

extracted with chloroform. Evaporation of the chloroform solution yielded 187.7 mg. of solid material, which after three recrystallizations from methylene chloride-diisopropyl ether furnished 102 mg. of white needles of m.p. 106.5–107°. Sublimation at 105°/0.003 mm. raised the m.p. to 109.5–110°. Mixed m.p. with VIIb: 85–100°. $\lambda_{\text{max}}^{\text{KBr}}$ 3.07, 5.71, 5.78, 6.06, 6.59, 7.60, and 8.13 μ .

Anal. Calcd. for $\text{C}_{15}\text{H}_{17}\text{NO}_5$: C, 61.85; H, 5.88; N, 4.81; methoxy, 10.63. Found: C, 61.61; H, 6.04; N, 4.85; methoxy, 10.92.

Methyl α -Benzamido- β,β -di-acetoxymethylacrylate (VIIId).—A solution of 4.05 g. (12.75 mmoles) of the azlactone IVd in 100 ml. of anhydrous methanol was heated under reflux for 48 hr. Evaporation gave an oil (4.30 g.), from which 2.29 g. (52%) of crystals of m.p. 97–102° could be separated by trituration with ether. Recrystallization from methylene chloride-diisopropyl ether raised the m.p. to 105–106°. $\lambda_{\text{max}}^{\text{KBr}}$ 3.08, 5.73–5.76, 6.04, 6.59, and 7.50 μ .

Anal. Calcd. for $\text{C}_{17}\text{H}_{19}\text{NO}_7$: C, 58.45; H, 5.48; N, 4.01; methoxy, 8.88; acetyl, 24.60. Found: C, 58.45; H, 5.77; N, 4.00; methoxy, 9.14; acetyl, 25.18.

The ethanolysis product (VIIIf) obtained in an analogous manner, had a melting point of 106.5–107°.

α -Benzamido- β,β -diacetoxymethylacrylic Acid (VIIg).—A solution of 500 mg. (1.58 mmoles) of the azlactone IVd in 20 ml. of 50% aqueous dioxane was heated under reflux for 30 min. On evaporation, a crystalline residue was obtained which on recrystallization from water yielded 465 mg. of the acid (m.p. 129–130°). The analytical sample obtained after two recrystallizations from ethyl acetate-hexane melted at 135–135.5°. $\lambda_{\text{max}}^{\text{KBr}}$ 2.06, 3.35–3.85, 5.72, 5.86, 6.00, 6.05, 6.63, 6.72, 8.06, and 8.23 μ .

Methyl α -Benzamido- β -acetoxymethyl- γ -methoxyisocrotonate (VIIe).—A mixture of 3.17 g. (10.0 mmoles) of the azlactone IVd and 0.98 g. (10.0 mmoles) of anhydrous potassium acetate in 50 ml. of anhydrous methanol was heated under reflux for 30 min.

The residue obtained after evaporation *in vacuo* was thoroughly extracted with benzene to yield 3.56 g. of a light yellow oil, which was subsequently chromatographed on 158 g. of neutral alumina (Woelm, activity II). The first oily fractions obtained on elution with benzene and benzene-ether (9:1) solidified on standing (510 mg., m.p. 88–96°) and gave on recrystallization from chloroform-hexane white needles of m.p. 100–101°. $\lambda_{\text{max}}^{\text{NaCl}}$ 3.05, 5.76, 5.83, 5.99, 6.07, 6.60, 6.74, 7.53, 8.10, 8.20, 9.25, and 9.35 μ .

Anal. Calcd. for $\text{C}_{16}\text{H}_{19}\text{NO}_6$: C, 59.80; H, 5.96; N, 4.36; methoxy, 19.30. Found: C, 59.61; H, 5.69; N, 4.27; methoxy, 19.08.

Elution of the column with chloroform-methanol (9:1) yielded 1.013 g. (84%) of benzamide of m.p. 115–120°.

Methyl α -Benzamido- β,β -dimethylacrylate (VIIa).—A solution of 151.5 mg. (0.435 mmole) of methyl α -benzamido- β,β -diacetoxymethylacrylate (VIIId) in 5 ml. of methanol was stirred with 50 mg. of prehydrogenated 5% palladium-charcoal catalyst (Baker) in an atmosphere of hydrogen. After an uptake of 0.885 mmoles of hydrogen (15 min. at room temperature), no more gas was consumed. Evaporation of the filtered solution gave 103.2 mg. (100%) of a solid, which on sublimation at 110°/0.005 mm yielded crystals of m.p. 137–137.5°, undepressed by an authentic specimen⁶ of methyl α -benzamido- β,β -dimethylacrylate. The infrared absorption spectra (KBr pellets) were superimposable. Similar results were obtained when dioxane was used as a solvent, with the exception that hydrogenation proceeded more slowly.

