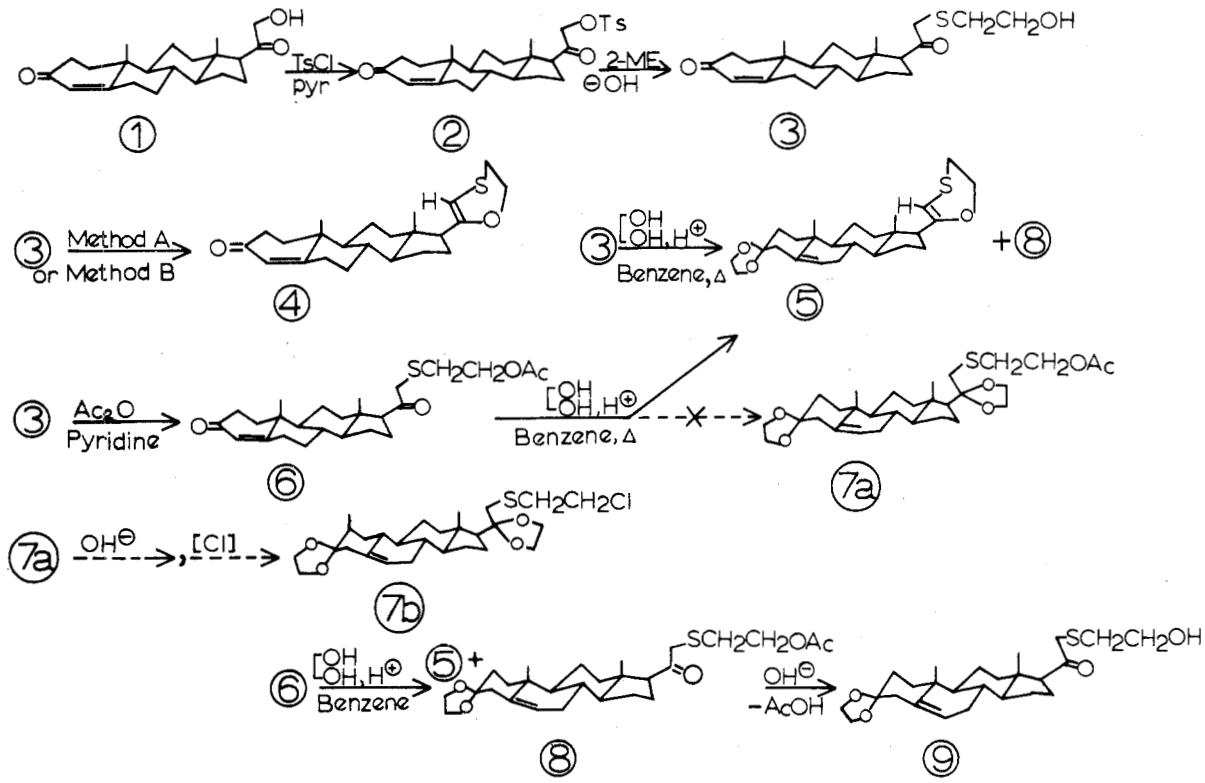
Treatment of 21-*p*-toluenesulfonyloxyprogesterone with 2-mercaptoethanol gives 21-hydroxyethylthioprogesterone. Under reaction conditions which usually produce chlorination of primary alcohols 21-hydroxyethylthioprogesterone cyclizes to 17β-(5′,6′-dihydro-1′,4′-oxathiin-2′-yl)-4-androsten-3-one. Following acetylation of the 21-hydroxyethylthio group of the title compound, acid-catalyzed ketalization of the resulting acetate gives a resolvable mixture of 3-ethylene ketals of 21-acetoxyethylthio-5-pregnene-3,20-dione and 17β-(5′,6′-dihydro-1′,4′-oxathiin-2′-yl)-5-androsten-3-one. The anticipated 3,20-diethylene ketal of 21-acetoxyethylthio-5-pregnene-3,20-dione could not be detected in the reaction mixture using a variety of reaction conditions. The C-21 sulfur atom is believed to influence the courses of the deacetylation and cyclization reactions. Mechanisms are proposed to account for these results. Nuclear magnetic resonance, infrared, and ultraviolet spectral properties of the new steroid dihydroxathiins are discussed.

