Steroidal Adducts. II.[1] Stereoselectivity in γ-Lactone Synthesis from a Steroidal Cyclic Anhydride

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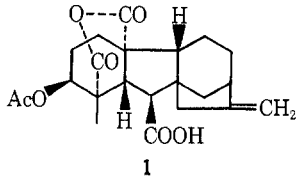
Reduction of the Inhoffen adduct **3** of ergosteryl acetate and maleic anhydride by sodium borohydride or lithium aluminum hydride gives a γ-lactone arising from reduction of the more hindered carbonyl group. Lithium tri-*t*-butoxyaluminohydride also attacks the more hindered carbonyl group but, unexpectedly, gives a lactol. These reactions are rationalized in terms of initial formation of an intramolecular complex between the less hindered anhydride carbonyl group, the C-3 acetate carbonyl group, and the cation of the reducing agent.

A potentially useful synthetic route to the γ-lactone function, present in many important polycyclic natural products, involves reduction of the cyclic anhydrides available from Diels–Alder reactions employing maleic anhydride as dienophile. Recent publications[2-6] have described the use of sodium borohydride, lithium aluminum hydride, and lithium tri-*t*-butoxyaluminohydride for this reduction, but the steric course of the reactions, in cases where two different lactones are possible, is still in question.

Bloomfield and Lee[2] found that in general the more sterically hindered of the two anhydride carbonyl groups is reduced preferentially, although from some simple substituted succinic anhydrides both possible lactones were obtained.[2,7] Cross and Stewart,[3] however, found that the six-membered-ring anhydride **1** with lithium aluminum hydride gave the δ-lactone **2**, the reduction in this case involving the less hindered anhydride carbonyl.



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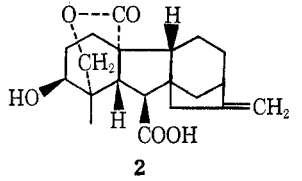

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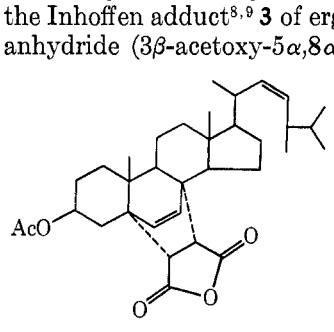
An interesting substrate to investigate the stereoselectivity of these hydride reductions appeared to be the Inhoffen adduct[8,9] **3** of ergosteryl acetate and maleic anhydride (3β-acetoxy-5α,8α-ethanoergosta-6,22-diene-1′β,2′β-dicarboxylic acid anhydride). The ring structure of this compound is highly rigid; the anhydride carbonyl groups differ only slightly from each other in steric accessibility. Treatment of the adduct **3** with sodium borohydride in dioxane at 95° for 2.5 hr[6] gave, in 30% yield, a compound, $C_{34}H_{50}O_4$ (**4**). That this is an acetoxy-γ-lactone was indicated by the ir spectrum (ν_{max} 1763, 1712 cm^{-1}) and by its further reduction with lithium aluminum hydride in dioxane at 95° to a triol **7**, $C_{32}H_{52}O_3$. Chromatography failed to show any other lactonic material. Only traces of other compounds, whose ir spectra lacked carbonyl absorption, were isolated. The acetoxy-γ-lactone is assigned the structure **4**, in which the *more* hindered of the two anhydride carbonyl groups of **3** has been reduced. In the nmr spectrum, the vinyl protons at C-6 and C-7 give an AB quartet at τ 3.88 and 4.37 (J_{AB} = 5 Hz). The C-3′ protons give complex signals at 5.86 and 6.28, the C-2′ proton, deshielded by the lactone carbonyl group, a multiplet signal at 6.91, and the C-1′ proton a doublet (J = 5 Hz) at 7.61. This last signal is superimposed on the C-4α proton signal[10] at τ 7.5. The acetate methyl signal falls at τ 8.03, and the three-proton singlets from C-18 and C-19 at 9.32 and 9.01, respectively. The structure **4**, rather than the isomeric structure **8**, was assigned on the basis of the moderately strong negative Cotton effect displayed in the ORD curve ($[\phi]_{MeOH}$ −2200° at 220 mμ, the first extreme; λ_0 was observed at 210 mμ). A negative Cotton effect would be predicted for structure **4**, but a positive one for the



