Possible Anchimeric Assistance in the Hydration–Decarboxylation of a Propiolic Acid. Synthesis of Methyl 3-(17β-Acetoxy-3-oxoandrosta-4,6-dien-17α-yl)propionate

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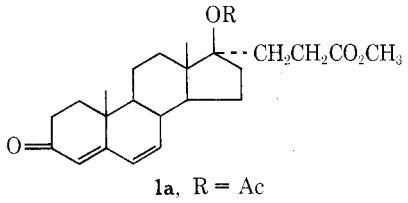
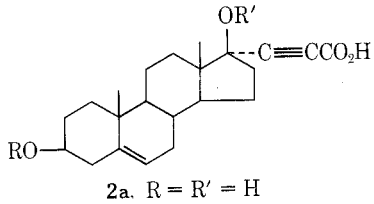
3-(3β,17β-Diacetoxyandrost-5-en-17α-yl)propiolic acid (**2b**) decomposes on prolonged standing or when treated with dilute acetic acid to afford 3β,17β-diacetoxy-17α-pregn-5-en-20-one (**9**). The facility with which this conversion is achieved suggests the participation of the neighboring acetoxy group in the transformation. Two processes were investigated for the synthesis of the title compound (**1a**). One involved acetylating **1b** with acetyl chloride and stannic chloride at low temperature. The other began with the diol propiolic acid **2a**. Successive methylation, acetylation, hydrogenation, selective hydrolysis, oxidation, and dehydrogenation converted **2a** into **1a**.

As part of an effort to determine the structural features which are essential for antimineralocorticoid activity, methyl 3-(17β-acetoxy-3-oxoandrosta-4,6-dien-17α-yl)propionate (**1a**) was prepared and tested. Two processes were investigated for the synthesis of this compound. The first made use of an observation that a 17β-hydroxy steroid with a 17α-alkynyl substituent is less likely to undergo elimination to generate a carbocation at C-17 than one in which the substituent at the 17α position is an alkyl group.[1]