Steroid alkylating agents were previously synthesized in this laboratory to serve as active site directed irreversible inhibitors for studies of the steroid binding site of 20β-hydroxy steroid dehydrogenase (E.C.1.1.1.53).[1-3] One of a series of isomeric bromoacetoxyprogesterone derivatives, 4-pregnen-16α-ol-3,20-dione 16-bromoacetate, terminates pregnancy in rats.[4] Similarly, the steroid alkylating agent 4-estren-17β-ol-3-one 17-bromoacetate is an interceptive agent in rats and primates.[5] The benzylic halide 1,3,5(10)-estratriene-2,4-dibromomethyl-3-ol-17-one 3-*O*-methyl ether was found to be a persistent anti-estrogen.[6] Predictably, all of the bromoacetoxyprogesterone derivatives which were synthesized are susceptible to hydrolysis in aqueous media possessing pH values above 7.0. Indeed, following inactivation of 20β-hydroxy steroid dehydrogenase with 4-pregnen-6β-ol-3,20-dione bromoacetate, or 4-pregnen-11α-ol-3,20-dione bromoacetate, at pH 7.0, the enzyme is readily reactivated by adjusting the pH to 8.0 or 9.0.[7] Similar alkaline conditions produce hydrolytic cleavage of the ester bond in conjugates between steroid bromoacetates and nucleophilic amino acids.[2]

Steroid alkylating agents possessing greater stability toward hydrolysis over a broad pH range compared to the bromoacetates are desirable for our biological experiments. Therefore, we attempted to synthesize 21-(2′-chloroethylthio)progesterone, which was expected to have the desired chemical properties. The present report describes the synthesis of 21-(2′-hydroxyethylthio)progesterone and the results obtained when this steroid and its derivatives were treated under conditions conventionally employed for chlorination of primary alcohols.

11-Deoxycorticosterone (**1**, Scheme I) was converted to the corresponding 21-toluenesulfonate (**2**) by Borrevang's procedure.[8] Upon treatment of **2** with alkaline 2-mercaptoethanol 21-(2′-hydroxyethylthio)-4-pregnene-3,20-dione (**3**) was obtained. Reaction of **3** with thionyl chloride in chloroform,[9] or hexamethylphosphorus triamide and carbon tetrachloride in chloroform,[10] did not provide the expected 21-(2′-chloroethylthio)-4-pregnene-3,20-dione (**3b**) but instead gave a new compound **4**. This steroid does not exhibit a 1700-cm^{-1} ir absorption (characteristic of a C-20 carbonyl), but has a strong 1630-cm^{-1} absorption. Compound **4** possesses an unusually strong ultraviolet absorption [λ_{max} (CH_3OH) 238 nm (ϵ 24 000)], more thoroughly discussed below. Elemental analysis, NMR, ir, and uv spectral data of **4** support the structural

Scheme I



assignment as represented in Scheme I. The NMR signal due to the C-4 proton appears as a broad singlet at τ 4.31 (similar to that observed for the corresponding vinyl protons in **1**, **2**, and **3**). The resonance signal due to the C-3′ vinyl proton in the 5′,6′-dihydro-1′,4′-oxathiin system is observed as a sharp singlet at τ 5.19. Group contribution calculations[11] predict this value for the C-3′ vinyl proton resonance signal.