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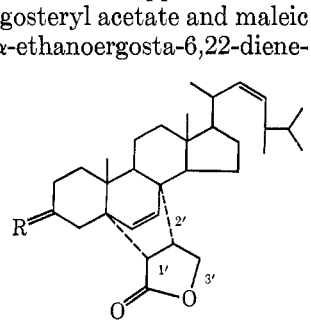
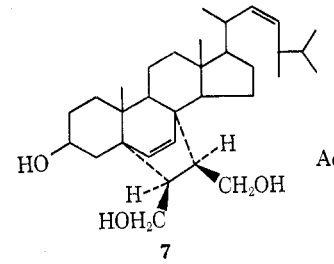


4, R = β-$OCOCH_3$, α-H
5, R = β-OH, α-H
6, R = =O



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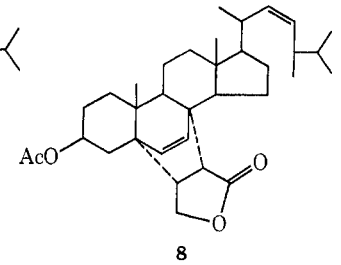

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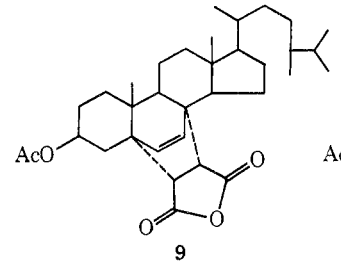

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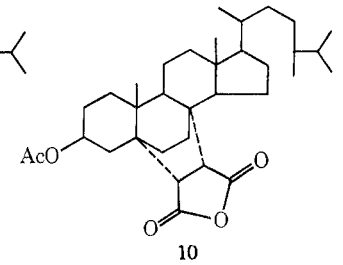

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(1) The paper by A. M. Lautzenheiser and P. W. Le Quesne, *Tetrahedron Lett.*, 207 (1969), is regarded as part I in this series.

(2) J. J. Bloomfield and S. L. Lee, *J. Org. Chem.*, **32**, 3919 (1967).

(3) B. E. Cross and J. C. Stewart, *Tetrahedron Lett.*, 3589 (1968).

(4) H. C. Brown, P. M. Weissman, and N. M. Yoon, *J. Amer. Chem. Soc.*, **88**, 1458 (1966).

(5) H. C. Brown and N. M. Yoon. *ibid.* **88**, 1464 (1966).

(6) N. Langlois and B. Gastambide, *C. R. H. Acad. Sci., Ser. C*, **264**, 1878 (1967).

(7) R. Granger and H. Techer, *C. R. H. Acad. Sci.*, **250**, 142 (1960).

(8) H. H. Inhoffen, *Ann. Chem.*, **508**, 81 (1934).

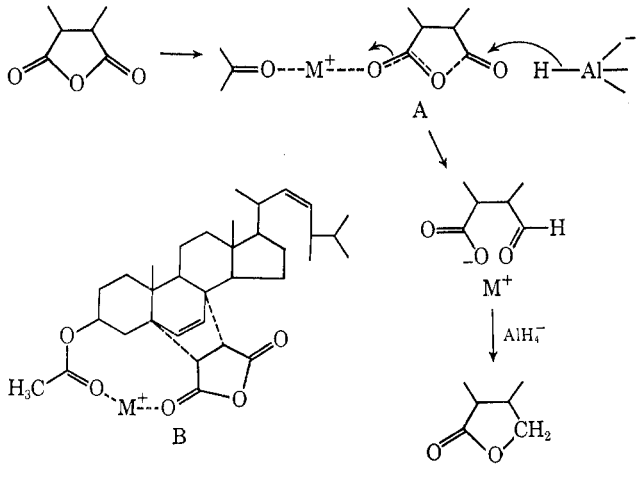
(9) D. N. Jones, P. F. Greenhalgh, and I. Thomas, *Tetrahedron*, **24**, 297 (1968).