1a, R = Ac
b, R = H

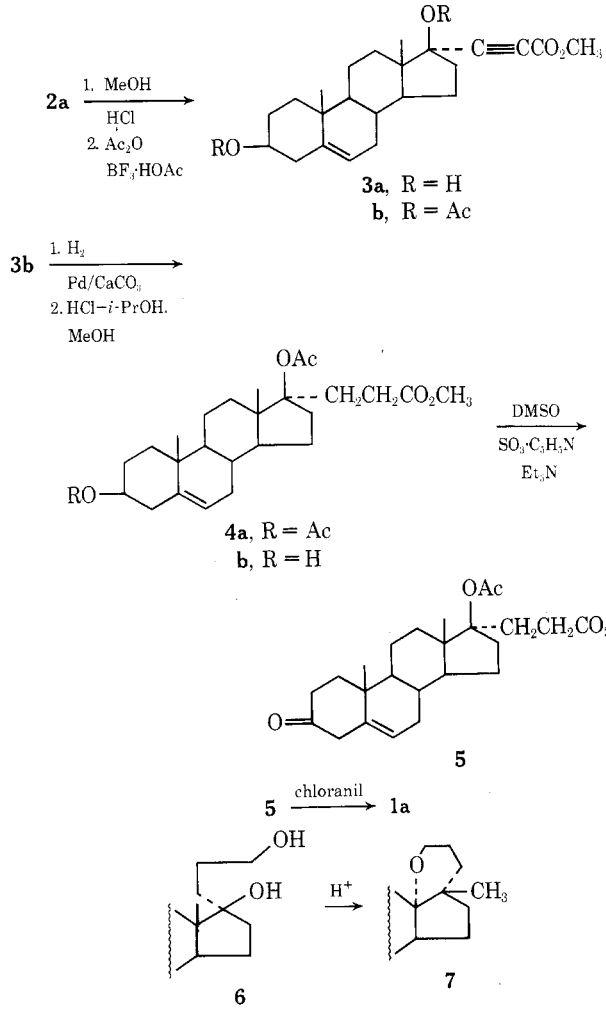


2a, R = R′ = H
b, R = R′ = Ac

The starting compound, the propiolic acid **2a**,[2] was converted into the methyl ester **3a** with methanol and hydrochloric acid. Acetylation of **3a** with acetic anhydride in the presence of boron trifluoride in acetic acid gave in good yield the diacetate **3b**.[3] Hydrogenation of the triple bond was accomplished over palladium on calcium carbonate. Although three ester groups are present in **4a**, selective hydrolysis of the C-3 acetoxy group was achieved with hydrogen chloride in methanol. Oxidation of the resultant product **4b** with dimethyl sulfoxide in the presence of sulfur trioxide–pyridine and triethylamine[4] gave predominantly the β,γ-unsaturated ketone **5**. The uv spectrum of the product indicated that the conjugated ketone was present, but in less than 10% amount. Earlier, Turner had shown that a β,γ-unsaturated ketone undergoes ready dehydrogenation with a high potential quinone to afford a linear dienone system.[5] When **5** was treated with chloranil, the desired product **1a** was, indeed, obtained. Chloranil was used instead of dichlorodicyanobenzoquinone in the present instance in order to minimize the possibility of further dehydrogenation at the 1,2 position.[5]

The alternate synthesis of **1a** involved finding conditions which would minimize dehydration and/or rearrangement. The diol **6** is known to undergo a Wagner–Meerwein rearrangement to afford, inter alia, the ether **7** in an acid medium.[6] Hence, several attempts were made to acetylate methyl 3-(17β-hydroxy-3-oxoandrosta-4,6-dien-17α-yl)propionate (**1b**) under basic conditions, but without success. The starting methyl ester **1b** was obtained from the spirolactone 8[2] by treatment with potassium hydroxide followed by alkylation of the resultant salt with methyl iodide in dimethylformamide.[7] Acetylation of **1b** with a mixture of acetic anhydride, triethylamine, and 4-dimethylaminopyridine[8] resulted mainly in the regeneration of the lactone **8**.

At the suggestion of Dr. Dryden, acetylation of **1b** with acetyl chloride and stannic chloride at low temperature was tried. When the reaction was allowed to proceed in dichloromethane at −40° for 20 min, the desired product **1a** was obtained in 47% yield. The principal by-product proved to be the spirolactone **8**.



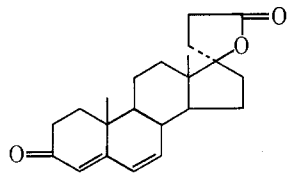
3a, R = H
b, R = Ac

4a, R = Ac
b, R = H

5

6

7



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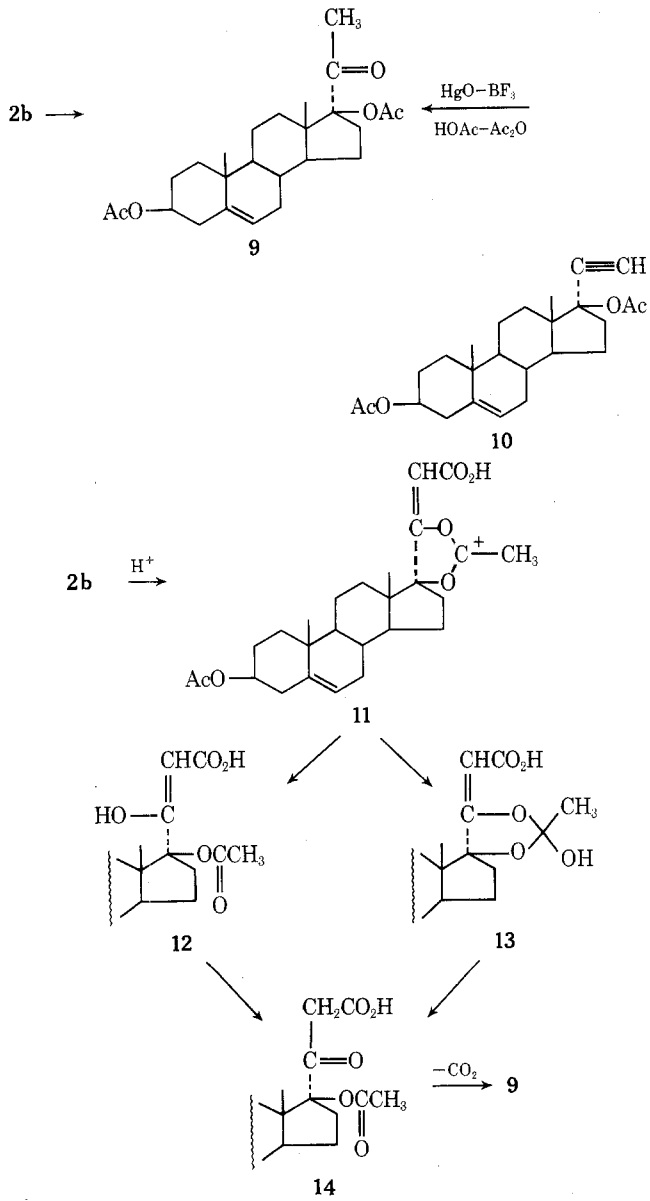
Of the two procedures which afforded **1a,** the one involving acetylation of **1b** with acetyl chloride and stannic chloride furnished the purer product. The uv absorption maximum (282 nm) of **1a** prepared in this manner has a molecular extinction coefficient (ϵ) of 25,800. The corresponding value for **1a** prepared by the other procedure is 22,590. A contaminant in the latter appears to be the 3-keto Δ^4-steroid, judging from the extent of the uv absorption at 240 nm and the appearance of faint signals at 70.5 and 53.5 Hz in the NMR spectrum of **1a** derived from the chloranil dehydrogenation of the β,γ-unsaturated ketone **5.** When tested in the standard antimineralocorticoid test,[2] **1a** failed to block the mineralocorticoid effect of deoxycorticosterone acetate at the screening dose of 2.4 mg.