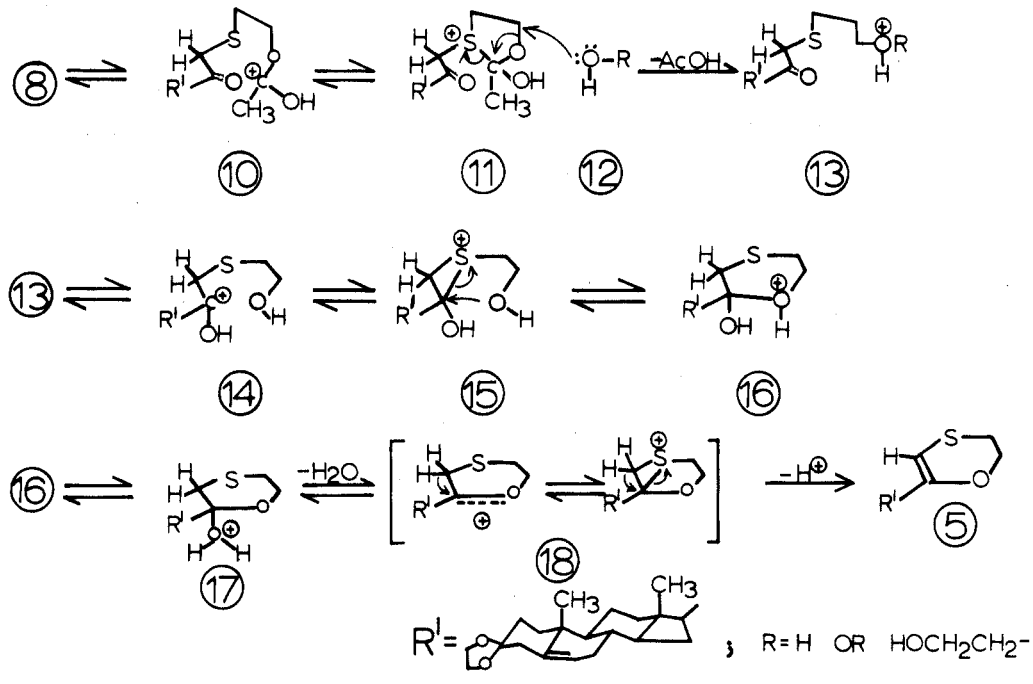
In an attempt to prepare the 3,20-diethylene ketal of **3**, the steroid was treated with ethylene glycol and *p*-toluenesulfonic acid in benzene under reflux. The only product obtained from the reaction was the monoketal **5**, containing the 5′,6′-dihydro-1′,4′-oxathiin system on the steroid D ring. The structure of **5** was established by elemental analysis and spectroscopic data. The ir spectrum of **5**, compared with that of **3**, lacks absorption at 3400 (C-2′, OH, 1700 (C-20, C=O), and 1650 cm^{-1} (C-3, C=O). However, a new band at 1630 cm^{-1} (–SCH=CO–), similar to that seen in the ir spectrum of **4**, is observed. Interestingly, compound **5**, which does not possess a 3-keto-Δ^4 chromophore, exhibits an uv absorption at λ_{max} (MeOH) 238 nm (ϵ 8500). This absorption must be due to the 5′,6′-dihydro-1′,4′-oxathiin system.[12] Moreover, this explains the unusually large uv extinction coefficient observed for **4** (i.e., ϵ 24 000). This is an ϵ value of 7000–8000 greater than that expected for a 3-keto-Δ^4 steroid. The NMR spectrum of **5** contains two vinyl proton signals: a sharp singlet at τ 5.15 (due to H-3′, as seen in **4**) and a narrow multiplet at τ 4.70 (H-6) which is slightly shifted upfield compared to the H-4 signal in **4**.

Acetylation of **3** with acetic anhydride in pyridine provided the corresponding acetate **6**. Conversion of the acetate **6** to the diketal **7a**, then deacetylation and chlorination of the hydroxyethyl side chain with hexamethylphosphorus triamide and CCl_4, had been planned (Scheme I). The C-20 ketal group was expected to prevent cyclization during the chlorination reaction. However, a mixture of **6**, ethylene glycol, and *p*-toluenesulfonic acid in benzene, heated under reflux for 18 h (in a Dean-Stark water separator), produced a reaction mixture containing only **5** and **8**. Base-catalyzed hydrolysis of **8** gave **9** which was isolated by short column silica gel chromatography. Longer periods of heating **6** produced **5** as the major product while shorter reaction times gave more of **8**, as determined by TLC analysis of the reaction mixtures. The structure of **9** was established by elemental analysis and comparison of the ir and NMR spectra of this compound with those discussed above. This steroid did not exhibit any uv absorption in the 210–290-nm region.

The relative ease with which **3** cyclizes to **4**, and **8** is deacetylated and cyclizes to **5**, is interesting. Cyclization of **3** to **4** by an acid-catalyzed sequence involving intermediates analogous to **14** → **16** → **17** (Scheme II) is well known for δ-hydroxybutyl alkyl ketones.[13] Conditions under which we first attempted to chlorinate **3** (Experimental Section, method A) contain a strong acid, and could well promote this sequence. However, the hexamethylphosphoramide–CCl_4 conditions of chlorination (method B) are not acidic and the by-products of this reaction are neutral.[10] Therefore, it is entirely likely that chlorination of the 21-(2′-hydroxyethylthio) group of **3** does occur, but that the resulting chloroethylthio steroid undergoes a rapid cyclization (**3** → **3b** ⇄ **3c** → **4**, Scheme III). This could occur by an internal nucleophilic displacement of the chlorine atom by the C-20 oxygen in the carbonyl or enol form, represented by equations in Scheme III. Neighboring group participation involving a β-thio atom is classical in nucleophilic reactions,[14] and thus can account for the results that we obtain from attempts to produce 21-(2′-chlorethylthio)progesterone directly from 21-(2′-hydroxyethylthio)-progesterone.