(10) *Cf.* A. van der Gen, W. A. Zunnebeld, U. K. Pandit and H. O. Huisman *ibid.*, **21**, 3651 (1965).

isomer **8**.[11] Some confirmation for the structure **4** was found in a comparison of the chemical shifts of the C-18 methyl group of this compound with those observed in the Inhoffen adduct **3**, and its dihydro derivative **9** and tetrahydro derivative **10**. In these three anhydrides, the C-18 signals fall at τ 9.26, 9.25, and 9.24, respectively.[9] In the lactone **4**, however, this signal is found at 9.32. This increased shielding is to be expected for a structure in which the anhydride carbonyl group nearer C-18 in the adduct **3** has been reduced. The other carbonyl group in **3** would be prevented by the etheno bridge from affecting the chemical shift of C-18. Further, hydrolysis of the acetoxy-γ-lactone **4** gave the hydroxy-γ-lactone **5**, $C_{32}H_{48}O_3$, which on oxidation with Jones reagent[12] gave the keto-γ-lactone **6**, $C_{32}H_{46}O_3$. The nmr spectrum of this compound showed, in particular, the C-1′ doublet signal at τ 7.11 (J = 5 Hz). This chemical shift, downfield 0.50 ppm from the equivalent signal in **4**, again supports the structure **4** rather than **8** for the hydride reduction product, since in **6** C-1′ is strongly under the deshielding influence of the 3-keto group.

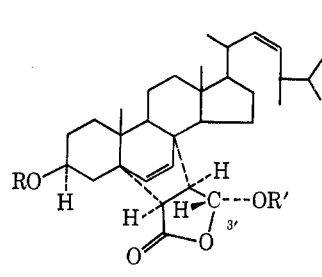
Treatment of the Inhoffen adduct **3** with lithium aluminum hydride in tetrahydrofuran at −55°[3] also gave the acetoxy-γ-lactone **4** in 40% yield. Again no other lactonic material was obtained.

These results may be interpreted in terms of the general mechanism below, proposed by Bloomfield and Lee[2] to account for the preferential reduction of the more hindered carbonyl group of cyclic anhydrides.

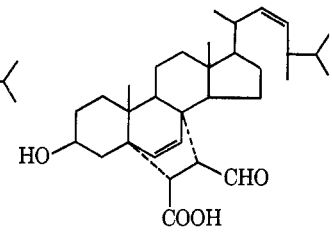


In this mechanism the less hindered carbonyl group complexes with the reagent cation and a carbonyl group from a second mole of substrate. The resulting bulky solvated complex A is then attacked by hydride at the other carbonyl. Dreiding models of the Inhoffen adduct **3** suggest that each anhydride carbonyl group could probably participate equally well in a bimolecular complex with a reagent cation. However, the acetate carbonyl group at C-3 appears from models to be able to participate readily with the less hindered anhydride carbonyl of **3** and a reagent cation in an intramolecular complex B. Reduction of this species would then take place preferentially at the anhydride carbonyl more remote from C-3, to give the acetoxy-γ-lactone **4**. The authors suggest that this may account for the stereoselectivity observed in these reactions.

Brown and coworkers[4,5] have described the reduction of cyclic anhydrides to lactones with lithium tri-*t*-butoxyaluminohydride, but as yet no work has been reported on the steric course of the reaction where two lactones are possible. It would be expected that any tendency toward reduction at the less hindered carbonyl group would be reflected in the results obtained with this reagent. Treatment of the Inhoffen adduct **3** with the reagent in tetrahydrofuran at 0° gave a single compound, $C_{34}H_{50}O_5$, isolated in 73% yield. No other products were detected chromatographically. The ir spectrum indicated the presence of a γ-lactone, an acetoxyl, and a hydroxyl function, in accord with which the compound readily gave an acetate, $C_{36}H_{52}O_6$, and a benzoate, $C_{41}H_{54}O_6$. These compounds are assigned the structures **11**, **12**, and **13**, respectively.