Interestingly, while the diol propiolic acid **2a** is a stable substance, the diacetate **2b** decomposed on prolonged standing. The product obtained after chromatography on silica gel proved to be 3β,17β-dihydroxy-17α-pregn-5-en-20-one 3,17-diacetate (**9**).[9a] The product was identical with a sample prepared by the mercuric oxide–boron trifluoride-catalyzed hydration[9b] of 3β,17β-dihydroxy-17α-pregn-5-en-20-yne 3,17-diacetate (**10**).



When **2b** was heated in dilute acetic acid, it was converted mainly into **9.** The presence of **9** in the reaction mixture was established not only by TLC and GLC, but also by isolation of the product and comparison with an authentic sample. The diol acid **2a** was recovered unchanged when similarly treated.

The conversion of **2b** to **9** appears to be facilitated by the presence of the acetoxy group at C-17. A priori the inductive effect of the acetoxy group is expected to retard hydration of the propiolic acid triple bond. However, in solvolytic studies it has been shown that a neighboring acetoxy group has a rate-enhancing effect. This has been attributed to anchimeric assistance involving the formation of a quasicyclic intermediate.[10a–c] Conceivably, this phenomenon occurs also in the protonation of the α-carbon atom of the propiolic acid, a step which has been shown to be rate determining in the acid-catalyzed hydration of certain substituted propiolic acids.[11] The participation of a neighboring acetoxy group in an electrophilic attack on a triple bond is not unprecedented, as such a process has been postulated in the addition of difluorocarbene to ethynyl carbinol acetates.[12]

In the transformation of **2b** to **9,** protonation of the α carbon is likely to be facilitated by the participation of the neighboring acetoxy group to furnish **11.** Solvolysis of **11** either at C-20 or at the carbocation affords, respectively, **12** and **13.** Both species can isomerize to the β-keto acid **14.** Decarboxylation of **14** will then yield **9.**

Experimental Section

Melting points were determined on a Fisher-Johns melting block and are uncorrected. NMR spectra were obtained on a Varian A-60 spectrometer using tetramethylsilane as an internal standard. Unless specified otherwise, optical rotations were determined in chloroform.

3-(3β,17β-Diacetoxyandrost-5-en-17α-yl)propiolic Acid (2b). A mixture of 2.0 g (5.58 mmol) of 3-(3β,17β-dihydroxyandrost-5-en-17α-yl)propiolic acid (**2a**),[2] 60 ml of isopropenyl acetate, and 200 mg of *p*-toluenesulfonic acid monohydrate was subjected to slow distillation over a period of 1.5 hr. After 200 mg of NaOAc was added, the reaction mixture was concentrated by distillation under reduced pressure. The residue was diluted with a large volume of water, and the mixture was extracted with ethyl acetate. The ethyl acetate extract was washed with water, treated with Darco, dried over Na_2SO_4, and distilled to dryness under reduced pressure. The residual oil was treated with 100 ml of 5% $NaHCO_3$ and heated until complete solution was achieved. The solution was cooled in an ice bath, whereupon the sodium salt of **2b** began to crystallize. The salt was collected and dried: ir (KBr) 3470 (H_2O), 1745, 1617 cm^{-1}; NMR (CD_3OD) 325 (br, 1, 6-H), 283 (s, CD_3OH, H_2O), 120 (s, 6, OAc), 64 (s, 3, 19-CH_3), 55.5 Hz (s, 3, 18-CH_3).