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Lactones Derived from 3-(17 β -Hydroxysteroid-16 β -yl)propionic Acids

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A series of steroid delta lactones was prepared for comparison with the previously described gamma lactones. The 3 β ,17 β -diacetoxo-5 α -androstan-16 β -ylacetic acid, the corresponding 5-unsaturated compound and 3,17 β -diacetoxo-1,3,5(10)-estratrien-16 β -ylacetic acid were converted by the Arndt-Eistert method into the corresponding propionic acids, which in turn yielded the desired lactones.

As a part of a continuing study of ring D modified steroidal hormones, we are reporting several new lactones having a three-carbon side chain structure at position 16 of the androstane and estrane nuclei. The 16 β -acetic acids of the androstane¹ and estrane² series described earlier served as intermediates in this work.

The 3 β ,17 β -diacetoxo-5 α -androstan-16 β -ylacetic acid (I)¹ was converted to its acid chloride II, which in turn was allowed to react with diazomethane to yield the diazo ketone III. The treatment of III with silver oxide in methanolic solution led to the isolation of methyl 3-(3 β ,17 β -diacetoxo-5 α -androstan-16 β -yl)propionate (IV) in variable yields. The alkaline hydrolysis of the latter (IV) and subsequent acidification of the reaction mixture gave the dihydroxy acid V which was converted to 3-(3 β ,17 β -dihydroxy-5 α -androstan-16 β -yl)propionic acid lactone (VI) at elevated temperature. The lactone VI was further characterized as the 3-acetate VII.

In order to overcome the erratic yields first encountered in the Arndt-Eistert rearrangement of the diazo ketone III, the latter was treated in benzyl alcohol

and 2,4,6-trimethylpyridine at elevated temperature.³ The resulting intermediate was hydrolyzed and finally subjected to pyrolysis to give the desired lactone VI in reproducible yields.

When VI was oxidized in a two-phase system,⁴ 3-(17 β -hydroxy-3-oxo-5 α -androstan-16 β -yl)propionic acid lactone (VIII) was obtained. From the latter (VIII) 3-(17 β -hydroxy-3-oxo-1,4-androstadien-16 β -yl)propionic acid lactone (IX) was prepared by bromination followed by the elimination of the elements of hydrogen bromide.⁵

In a similar manner the available 3 β ,17 β -diacetoxo-5 α -androsten-16 β -ylacetic acid (X)¹ was converted to the acid chloride XI, which gave rise to the diazo ketone XII. This intermediate (XII) was subjected to the Arndt-Eistert rearrangement under the conditions recommended by Wilds and Meader³ and the crude inter-