11, R = −COCH$_3$; R′ = −H
12, R = R′ = −COCH$_3$
13, R = −COCH$_3$; R′ = −COPh



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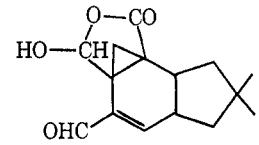

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The lactol structure **11** for the reduction product was established by its smooth reduction with sodium borohydride[13] to the lactone **4** in 82% yield, and by the nmr spectrum, which clearly established the stereochemistry shown. An AB quartet at τ 3.93 and 4.43 (J_{AB} = 4 Hz) arises from the etheno bridge. A one-proton doublet at τ 4.77 (J = 1 Hz) is ascribed to the β-oriented 3′ proton of the hemiacetal, weakly coupled to the C-2′ proton. The C-1′ and C-2′ protons give rise to two pairs of doublets (J = 12 and 5 Hz) at τ 7.40 and 7.15, respectively. Each component of the latter signal is again split by the C-3′ proton (J = 1 Hz). The C-4α proton signal falls at τ 7.52, and the C-18 and C-19 signals at 9.33 and 9.00, respectively.

The formation of a lactol rather than a lactone in this reaction appears to be unprecedented, but may be rationalized in terms of steric hindrance by the etheno bridge to the approach of a second anion of reducing agent, the first having approached preferentially from the underside of the anhydride group, forming the C-3′ epimer of **11**. The observed α orientation, relative to the plane of the lactol group, of the hydroxyl group in **11** would arise from opening and reclosure of the lactol ring during work-up of the reaction. That the α orientation of this hydroxyl group is more stable than the β was proved by mild hydrolysis of **11** to hydroxy-aldehydo acid **14**, $C_{32}H_{48}O_4$, which on treatment with acetic anhydride gave the lactol acetate **12** in high yield. Although the lactol was readily hydrolyzed by

(11) J. P. Jennings, W. Klyne, and P. M. Scopes, *J. Chem. Soc.*, 7211, 7229 (1965).

(12) K. Bowden, I. M. Heilbron, E. R. H. Jones, and B. C. L. Weedon, *ibid.*, 39 (1946).

(13) N. W. Atwater and J. W. Ralls, *J. Amer. Chem. Soc.*, **82**, 2011 (1960).

aqueous alkali, it was, unlike many lactols, sufficiently stable with respect to the aldehydo acid tautomer to be inert to diazomethane; *cf.*, for example, marasmic acid **15**,[14] which reacts with diazomethane readily.

These reactions establish that lithium tri-*t*-butoxyaluminohydride, like sodium borohydride and lithium aluminum hydride, reduces the more hindered anhydride carbonyl group of the Inhoffen adduct **3**, and supports the proposed initial formation of a complex of the less hindered carbonyl group, another carbonyl group, and the reagent cation in these reductions. Further work is in progress with the object of predicting and directing the steric course of reactions of this kind.

Experimental Section

Analyses were performed by Spang Microanalytical Laboratories, Ann Arbor, Mich. Melting points were determined on a Thomas–Hoover capillary apparatus. Optical rotations were measured in a 0.2-dm cell with a Bendix–Ericsson automatic polarimeter, and nmr spectra with a Varian HA-100 spectrometer in deuteriochloroform solution, using tetramethylsilane as internal reference. Infrared spectra were taken using a Perkin–Elmer 237 instrument, and ORD measurements on a JASCO UV/ORD/CD spectrophotometer. Tlc employed Eastman "Chromagram" silica gel on plastic sheets, and the developing solvent was 20% ether in benzene.