Anal. Calcd for $C_{26}H_{33}O_6Na \cdot 2H_2O$: C, 62.38; H, 7.45. Found: C, 62.69; H, 7.07.

The preparation was repeated starting with 20 g (55.8 mmol) of **2a** and a proportionately larger quantity of reagents. The salt, however, was not isolated. Instead, the mixture containing the salt was acidified with 6 *N* HCl. The resultant solid, **2b,** was collected, washed well with water, and dried: yield 23 g (93%); mp 104–108°; ir (KBr) 3200, 2217, 1740 cm^{-1}; NMR ($CDCl_3$) 325 (br, 1, 6-H), 124, 122.5 (s, s, 6, OAc), 62.5 (s, 3, 19-CH_3), 53 Hz (s, 3, 18-CH_3).

Anal. Calcd for $C_{26}H_{34}O_6$: C, 70.56; H, 7.74. Found: C, 70.12; H, 7.73.

3β,17β-Diacetoxy-17α-pregn-5-en-20-one (9). A. After standing for ca. 1 year, a bottle of **2b** was found to have undergone considerable decomposition. A 2.0-g sample was chromatographed on 200 g of silica gel. Elution with 5% ethyl acetate in benzene gave 1.1 g of a solid which was crystallized from ethyl acetate–hexane to yield 0.9 g of **9,** mp 191–194°, $[\alpha]^{25}D$ −54° (*c* 1.0, dioxane) (lit.[9a] mp 194–195°, $[\alpha]D$ −54°). Admixture with an authentic sample of

9, prepared as described in the literature,[9a,b] resulted in no depression of the melting point. The ir spectra of the two samples were identical.

B. A 1.2-g (2.8 mmol) sample of freshly prepared **2b** was dissolved in 50 ml of glacial acetic acid and 50 ml of water. The reaction mixture was heated under reflux for 40 min. TLC showed the absence of starting material. The cooled mixture was distilled nearly to dryness under reduced pressure. The resultant mixture was extracted with chloroform. The chloroform extract was washed successively with 5% $NaHCO_3$ and water, dried over $MgSO_4$, and evaporated to dryness to afford 0.95 g of a solid. TLC indicated that the major component of the residue had the same R_f value as **9**. GLC revealed that it had an identical retention time with that of **9** and that it comprised 76.5% of the residue. The solid was chromatographed on silica gel to afford 0.65 g (56%) of **9**: mp 191–193°; NMR ($CDCl_3$) 326 (br, 1, 6-H), 127.5, 124.5, 122 (s, s, s, 9, $-COCH_3$ and $-OAc$), 62.5 Hz (s, 6, 18-CH_3, 19-CH_3); ir ($CHCl_3$) 1740, 1375, 1260, 1045 cm^{-1}. The NMR and ir spectra were identical with those of an authentic sample of **9**.

Attempted Solvolysis of 3-(3β,17β-Dihydroxyandrost-5-en-17α-yl)propiolic Acid (2a). A 120-mg (0.34 mmol) sample of **2a** in 30 ml of glacial acetic acid and 20 ml of water was heated under reflux for 40 min. The cooled reaction mixture was poured into a large volume of water. The solid product was collected by filtration, washed with water, and dried, yield 109 mg (91%), mp 228–233° (lit.[2] mp 234–235° dec). The melting point was undepressed when the product was admixed with the starting acid **2a**. The ir spectra of the two samples were identical.