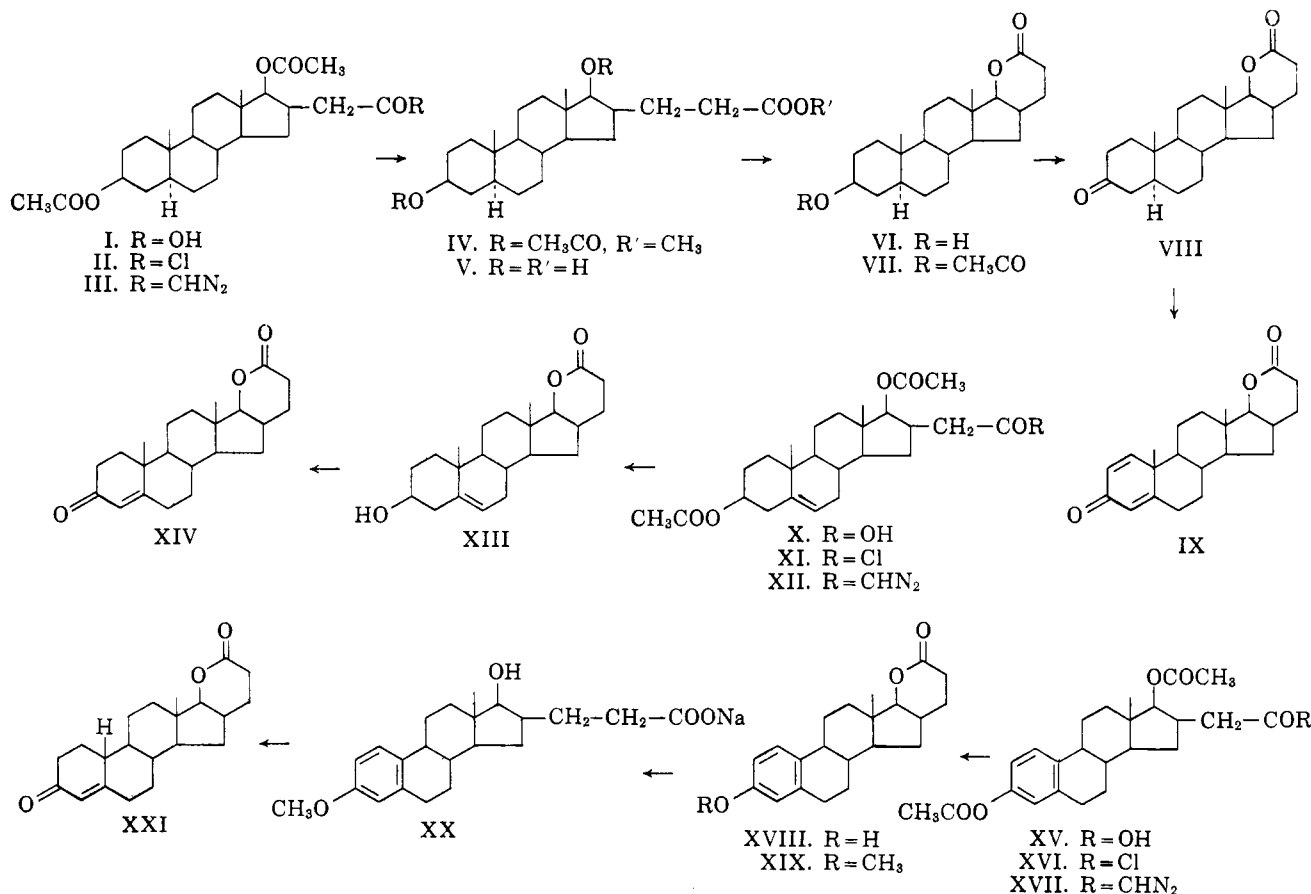
(3) A. L. Wilds and A. L. Meader, Jr., *J. Org. Chem.*, **13**, 763 (1948). We wish to express our thanks to Dr. C. Hummel Winestock for calling attention to this work.

(4) W. F. Bruce, "Organic Syntheses," Coll. Vol. II, John Wiley and Sons, New York, N. Y., 1943, p. 139.

(5) R. Joly, J. Warnant, G. Nominé, and D. Bertin, *Bull. soc. chim. France*, 366 (1958). P. Wieland, K. Heusler, and A. Wettstein, *Helv. Chim. Acta*, **43**, 523 (1960).

(1) P. Kurath and W. Cole, *J. Org. Chem.*, **26**, 1939 (1961).

(2) P. Kurath and W. Cole, *ibid.*, **26**, 4592 (1961).



mediate was treated as in the case of the corresponding saturated compound above to give, in good yield, 3-(3 β ,17 β -dihydroxy-5-androsten-16 β -yl) propionic acid lactone (XIII). The oxidation of XIII under acidic conditions⁶ led to the isolation of 3-(17 β -hydroxy-3-oxo-4-androsten-16 β -yl)propionic acid lactone (XIV).

For the δ -lactones in the estrane series, 3,17-diacetoxy-1,3,5(10)-estratrien-16 β -ylacetic acid (XV)² served as starting material. Its acid chloride XVI was converted via the diazo ketone XVII to 3-[3,17-dihydroxy-1,3,5(10)-estratrien-16 β -yl]propionic acid lactone (XVIII), using procedures analogous to those outlined above for the androstane series. The 3-methyl ether XIX was prepared from the crude Arndt-Eistert hydrolysis product or from the phenolic lactone XVIII in the usual manner with dimethyl sulfate in an alkaline solution followed by pyrolysis of the crude intermediate. Treatment of the methoxylactone XIX with sodium hydroxide gave rise to sodium 3-[17 β -hydroxy-3-methoxy-1,3,5(10)-estratrien-16 β -yl]propionate (XX) and the latter (XX) was subjected to a Birch reduction⁷ under typical conditions.⁸ The crude intermediate from the Birch reduction was treated with acid and the product heated to yield the desired 3-(17 β -hydroxy-3-oxo-4-estren-16 β -yl)propionic acid lactone (XXI).