Reduction of the Inhoffen Adduct to the Acetoxylactone 4 with Sodium Borohydride.[6]—The adduct[8,9] (1 g) and sodium borohydride (130 mg) were heated at 95° in dioxane (10 ml) for 2.5 hr. The solution was let cool, diluted with water, and extracted with ether. The ethereal solution was dried (Na_2SO_4) and concentrated to a gum, which was chromatographed in pentane on Florisil (deactivated with 7% water, 20 g). Elution with 25% ether in pentane gave the crude acetoxylactone **4**: mp 162–164°; 300 mg. Repeated recrystallization from ethyl acetate–methanol gave an analytical sample as flat needles: mp 166–167°; $[\alpha]^{23}D$ −69° (*c* 1.0, $CHCl_3$); ir (KBr) 1763 (γ-lactone C=O), 1712 cm^{-1} (acetate C=O); nmr τ 3.88, 4.37 (2 H, AB q, J = 5 Hz, C-6 and C-7 H), 4.92 (2 H, m, C-22, -23 H), 5.18 (1 H, m, C-3α H), 5.86 (1 H, t) and 6.28 (1 H, m) (C-3′ H's), 6.91 (1 H, m, C-2′ H), 7.40 (1 H, m, C-4α H), 7.64 (1 H, d, J = 5, C-1′ H), 8.03 (3 H, s, C-3 CH_3COO–), 9.01 (3H, s, C-19 CH_3), 9.32 (3 H, s, C-18 CH_3). *Anal.* Calcd for $C_{34}H_{50}O_4$: C, 78.12; H, 9.64. Found: C, 78.21; H, 9.63. In other runs, small amounts of starting material were sometimes eluted by ether. More polar solvents eluted small quantities of the hydroxylactone **5**, identified by tlc and reacetylation to the acetoxylactone **4**. Very polar solvents eluted intractable materials whose ir spectra lacked γ-lactone carbonyl peaks, but contained peaks at 3450 (O–H) and 1705 cm^{-1} (carboxylic acid C=O).

Reduction of the Acetoxylactone 4 to the Triol 7.—The acetoxylactone (100 mg) was heated in dioxane (5 ml) with lithium aluminum hydride (14 mg) at 95° for 4 hr. The reaction mixture, after quenching with 50% aqueous dioxane, was acidified with 2 *N* HCl and extracted with chloroform. The chloroform extract was dried (Na_2SO_4) and concentrated to a white solid, which was crystallized from ethyl acetate–methanol to give the triol **7** as needles (29 mg): mp 238–241°; $[\alpha]^{27}D$ −65.5° (*c* 1.0, pyridine); ir (KBr) 3280 cm^{-1} (bonded O–H). *Anal.* Calcd for $C_{32}H_{52}O_3$: C, 79.28; H, 10.81. Found: C, 79.33; H, 10.73.

Reduction of the Inhoffen Adduct to the Acetoxylactone 4 with Lithium Aluminum Hydride.—A solution of the Inhoffen adduct (1 g) in tetrahydrofuran (4 ml) was added dropwise to a stirred solution of lithium aluminum hydride (80 mg) in tetrahydrofuran (4 ml) at −55° (acetone–CO_2 bath). The mixture was let warm to 0° during 90 min, stirred at this temperature for 20 min, and then cooled to −15°, when excess 6 *N* HCl was gradually added with stirring. Dilution with water and work-up *via* ether gave a solid product which was heated under reflux with acetic anhydride (10 ml) for 1 hr. Removal of the acetic anhydride under reduced pressure and crystallization of the product several times from ethyl acetate–methanol gave the acetoxylactone **4** (400 mg) of virtually identical melting point, ir spectrum, and optical rotation with those of the material obtained from sodium borohydride reduction in dioxane.