Methyl 3-(3β,17β-Dihydroxyandrost-5-en-17α-yl)propiolate (3a). A mixture of 20.0 g (55.8 mmol) of 3-(3β,17β-dihydroxyandrost-5-en-17α-yl)propiolic acid (**2a**), 150 ml of methanol, and 2 ml of aqueous 12 *N* HCl was heated under reflux in an atmosphere of N_2 for 3.5 hr, during which time a crystalline product formed. The reaction mixture was cooled to room temperature, and the crystalline ester **3a** was collected and dried: yield 18.8 g (90.5%); mp 236–240°; $[\alpha]^{25}D$ −133° (*c* 1.0, dioxane); ir (KBr) 3490, 3380, 2230, 1705 cm^{-1}; NMR ($CDCl_3$) 324 (br, 1, 6-H), 228 (s, 3, CO_2CH_3), 62.5 (s, 3, 19-CH_3), 54 Hz (s, 3, 18-CH_3).

Anal. Calcd for $C_{23}H_{32}O_4$: C, 74.16; H, 8.66. Found: C, 74.06; H, 8.65.

Methyl 3-(3β,17β-Diacetoxyandrost-5-en-17α-yl)propiolate (3b). A mixture of 10.0 g (26.84 mmol) of **3a**, 200 ml of glacial acetic acid, 50 ml of acetic anhydride, and 3 ml of the $BF_3 \cdot 2HOAc$ complex was allowed to stand at room temperature for 20 hr. The reaction mixture was diluted with water and then extracted with ether. The ether extract was washed successively with 5% Na_2CO_3 and water, dried over $MgSO_4$, and distilled to dryness under reduced pressure. The residual oil was stirred with water for 2 hr, when a crystalline product formed. The solid was collected and dried. Crystallization from hexane afforded 10.8 g (88%) of **3b**: mp 118–120°; $[\alpha]^{25}D$ −113° (*c* 1.0); ir (KBr) 2230, 1752, 1737, 1715, 1678 cm^{-1}; NMR ($CDCl_3$) 324 (br, 1, 6-H), 275 (br, 1, 3-H), 226 (s, 3, CO_2CH_3), 123, 121 (s, s, 6, OAc), 62.5 (s, 3, 19-CH_3), 54 Hz (s, 3, 18-CH_3).

Anal. Calcd for $C_{27}H_{36}O_6$: C, 71.02; H, 7.95. Found: C, 71.26; H, 8.02.

Methyl 3-(3β,17β-Diacetoxyandrost-5-en-17α-yl)-propionate (4a). A solution of 5.0 g (10.9 mmol) of **3b** in 300 ml of methanol was hydrogenated over 438 mg of 5% palladium on calcium carbonate at atmospheric pressure and room temperature. After the calculated amount of hydrogen was absorbed in 3 hr, the catalyst was removed by filtration. The filtrate was distilled to dryness under reduced pressure to afford an oily residue, which was chromatographed on 100 g of silica gel. Elution with 2% ethyl acetate in benzene afforded an oil. The oil was crystallized from hexane to yield 3.25 g (64.5%) of **4a**: mp 85–87°; $[\alpha]^{25}D$ −78° (*c* 0.98); ir (KBr) 1743 cm^{-1}; NMR ($CDCl_3$) 325 (br, 1, 6-H), 280 (br, 1, 3-H), 219 (s, 3, CO_2CH_3), 120.5, 118.5 (s, s, 6, OAc), 61.5 (s, 3, 19-CH_3), 50 Hz (s, 3, 18-CH_3).

Anal. Calcd for $C_{27}H_{40}O_6$: C, 70.40; H, 8.75. Found: C, 70.34; H, 8.84.

Methyl 3-(17β-Acetoxy-3β-hydroxyandrost-5-en-17α-yl)-propionate (4b). A mixture of 2.0 g (4.34 mmol) of **4a**, 20 ml of methanol, and 2 ml of an isopropyl alcohol solution of HCl (0.273 g/ml) was stirred at room temperature for 3 hr. The reaction mixture was then cooled in an ice bath, whereupon **4b** crystallized from the solution. The product was collected: yield 1.2 g (66%); mp 142–146° $[\alpha]^{25}D$ −90° (*c* 0.4); ir (KBr) 3545, 1735 cm^{-1}; NMR ($CDCl_3$) 323 (br, 1, 6-H), 219.5 (s, 3, CO_2CH_3), 210 (br, 1, 3-H), 119.5 (s, 3, 17-OAc), 61 (s, 3, 19-CH_3), 50 Hz (s, 3, 18-CH_3) Hz.