The tendency of the acetoxy group of **8** to be deacetylated under conditions which do not ordinarily bring about this reaction[15] may be associated with participation of the C-21 sulfur atom. Deacetylation of **8**, leading to cyclization of the resulting hydroxyethylthio group in **13** or **14** (Scheme II), can be rationalized by a mechanism involving C-21 sulfur participation through intermediate structures **10** and **11**, wherein **12** (R = H) is a water molecule. However, the reaction mixture which produces **5** and **8** contains a large excess of ethylene glycol, relative to water. If ethylene glycol (**12**, R = $HOCH_2CH_2$, Scheme II) would react with **11** then formation

Scheme II



of the 2′-hydroxyethoxy ether of **14** (i.e., **13**, R = $HOCH_2CH_2$–) would occur. Cyclization of this compound is not expected to take place. There is no evidence that this ether is formed in the reaction mixture.

An alternative mechanism which accounts for the deacetylation and cyclization of **8** promoted by the C-21 sulfur atom is represented by equations in Scheme III. In this case protonation of the acetoxy group of **8** gives **10**, in equilibrium with the enol intermediate **21**. The sulfur atom forms the respective cyclic sulfonium intermediates **19** and/or **23**. Deprotonation of these species gives **5**. Although the cyclization mechanisms represented in Schemes II and III appear to be equally probable in terms of sulfur participation, our failure to detect a product resulting from the reaction of **11** + **12** (Scheme II), where **12** is ethylene glycol, leads us to favor the mechanism shown in Scheme III.

Experimental Section

All melting points were determined in a Mel-Temp apparatus and are reported uncorrected. Ultraviolet spectra were determined in methanol with a Beckman Model 25 spectrophotometer. Infrared spectra were determined in KBr, unless otherwise stated, with a Beckman Acculab 4 spectrometer. Nuclear magnetic resonance spectra were determined in deuteriochloroform with tetramethylsilane as internal standard, in a Varian T-60 spectrometer, and are reported as τ values. Elemental analyses were performed by Galbraith Laboratories, Knoxville, Tenn. All the reactions were monitored by thin layer chromatography with Eastman silica gel sheets (no. 6060 containing a fluorescent indicator). Chloroform (Fisher Scientific, C-574, containing 0.75% ethanol) was used to develop the chromatograms. Iodine and/or ultraviolet light were used for visualization. Silica gel G, E. Merck AG-Darmstadt, was used as adsorbent for short column chromatography.[16] Optical rotations were determined in chloroform using 2% solutions in a 1-dm semimicro (2.5 ml) tube with a Dr. Steeg & Reuter Model SR-5 polarimeter. Removal of solvents was carried out under reduced pressure in a Buchler flash evaporator.

4-Pregnene-21-ol-3,20-dione 21-*p*-Toluenesulfonate (2). Compound **2** was prepared by a method similar to that described by Borrevang[8] for the synthesis of 4-pregnene-17α,21-diol-3,20-dione 21-*p*-toluenesulfonate. A solution of 5.0 g of deoxycorticosterone (**1**) in 30 ml of dry pyridine was cooled to −20 °C, then mixed with a solution of 3.0 g of *p*-toluenesulfonyl chloride in 30 ml of CH_2Cl_2 at −20 °C. The resulting solution was allowed to stand at −15 °C for 14 h. Following dilution with 200 ml of methylene chloride, the mixture was washed thrice with dilute HCl, four times with dilute $NaHCO_3$, and twice with water. After drying (Na_2SO_4) the solution was concentrated to dryness. Crystallization of the residue from acetone–ethanol gave 5.0 g (76%) of **2**, mp 151–153 °C, $[\alpha]^{25}D$ +131° (lit.[17] mp 170–171 °C) (Borrevang states that steroid tosylates generally exhibit variable melting points.[8]). Anal. Calcd for $C_{28}H_{36}O_5S$: C, 69.39; H, 7.49; S, 6.62. Found: C, 69.54; H, 7.19; S, 6.86. Ir ν_{max} (KBr) 2950, 1707, 1668, 1370, 1177 cm^{-1} supports structure **2**.

21-(2′-Hydroxyethylthio)-4-pregnene-3,20-dione (3). To 400 mg of **2** in 10 ml of ethanol were added in succession 160 mg of 2-mercaptoethanol dissolved in 5 ml of ethanol and 80 mg of NaOH dissolved in 1 ml of water. The resulting mixture was heated under gentle reflux with magnetic stirring for 30 min, then cooled and an equal volume of water was added, giving an oily precipitate. The mixture was distributed between 50 ml of ether and an additional 25 ml of water and separated. The ethereal layer was washed twice with 25 ml of water, dried (Na_2SO_4), and concentrated to dryness. Crystallization of the residue from acetone–cyclohexane gave 110 mg (34%) of **3**: mp 110 °C; $[\alpha]^{25}D$ +164°; λ_{max} 240 nm (ϵ 20 000). Anal. Calcd for $C_{23}H_{34}O_3S$: C, 70.73; H, 8.77; S, 8.21. Found: C, 70.58; H, 8.60; S, 8.05. The ir data, ν_{max} (KBr) 3410 (OH), 1700 (C-20, C=O), 1662 cm^{-1} (C-3, C=O), support structure **3**. The structural assignment was further confirmed by the NMR spectrum of this compound.