Reduction of the Inhoffen Adduct to the Lactol (11) with Lithium Tri-*t*-butoxyaluminohydride.—A solution of the Inhoffen adduct (1 g) in tetrahydrofuran (35 ml) was cooled to 0° and added in one portion to a stirred solution of lithium tri-*t*-butoxyaluminohydride (2 g) in tetrahydrofuran (35 ml), which was also at 0°. After 2 hr, 50% aqueous tetrahydrofuran was added until the solution was cloudy, and then excess 2 *N* HCl was added. The product, obtained *via* ether, had mp 205–210° (730 mg). Recrystallization from benzene–hexane gave the lactol **11** as fine needles: mp 219–221°; $[\alpha]^{23}D$ −37° (*c* 1.0, $CHCl_3$); ir (KBr) 3400 (bonded O–H), 1765 (γ-lactone C=O), 1730 cm^{-1} (acetate C=O); nmr τ 3.93, 4.43 (2 H, AB q, J = 4 Hz, C-6 and C-7 H), 4.77 (1 H, d, J = 1, C-3′ H), 4.94 (2 H, m, C-22, -23 H), 7.15 (1 H, d of d, J = 5, 1, C-2′ H), 7.40 (1 H, d, J = 5, C-1′ H), 8.00 (3 H, s, C-3 CH_3 COO–), 9.00 (3 H, s, C-19 CH_3), 9.33 (3 H, s, C-18 CH_3). *Anal.* Calcd for $C_{34}H_{50}O_5$: C, 75.80; H, 9.36. Found: C, 76.06; H, 9.37. Treatment of this compound with acetic anhydride–pyridine gave the lactol acetate **12** as rhombs from ethanol: mp 201–203°; $[\alpha]^{23}D$ −41° (*c* 1.0, $CHCl_3$); ir (KBr) 1770 (γ-lactone C=O), 1745 (lactol acetate C=O), 1718 cm^{-1} (acetate C=O); nmr τ 3.83, 4.25 (2 H, AB q, J = 4 Hz, C-6 and C-7 H), 3.94 (1 H, d, J = 1.5, C-3′ H), 4.86 (2 H, m, C-22, -23 H), 5.05 (1 H, m, C-3α H), 6.96 (1 H, d of d, J = 5, 1.5, C-2′ H), 7.37 (1 H, d, J = 5, C-1′ H), 7.88 (3 H, s, lactol acetate CH_3COO–), 8.01 (3 H, s, C-3 CH_3-COO–), 8.95 (3 H, s, C-19 CH_3), 9.26 (3 H, s, C-18 CH_3). *Anal.* Calcd for $C_{36}H_{52}O_6$: C, 74.44; H, 9.03. Found: C, 74.30; H, 8.92%. With benzoyl chloride and pyridine the lactol **11** gave the lactol benzoate **13** as needles from aqueous ethanol: mp 223–224°; $[\alpha]^{23}D$ −7° (*c* 1.0, $CHCl_3$); ir (KBr) 1770 (γ-lactone C=O), 1709 cm^{-1} (acetate C=O and lactol benzoate C=O); nmr τ 2.08, 2.65 (5 H, m, benzoate C_6H_5–), 3.74 (1 H, d, J = 1.5 Hz, C-3′ H), 3.83, 4.26 (2 H, AB q, J = 4, C-6 and C-7 H), 4.90 (2 H, m, C-22, -23 H), 5.07 (1 H, m, C-3α H), 6.85 (1 H, d of d, J = 5, 1, C-2′ H), 7.32 (1 H, d, J = 5, C-1′ H), 8.16 (3 H, s, C-3 CH_3COO–), 8.98 (3 H, s, C-19 CH_3), 9.29 (3 H, s, C-18 CH_3). *Anal.* Calcd for $C_{41}H_{54}O_6$: C, 76.60; H, 8.47. Found: C, 76.74; H, 8.51%.

Hydrolysis of the Lactol 11.—A solution of the lactol (500 mg) and potassium hydroxide (180 mg) in methanol (30 ml) and ether (15 ml) was held at 20° for 2 days. The solution was acidified with HCl and concentrated under reduced pressure. The product was partitioned between dilute HCl and ethyl acetate, and the organic layer dried (Na_2SO_4) and concentrated to give the crude hydroxyaldehydo acid **14**, mp 235–240°. Two crystallizations from acetone–hexane gave analytically pure material as small plates (250 mg): mp 295° dec; $[\alpha]^{27}D$ −19° (*c* 1.0, pyridine); ir (KBr) 3380, 3200 (O—H), 1730 (acid C=O) 1718 cm^{-1} (shoulder) (aldehyde C=O). *Anal.* Calcd for $C_{35}H_{50}O_4$: C, 77.37; H, 9.74. Found: C, 77.09; H, 9.79.

Acetylation of the Hydroxyaldehydo Acid 14.—The compound (100 mg) was heated under reflux with acetic anhydride (10 ml) for 1 hr. Removal of solvent under reduced pressure and crystallization from ethanol gave the lactol acetate **12** (95 mg), mp 201–202°, of identical ir spectrum and R_f in tlc with that previously obtained.