Anal. Calcd for $C_{25}H_{38}O_5$: C, 71.74; H, 9.15. Found: C, 71.45; H, 9.11.

Methyl 3-(17β-Acetoxy-3-oxoandrost-5-en-17α-yl)propionate (5). To a mixture of 10.0 g (23.89 mmol) of **4b** in 100 ml of dimethyl sulfoxide were added in succession 50 ml of triethylamine and a solution of 20 g of the sulfur trioxide–pyridine complex[4] in 100 ml of dimethyl sulfoxide. The reaction mixture was stirred under N_2 for 0.5 hr and then poured into a large volume of ice water. The resultant precipitate **5** was collected, washed with water, and dried: yield 9.1 g (91.5%); mp 127–131°; ir (KBr) 1749, 1735, 1722, 1680 cm^{-1}; NMR ($CDCl_3$) 320 (br, 1, 6-H), 219.5 (s, 3, CO_2CH_3), 120 (s, 3, 17-OAc), 71 (s, 3, 19-CH_3), 51.5 Hz (s, 3, 18-CH_3). The product showed slight uv absorption at 240 nm (ε 1460).

Methyl 3-(17β-Acetoxy-3-oxoandrosta-4,6-dien-17α-yl)propionate (1a). A. A mixture of 4.0 g (9.6 mmol) of **5**, 500 ml of *tert*-butyl alcohol, and 12.0 g (48 mmol) of chloranil was heated under reflux for 24 hr in a N_2 atmosphere. The reaction mixture was coooled to room temperature. The precipitate was removed by filtration, and the filtrate was distilled to dryness under reduced pressure. The residual oil was extracted with ethyl acetate. The ethyl acetate extract was washed successively with water, 5% KOH, and water again. It was then dried over $MgSO_4$ and distilled nearly to dryness under reduced pressure. The semisolid residue was crystallized first from ethyl acetate–ether and then from methanol to afford 2.2 g (55%) of **1a**: mp 184–187°; uv max (MeOH) 282 nm (ε 22,590); ϵ_{240} 4165; ir (KBr) 1745, 1735, 1673, 1623, 1591 cm^{-1}; NMR ($CDCl_3$) 368 (s, 6-H, 7-H), 341.5 (s, 1, 4-H), 221 (s, 3, CO_2CH_3), 121.5 (s, 3, 17-OAc), 68 (s, 3, 19-CH_3), 55.5 Hz (s, 3, 18-CH_3). The NMR spectrum also displayed weak signals at 70.5 and 53.5 Hz.

B. To a mixture of 7.7 ml of stannic chloride and 40 ml of dichloromethane, stirred at −13°, was added dropwise a solution of 17 ml (238 mmol) of acetyl chloride in 40 ml of dichloromethane. The resultant solution was then cooled to −44°, following which a solution of 24.9 g (67 mmol) of **1b** (vide infra) in 300 ml of dichloromethane was added over a period of 12 min. The reaction mixture was stirred at −40° for 8 min. A solution of 50 g of potassium sodium tartrate and 50 g of $KHCO_3$ in 500 ml of water was carefully added. The reaction mixture was stirred for 1 hr at −5 to 9°. The organic phase was separated, washed successively with 10% $KHCO_3$ and water, dried over Na_2SO_4, and distilled nearly to dryness under reduced pressure. The solid residue was triturated with 25 ml of hot methanol. The solid was collected by filtration and washed with a mixture of isopropyl ether and methanol. It was dissolved in 700 ml of hot methanol. The solution was concentrated until crystallization ensued. The crystalline ester **1a** was collected, washed with isopropyl ether–methanol, and dried: yield 13.1 g (47%); mp 193–194°; $[\alpha]^{25}D$ −27.6° (*c* 1.0); uv max (MeOH) 282 nm (ε 25,800); ϵ_{240} 3520. Except for the absence of the signals at 70.5 and 53.5 Hz, the NMR spectrum of **1a** thus prepared was identical with that of the sample of **1a** prepared by the preceding procedure.

Anal. Calcd for $C_{25}H_{34}O_5$: C, 72.43; H, 8.27. Found: C, 72.45; H, 8.33.