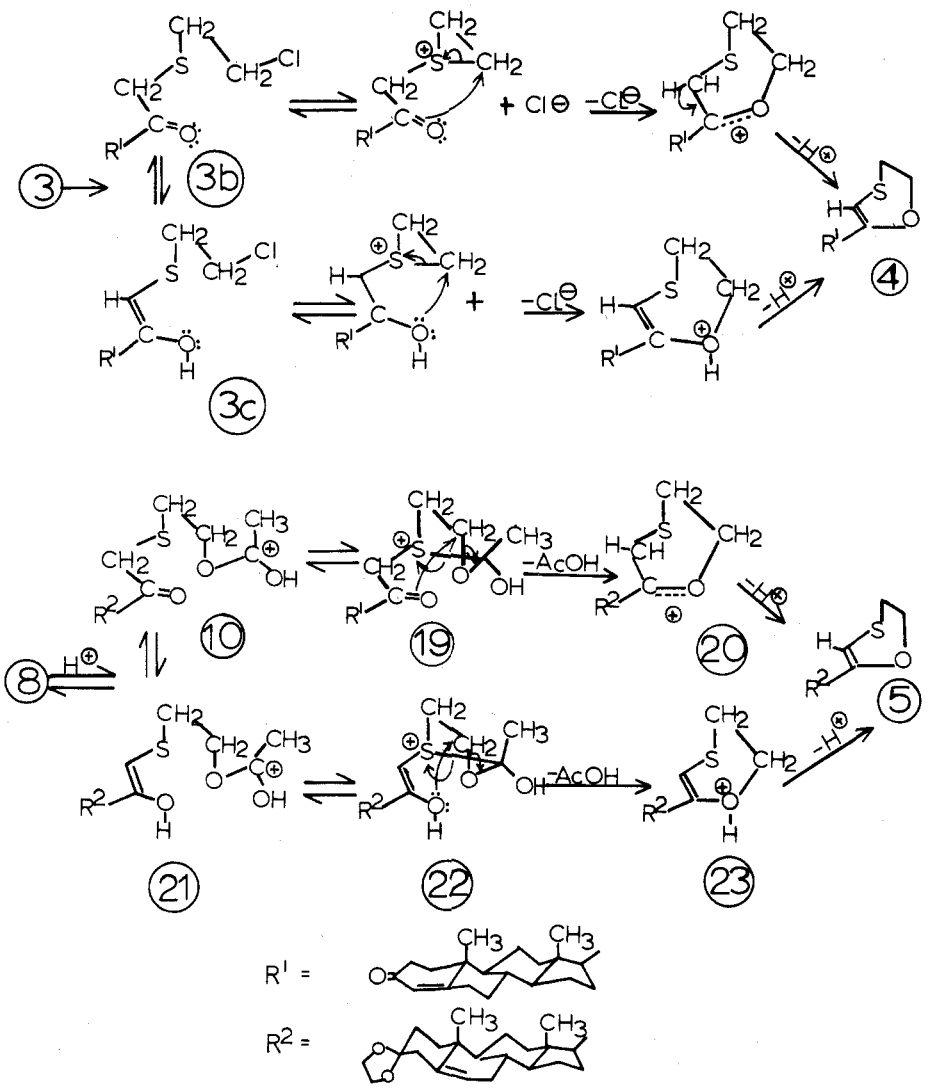
17β-(5′,6′-Dihydro-1′,4′-oxathiin-2′-yl)-4-androsten-3-one (4). Method A. To a solution of 300 mg of **3** in 1 ml of chloroform was added dropwise and with stirring 0.06 ml of thionyl chloride in 0.5 ml of chloroform and the resulting solution was stirred for 3.5 h, then concentrated to dryness. Residual thionyl chloride was chased by evaporating CCl_4 from the oily residue. Crystallization of the residue from acetone gave 60 mg of **4**: mp 168–171 °C; $[\alpha]^{25}D$ +145°; λ_{max} 238 nm (ϵ 24 000). Anal. Calcd for $C_{23}H_{32}O_2S$: C, 74.16; H, 8.66; O, 8.59; S, 8.59. Found: C, 73.76; H, 9.02; O, 8.76; S, 8.58.