Reduction of the Lactol 11 to the Acetoxylactone 4 with Sodium Borohydride.—The lactol (500 mg) was dissolved in ethanol (45 ml), and a solution of sodium borohydride (150 mg) in water (5 ml) was added. The precipitate initially formed redissolved on addition of water (20 ml) followed by ethanol (20 ml). After 3 hr at 20° the mixture was poured into water, excess HCl added, and the product obtained *via* ether. Crystallization from ethyl acetate–methanol and aqueous ethanol gave the acetoxylactone **4** (414 mg), mp 163°, of identical infrared spectrum and rotation with that obtained above.

Hydrolysis and Oxidation of the Acetoxylactone 4.—A solution of the acetoxylactone (500 mg) and potassium hydroxide (150 mg) in methanol (30 ml) was heated under reflux for 1 hr. Solvent was removed under reduced pressure, and the product partitioned between ethyl acetate and dilute HCl. The organic layer was dried (Na_2SO_4) and concentrated, the hydroxylactone **5** being obtained from ethyl acetate–hexane as needles (344 mg): mp 225.5–227°; $[\alpha]^{23}D$ −89° (*c* 1.0, $CHCl_3$); ir (KBr) 3430 (O–H), 1740 cm^{-1} (H-bonded γ-lactone C=O). *Anal.* Calcd for $C_{32}H_{48}O_3$: C, 79.95; H, 10.07. Found: C, 79.87; H,

(14) J. J. Dugan, P. de Mayo, M. Nisbet, J. R. Robinson, and M. Anchel, *J. Amer. Chem. Soc.*, **88**, 2838 (1966).

10.02. Oxidation of this compound (150 mg) in acetone solution (10 ml) with Jones reagent[12] (4 drops) and work-up *via* ethyl acetate gave the ketolactone **6** (110 mg), obtained from aqueous ethanol as needles: mp 232.5–233°; $[\alpha]^{23}D$ −79° (*c* 1.0, $CHCl_3$); ir (KBr) 1750 (γ-lactone C=O), 1718 cm^{-1} (6-ring ketone C=O); nmr τ 3.78, 4.26 (2 H, AB q, J = 4 Hz, C-6 and C-7 H), 4.89 (2 H, m, C-22, -23 H), 5.93 (1 H, t) and 6.35 (1 H, m, C-3′ H's), 7.11 (1 H, d, J = 5, C-1′ H), 7.25 (1 H, m, C-2′ H), 8.91 (3 H, s, C-19 CH_3), 9.24 (3 H, s, C-18 CH_3). *Anal.* Calcd for $C_{32}H_{46}O_3$: C, 80.29; H, 9.69. Found: C, 80.42; H, 9.67.

Registry No.—**4**, 22965-85-1; **5**, 22965-86-2; **6**, 22965-87-3; **7**, 3930-58-3; **11**, 22965-89-5; **12**, 22965-90-8; **13**, 22965-91-9; **14**, 22950-89-6.

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Studies on the Heterolytic Fragmentation of Pregnane-16,20-diol Derivatives to Androst-16-enes[1]

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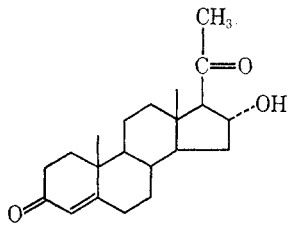
Heterolytic fragmentation of pregn-4-ene-3β,16α,20β-triol 16-tosylate and 16-mesylate with potassium *t*-butoxide afforded androst-4,16-dien-3β-ol as the principal product. In addition, 16β,20β-epoxypregn-4-en-3β-ol, 3β-hydroxypregn-4-en-20-one, and pregna-4,16-diene-3β,20β-diol were obtained. Sodium 3β,20β-dihydroxypregn-4-en-16α-yl sulfate was recovered unchanged under the same condition. Only poor yields of the fragmentation product, 5α-androst-16-en-3β-ol, were obtained from the C-20 epimers of 5α-pregnane-3β,16β,20-triol 3-acetate 16-mesylate. In addition, 3β-hydroxy-5α-pregnan-20-one and the corresponding 5α-pregn-16-ene-3β,20-diol were obtained; there was no evidence for 16,20-oxetane formation from the 16β-mesylates. The stereochemistry of the fragmentation reaction is discussed. The possibility of 16α-hydroxyprogesterone as an intermediate in the biochemical transformation of progesterone to Δ^{16}-C_{19} steroids by boar testis homogenate was examined.