The methanol trituration solution was concentrated. The residue was diluted with isopropyl ether to afford 3.4 g (15%) of 3-(17β-hydroxy-3-oxoandrosta-4,6-dien-17α-yl)propionic acid γ-lactone (**8**) whose NMR spectrum was identical with that of an authentic sample of **8**.[2]

Methyl 3-(17β-Hydroxy-3-oxoandrosta-4,6-dien-17α-yl)propionate (1b). A mixture of 1 kg (2.94 mol) of 3-(17β-hydroxy-3-oxoandrosta-4,6-dien-17α-yl)propionic acid γ-lactone (**8**),[2] 10 l. of methanol, and 0.7 l. of 4.0 *N* methanolic potassium hydroxide was heated under reflux for 50 min. The mixture was then filtered, and the filtrate was concentrated to 1 l. by distillation at atmospheric pressure. The residue was diluted with 6 l. of ethyl acetate. The resultant mixture was concentrated to 100 ml by distillation under reduced pressure. The residue was diluted with a fresh portion of ethyl acetate. The solid potassium salt was collected by filtration, washed with ethyl acetate, and dried.

A 198-g (0.5 mol) sample of the salt was combined with 142 g (1.0 mol) of methyl iodide in 1 l. of dimethylformamide.[7] The reaction mixture was allowed to stand at room temperature for 21 hr, after which it was poured into 5 l. of ice water. The resultant precipitate was collected by filtration and washed with water. The wet solid was dissolved in 1.3 l. of tetrahydrofuran. After 250 ml of hexane was added, the resultant solution was washed successively with 5% potassium bicarbonate and water. The solution was then dried over Na_2SO_4. Removal of the solvents by distillation under reduced pressure gave an oil which was thrice crystallized from isopropyl acetate to afford 112.6 g (61%) of **1b**: mp 144–145.5°; ir

($CHCl_3$) 1734, 1658 cm^{-1}; NMR ($CDCl_3$) 367 (s, 2, 6-H, 7-H), 340.5 (s, 1, 4-H), 221.5 (s, 3, CO_2CH_3), 68 (s, 3, 19-CH_3), 58.5 Hz (s, 3, 18-CH_3).

Anal. Calcd for $C_{23}H_{32}O_4$: C, 74.16; H, 8.66. Found: C, 74.26; H, 8.82.

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Registry No.—**1a**, 54498-03-2; **1b**, 54498-04-3; **2a**, 3460-93-3; **2b**, 54516-82-4; **2b** sodium salt, 54498-05-4; **3a**, 54498-06-5; **3b**, 54498-07-6; **4a**, 54498-08-7; **4b**, 54498-09-8; **5**, 54498-10-1; **8**, 976-71-6; **9**, 1176-21-2.

References and Notes

(1) J. H. Dygos and L. J. Chinn, *J. Org. Chem.*, **38**, 4319 (1973).
(2) J. A. Cella, E. A. Brown, and R. R. Burtner, *J. Org. Chem.*, **24**, 743 (1959).
(3) We are grateful to Dr. Walter R. Benn for providing us with the acetylation procedure. See also ref 9b.
(4) J. R. Parikh and W. von E. Doering, *J. Am. Chem. Soc.*, **89**, 5505 (1967).
(5) A. B. Turner, *J. Chem. Soc. C*, 2568 (1968).
(6) E. A. Brown, *J. Med. Chem.*, **10**, 546 (1967).
(7) A. J. Parker, *Adv. Org. Chem.*, **5**, 36 (1965).
(8) W. Steglich and G. Höfle, *Angew. Chem., Int. Ed. Engl.*, **8**, 981 (1969).
(9) (a) M. W. Goldberg, R. Aeschbacher, and E. Hardegger, *Helv. Chim. Acta*, **26**, 680 (1943); (b) C. W. Shoppee, *ibid.*, **27**, 8 (1944). The configuration at C-17 of the compounds described in these publications was incorrectly assigned because of the erroneous assumption that ethynylation of a 17-keto steroid proceeded stereoselectively from the β side of the molecule.
(10) (a) S. Winstein, H. V. Hess, and R. E. Buckles, *J. Am. Chem. Soc.*, **64**, 2796 (1942); (b) S. Winstein, C. R. Lindergren, H. Marshall, and L. L. Ingraham, *ibid.*, **75**, 147 (1953); (c) Ö. K. J. Kovács, G. Schneider, L. K. Láng, and J. Apjok, *Tetrahedron*, **23**, 4186 (1967), and references cited therein.
(11) D. S. Noyce, M. A. Matesich, and P. E. Peterson, *J. Am. Chem. Soc.*, **89**, 6225 (1967).
(12) E. Velarde, P. Crabbé, A. Christensen, L. Tökés, J. W. Murphy, and J. H. Fried, *Chem. Commun.*, 725 (1970).