Ir spectrum of **4** shows the absence of an hydroxyl group (3400 cm^{-1}), or a band (1700 cm^{-1}) characteristic of the C-20 keto group, but exhibits a strong ν_{max} (KBr) at 1630 cm^{-1}, which is characteristic of the 5′,6′-dihydro-1′,4′-oxathiin system.[18,19] The structure **4** was further confirmed by NMR spectroscopy (see the discussion above).

Method B. A solution of 170 mg of hexamethylphosphorus triamide in 0.5 ml of chloroform was added dropwise and with stirring to an ice–water cooled solution of **3** (390 mg) dissolved in a mixture of 1 ml of chloroform and 4 ml of CCl_4. The resulting solution was heated under gentle reflux for 5 h. The solution was then concentrated under vacuum to about 1 ml and was washed with three 15-ml portions of water. The organic residue was dissolved in 20 ml of chloroform, washed with water, dried (Na_2SO_4), and concentrated to dryness. Crystallization of the residue from acetone gave 120 mg of **4**, mp 169–171 °C. Compound **4** was found to have identical melting point, TLC, and ir spectra with the material obtained from method A.

17-(5′,6′-Dihydro-1′,4′-oxathiin-2′-yl)androst-5-en-3-one Cyclic Ethylene Ketal (5). Compound **3** (390 mg), 0.375 ml of ethylene glycol, and 51 mg of *p*-toluenesulfonic acid in 30 ml of benzene were heated under reflux for 19 h, using anhydrous Na_2SO_4 in the side arm of a Dean-Stark apparatus to remove water. The reaction mixture

Scheme III



was allowed to come to room temperature, and then was stirred for 0.5 h, after addition of 3 drops of tributylamine. The resulting mixture was washed with water and dried (Na_2SO_4). Evaporation of solvent followed by crystallization of the residue from ethyl acetate gave 220 mg of **5**: mp 226–227 °C; λ_{max} 230 nm (ϵ 8500). Anal. Calcd for $C_{25}H_{36}O_3S$: C, 72.08; H, 8.71; O, 11.52; S, 7.69. Found: C, 72.12; H, 8.82; O, 11.53; S, 7.70.

The ir spectrum of **5** contained no carbonyl or hydroxyl absorptions. Presence of strong ν_{max} at 1630 cm^{-1} supports structure[18,19] **5**, which was further confirmed by its NMR spectrum. The integrated NMR spectrum of **5** contains the signals τ 4.70 (one proton, broad singlet, H-6), 5.15 (one proton, singlet, H-3′), 5.43–5.84 (two protons, multiplet, H-6′), 6.9–7.23 (two protons, multiplet, H-5′), 8.94 (three protons, singlet, H-19), 9.3 (three protons, singlet, H-18), 6.07 (four protons, singlet, OCH_2CH_2O ketal).

21-(2′-Acetoxyethylthio)-4-pregnene-3,20-dione (6). A solution of **3** (200 mg) in 0.5 ml of pyridine and acetic anhydride (0.5 ml) was heated on a steam bath for 0.5 h. The reaction mixture was allowed to come to room temperature, then ice water was added and the mixture was extracted with chloroform. The extract was washed with water, dried (Na_2SO_4), and concentrated to dryness. TLC analysis indicated the presence of one component in the residue. The ir bands, in CCl_4 solutions, ν_{max} 1743 (acetate C=O), 1708 (C-20, C=O), and 1680 cm^{-1} (C-3, C=O), support structure **6**. Compound **6** resisted crystallization, and was therefore used as an oil in the ketalization experiment described below.

Ketalization of 21-(2′-Acetoxyethylthio)-4-pregnene-3,20-dione to 8. Compound **6** (475 mg), 0.4 ml of ethylene glycol, 50 mg of *p*-toluenesulfonic acid, and 30 ml of benzene were heated under reflux for 18 h with anhydrous Na_2SO_4 in the side arm of a Dean-Stark apparatus. The cooled solution was stirred for 0.5 h with 0.65 ml of tributylamine. The resulting solution was washed with water, dried, and concentrated to dryness. Treatment of the solid residue with ethyl acetate gave 80 mg of a crystalline material, mp 206–212 °C which increased to 225–227 °C after two crystallizations from ethyl acetate. This product was found to be identical with **5** by a comparison of its melting point, mixture melting point, TLC, and ir with those of an authentic sample of **5** which had been prepared from **3**. The TLC of the mother liquor from the first ethyl acetate crystallization contained a forward migrating spot with mobility similar to **6**, but was not uv absorbing. This solution containing compound **8** was concentrated to dryness, and the residue was subjected to base-catalyzed hydrolysis, described below.