The stereospecific heterolytic fragmentation[3] of the C-20 epimers of 20-chloro-16β-hydroxypregnanes to 16,17-secopregn-17(20)-en-16-als has been reported by Adam and Schreiber.[4] In the present investigation the stereochemical requirements of the fragmentation of 16,20-dihydroxypregnane derivatives have been studied using the 16-mesylate and sulfate derivatives.

The compounds for fragmentation studies were prepared in essentially similar manner. Pregn-4-ene-3β,16α,20β-triol 16-tosylate (**2a**) was synthesized by tosylation of 16α-hydroxyprogesterone (**1**), followed by reduction with sodium borohydride. The 16-mesylate **2b** and the sodium sulfonoxy derivative **2c** were prepared from **1** with methanesulfonyl chloride and trimethylamine sulfur trioxide, respectively. In all instances sodium borohydride reduction led to the predominant formation of the 3β,20β isomers; only trace amount of the 20α epimer appeared to be present. However, with the 20-keto-16β-mesylate the reduction was not stereoselective. Thus reduction of 3β,16β-dihydroxy-5α-pregnan-20-one 3-acetate 16-mesylate afforded both 5α-pregnane-3β,16β,20β-triol 3-acetate 16-mesylate (**7a**) and its 20α epimer **7b** in a 3:2 ratio. The orientation of the C-20 hydroxyl group was assigned from their nmr spectra. The epimer in which the C-18 methyl proton signals appeared at δ 0.97 was assigned the 20β-hydroxy structure **7a** and that which had δ 0.83, the 20α structure **7b** by comparison with the nmr data obtained from the C-20 epimers of 20-hydroxypregn-4-en-3-one and 5α-pregnane-3β,20-diol 3-monoacetate. Confirmation was subsequently



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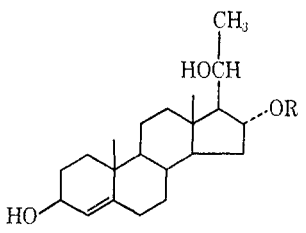
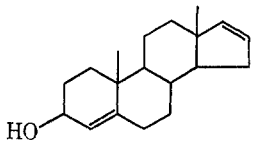


2a, R = $CH_3C_6H_4SO_2$
b, R = CH_3SO_2
c, R = SO_3Na



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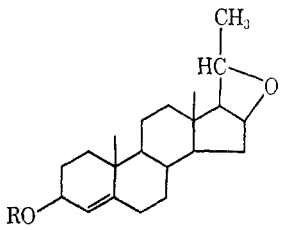
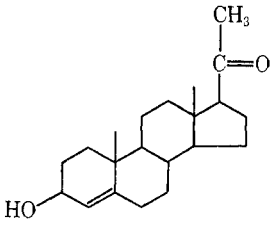


4a, R = H
b, R = CH_3CO



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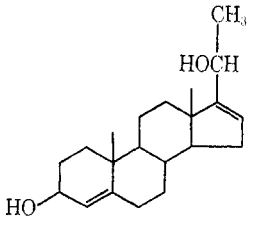

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achieved upon isolation of the known 5α-pregn-16-ene-3β,20α-diol (**10b**) from the fragmentation reaction of **7b**.

The fragmentation reaction was carried out with potassium *t*-butoxide in *t*-butyl alcohol under reflux for 1 hr. Tosylate **2a** gave an array of products from which four compounds were characterized. The fragmentation product androst-4,16-dien-3β-ol (**3**) was the princi-

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(2) Visiting Scientist 1967–1969, on leave from Tokyo Biochemical Research Institute, Japan.

(3) C. A. Grob and P. W. Schiess, *Angew. Chem. Intern. Ed. Engl.*, **6**, 1 (1967).

(4) G. Adam and K. Schreiber, *Ann.* **709**, 191 (1967).