Photolysis of Some Carbohydrate Dithiobis(thioformates)[1a]

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The photolysis of several oxidatively coupled xanthates of model sugar compounds has been investigated. The photolysis of bis(1,2:3,4-di-*O*-isopropylidene-α-D-galactopyranos-6-yl)dithiobis(thioformate) (**2**) gave the xanthate ester, bis(6-deoxy-1,2:3,4-di-*O*-isopropylidene-α-D-galactopyranos-6-yl) 6-*O*,6′-*S*-dithiocarbonate (**5**), in 78% yield. In concentrated solutions, bis(1,2:3,4-di-*O*-isopropylidene-α-D-galactopyranos-6-yl) tetrathiobis(thioformate) (**3**) was produced along with **5**. The photolysis of bis(1,2:5,6-di-*O*-isopropylidene-α-D-glucofuranos-3-yl) dithiobis(thioformate) (**14**) gave bis(3-deoxy-1,2:5,6-di-*O*-isopropylidene-α-D-glucofuranos-3-yl) 3-*O*,3′-*S*-dithiocarbonate (**15**), in which an oxygen atom on the sugar ring has been replaced with sulfur with retention of configuration. A cyclic mechanism in which either the excited thiocarbonyl sulfur or a sulfur of the disulfide linkage attacks the carbon giving a front-side displacement of oxygen has been proposed to account for the observed results.

The relatively high efficiency with which sulfur compounds absorb light, especially compounds which contain the thiocarbonyl group, has resulted in a large number of reports on the photochemistry of organic sulfur compounds.[2-4] The xanthate group [λ_{max} (H_2O) 305 nm (ϵ 12,000–17,000)] and derivatives thereof exhibit a very strong absorbance of uv light and, therefore, have the potential of photochemical transformations by direct irradiation. The photolyses of some xanthate esters have been reported. Okawara and coworkers subjected *O*-ethyl *S*-benzyl xanthate to uv irradiation and found benzyl mercaptan and carbonyl sulfide as major products, which were obtained in low yields.[5-7] When styrene or methyl methacrylate was added to the reaction mixture, polymerization occurred, indicating a free-radical mechanism for the photodecomposition of the xanthate ester. Photolysis of *O*-benzyl *S*-methyl xanthate in the presence of cyclohexene gave methyl mercaptan, carbonyl sulfide, 3-benzylcyclohexene, and 3-(2-cyclohexene-1-yl)cyclohexene (**1**). The xanthate ester, *O*-diphenylmethyl *S*-methyl xanthate, gave 1,1,2,2-tetraphenylethane and **1**. The results suggested the formation of a carbene intermediate. In ethanol no decomposition of *O*-benzyl *S*-methyl xanthate occurred. However, addition of triethylamine gave methyl benzyl thioether, *S*-benzyl ethyl thiocarbonate, dibenzyl thioether, and dibenzyl disulfide.[8]

Acyl xanthate esters have been photolyzed and produced acyl radicals and xanthate radicals.[9] The acyl radical then loses carbon monoxide, and a recombination reaction occurs between the new alkyl radical and the xanthate radical to give a xanthate ester which is stable to Pyrex-filtered light. Shah, Singh, and George[10,11] observed that the photolytic decomposition of a dixanthate gave a mixture of dimeric compounds which appeared to be formed from a carbene intermediate. Another similar xanthate ester was prepared by Schonberg and Sodtke[12] and was photolyzed to produce a coupled product.

Xanthates have been used as photoinitiators in polymerization reactions[5,7,13-16] and incorporated in polymers for grafting sites.[15,16]

We have previously reported on the ground-state chemistry of the oxidatively coupled xanthate, dithiobis(thioformate), which is also called xanthide.[17]

Because of the strong absorption of light by the xanthide group [λ_{max} (EtOH) 230–240 nm (ϵ 15,800–18,900), 280–290 (6600–8900)],[18] the photoreactivity of xanthate derivatives,