21-(2′-Hydroxyethylthio)-5-pregnene-3,20-dione Cyclic 3-Ethylene Ketal (9). To a solution of 380 mg of **8** in 5 ml of CH_3OH was added 90 mg of sodium methoxide dissolved in 5 ml of CH_3OH. The resulting solution was stirred at room temperature for 23 h, then concentrated to dryness. The semisolid residue was extracted with chloroform, the chloroform extract was washed with water and dried (Na_2SO_4), and the solvent was removed, leaving an oily residue (280 mg) which resisted crystallization. The oil was chromatographed on a short column of silica gel G (15 g) with chloroform, giving **9** as a white, crystalline material, mp 101–104 °C. Recrystallization of **9** from acetone–petroleum ether gave crystals of mp 117–119 °C; $[\alpha]^{25}D$ +50°; no detectable uv absorption in the range 215–300 nm. Anal. Calcd for $C_{25}H_{38}O_4S$: C, 69.09; H, 8.81; S, 7.38. Found: C, 68.99; H, 8.85; S, 7.16. The strong ir bands, ν_{max} 3220 (C-2′, OH) and 1690 cm^{-1} (C-20, C=O), support structure **9**. The structure assigned to **9** was confirmed by the NMR spectrum.

Acknowledgments. This work was supported by Research Grants AM 16854 and HD 00379 from the National Institutes of Health. F. Sweet is recipient of U.S. Public Health Service Research Career Development Award HD 70788. The authors gratefully acknowledge the NMR spectra provided by Dr.

Timothy B. Patrick of the Chemistry Department, Southern Illinois University at Edwardsville, and the technical assistance of Mr. Mitch Sasa.

Registry No.—1, 64-85-7; 2, 58958-13-7; 3, 58958-14-8; 4, 58958-15-9; 5, 58958-16-0; 6, 58958-17-1; 8, 58958-18-2; 9, 58958-19-3; *p*-toluenesulfonyl chloride, 98-59-9; 2-mercaptoethanol, 60-24-2.

References and Notes

(1) (a) F. Sweet, F. Arias, and J. C. Warren, *J. Biol. Chem.*, **247**, 3424 (1972); (b) F. Arias, F. Sweet, and J. C. Warren, *ibid.*, **248**, 5641 (1973); (c) R. Strickler, F. Sweet, and J. C. Warren, *ibid.*, **250**, 7656 (1975).
(2) F. Sweet and J. C. Warren, *Biochem. Biophys. Acta*, **260**, 759 (1972).
(3) J. C. Warren, F. Arias, and F. Sweet, *Methods Enzymol.*, **36**, 1 (1975).
(4) S. W. Clark, F. Sweet, and J. C. Warren, *Biol. Reprod.*, **11**, 519 (1974).
(5) S. W. Clark, F. Sweet, and J. C. Warren. *Am. J. Obstet. Gynecol.*, **121**, 864 (1975).
(6) K. N. Rao, F. Sweet, and J. C. Warren, *Steroids*, **24**, 63 (1974).
(7) F. Sweet, *Steroids*, in press.
(8) P. Borrevang, *Acta Chem. Scand.*, **9**, 587 (1955).
(9) E. L. Eliel, M. T. Fisk, and T. Prosser, "Organic Syntheses", Collect. Vol. IV, Wiley, New York, N.Y., 1963, p 169.
(10) I. M. Downie, J. B. Lee, and M. F. S. Matough, *Chem. Commun.*, 1350 (1968).
(11) A. J. Gordon and R. A. Ford, "The Chemist's Companion", Wiley, New York, N.Y., 1972, p 256.
(12) R. C. Elderfield, Ed., "Heterocyclic Compounds", Vol. 6, Wiley, New York, N.Y., 1957, p 90.
(13) A. Lipp, *Justus Liebigs Ann. Chem.*, **289**, 181 (1896).
(14) (a) E. S. Gould, "Mechanism and Structure in Organic Chemistry", Holt, Rinehart and Winston, New York, N.Y., 1960, pp 572–573; (b) J. Hine, "Physical Organic Chemistry", McGraw-Hill, New York, N.Y., 1962, pp 144–145, 178–180.
(15) S. Bernstein, M. Heller, and S. M. Stolar, *J. Am. Chem. Soc.*, **76**, 5674 (1954).
(16) B. J. Hunt and W. Rigby, *Chem. Ind. (London)*, 1868 (1967).
(17) T. Reichstein and H. G. Fuchs, *Helv. Chim. Acta*, **23**, 676 (1940).
(18) M. Tomoeda, A. Ishida, and T. Koga, *Chem. Pharm. Bull.*, **15**, 887 (1967); **13**, 1078 (1965).
(19) L. F. Fieser, C. Yuan, and T. Goto, *J. Am. Chem. Soc.*, **82**, 1996 (1960).

Daunomycinone Analogues via the Diels–Alder Reaction. Synthesis and Chemistry of Some 6,11-Dihydroxy-5,12-naphthacenediones[1]

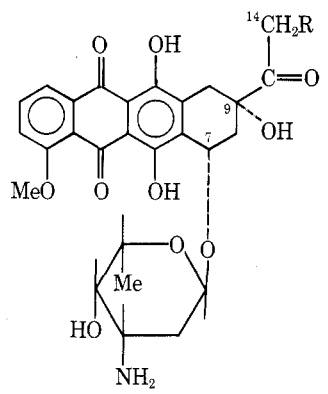
William W. Lee,* Abelardo P. Martinez, Thomas H. Smith,[1] and David W. Henry

Life Sciences Division, Stanford Research Institute, Menlo Park, California 94025

Received May 21, 1975

Quinizarinquinone reacts with 1,3-butadiene and 1-acetoxy-1,3-butadiene, but not 2-methoxy-1,3-butadiene, mainly at the external double bond to give end adducts **5a** and **5b**, respectively. Their transformation into, and the chemistry of, various dihydroxynaphthacenedione derivatives are described. These include **13d** (a simplified aglycone of daunomycinone), the 5,6,11,12-tetramethoxynaphthacenes, **17** and **19a**, and the oxidative demethylation of **17** to a 5,6,11,12-naphthacenetetrone, **18**, as well as the dihydroxytrione **22b**.

The anthracycline antibiotics daunorubicin (**1**) and adriamycin (**2**) have shown promise for clinical use against a variety of tumors, including solid ones.[2] In addition, daunorubicin benzhydrazone (**3**, methyl ketone O of **1** replaced by $NNHCOC_6H_5$) has clinical activity against acute myeloblastic and lymphoblastic leukemia.[3] Thus, various changes in this system appear compatible with retention of antitumor properties.



1, R = H, daunorubicin
2, R = OH, adriamycin

A number of derivatives at the ketone and amine functions of daunorubicin and adriamycin synthesized in our laboratories[4] and elsewhere[5,6] show a modified spectrum of both toxicity and antitumor activity against various experimental tumors in mice. These results led us to examine other structural variations and also routes that may lead to a synthesis of **1** and **2**.

This paper reports some studies on (1) the Diels–Alder reaction as a route to the 6,11-dihydroxy-5,12-naphthacenedione ring system of **1** and **2**, (2) some chemistry of, and blocking methods for, the quinizarin system of these rings, (3) an assessment of this route to the aglycones of **1** and **2** and their analogues.

The Diels–Alder reaction of quinizarinquinone (**4a**) with suitable butadienes offers a possible quick entry into the dihydroxynaphthacenedione ring system if addition occurs at the C-2 double bond. Inhoffen et al.[7] studied the reaction of several dienes with **4** and observed that the internal double bond competed with the double bond at C-2. Only with 1,4-diacetoxybutadiene was any end adduct **5c** isolated. In the other cases, they found that the formation of an internal adduct (e.g., **6c**) or diadduct (e.g., **7b**[8] or an isomer; isolated as **10b**) predominated. We find that under proper reaction conditions, the desired end adducts of structure **5** may become the predominant products for some, but not all, butadienes.

Reaction of quinizarinquinone (**4a**) with excess 1,3-butadiene in hot benzene for several hours afforded the red end adduct **5a** as the main product, the pale-beige internal adduct **6a** as a minor product, and only TLC and mass spectral indications of the diadduct **7a**. Unlike butadiene, excess 1-acetoxy-1,3-butadiene[9] reacted with **4a** in hot benzene to give mainly the diadduct **7b**, essentially as reported.[7] However, **4a** and a limited excess of 1-acetoxy-1,3-butadiene reacted in acetonitrile to afford primarily **5b**,[8] together with some internal adduct **6b**[8] and some diadduct **7b**.

The reaction of **4a** with 2-methoxybutadiene was disappointing. Under a wide variety of conditions, the major product was the center adduct **6d**, accompanied by some diadduct **7c**. The desired end adduct **5d** was never formed in sufficient quantity to warrant attempts at its separation from the major product **6d**. Compound **5d** is wanted as the precursor to the versatile ketone **22b**. Thus the reaction of butadienes with **4** cannot always be directed to give the end ad-