Several of the lactones—*e.g.*, VI, XIII, and XVIII—were obtained after a pyrolysis step. It appeared desirable to investigate if any of the asymmetric centers were changed during this treatment. The mild alkaline hydrolysis of 3-(3 β ,17 β -dihydroxy-5 α -androstan-16 β -yl)

propionic acid lactone (VI) followed by acidification of the reaction mixture gave 3-(3 β ,17 β -dihydroxy-5 α -androstan-16 β -yl)propionic acid (V) in good yield. It was thus demonstrated that the stereochemistry at C-16 and/or C-17 was not altered during the pyrolysis procedure employed for the lactonization of V to VI. The stereochemical relationship of the lactones described in this paper was demonstrated by comparison of their optical rotations. A positive shift ($\Delta M_D +297^\circ$ to $+362^\circ$) in molecular rotation caused by the 17 β -hydroxy-16 β -ylpropionic acid lactone structure, as compared with the parent 17 β -hydroxy steroid having no substituent at C-16, is observed. The molecular rotation differences are presented in Table I.

Experimental⁹

Methyl 3-(3 β ,17 β -Diacetoxy-5 α -androstan-16 β -yl)propionate (IV).—A mixture of 5.48 g. of 3 β ,17 β -diacetoxy-5 α -androstan-16 β -ylacetic acid (I), 2.3 ml. of thionyl chloride, 3 drops of pyridine, and 124 ml. of anhydrous ether was allowed to stand at room temperature with occasional swirling for 3 hr.¹⁰ The reaction mixture was freed from a small amount of insoluble residue by filtration. The solvent was evaporated to leave a residue of 5.763 g. of crude acid chloride II, m.p. 147–149°, $\lambda_{\text{max}}^{\text{CHCl}_3}$ 5.55 μ , 5.77 μ , 8.05 μ .

The above prepared crude acid chloride II was dissolved in 120 ml. of methylene chloride and added over a period of 15 min. to an ice cold solution of diazomethane, made from 20.5 g. of N-nitrosomethylurea, and 85 ml. of 40% potassium hydroxide solution in 430 ml. of methylene chloride,¹¹ according to the ex-

(6) P. L. Julian, W. Cole, A. Magnani, and E. W. Meyer, *J. Am. Chem. Soc.*, **67**, 1728 (1945).

(7) A. J. Birch, *Quart. Revs.*, **4**, 69 (1950).

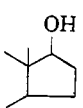
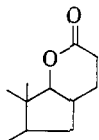
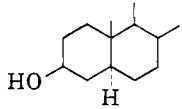
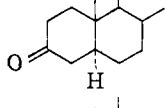
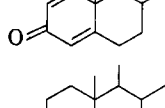
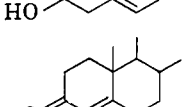
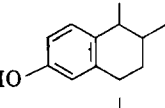
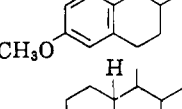
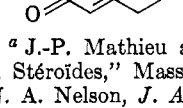
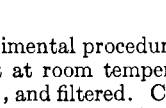
(8) J. A. Cella, E. A. Brown, and R. R. Burtner, *J. Org. Chem.*, **24**, 743 (1959).

(9) The melting points are uncorrected and were determined on a Fisher-Johns melting point apparatus unless stated otherwise. The optical rotations were measured in a 1-dm. tube in chloroform solution unless stated otherwise. The values have a limit of error of $\pm 2^\circ$. The infrared spectra were recorded on a Perkin-Elmer infrared spectrophotometer, Model 21.

(10) W. Cole and P. L. Julian, *J. Am. Chem. Soc.*, **67**, 1369 (1945).

(11) W. E. Bachmann and W. S. Struve, *Org. Reactions*, **1**, 38 (1942).

TABLE I
 COMPARISON OF MOLECULAR ROTATIONS

Partia structure			AMP
	+12° ^a	+333° ^c	+321° (ethanol, chloroform)
	+87° ^a	+397° ^c	+310° (chloroform)
	+63° ^a	+425° ^c	+362° (chloroform)
	-160° ^a	+138° ^c	+298° (chloroform)
	+340° ^a	+637° ^c	+297° (chloroform)
	+215° ^a	+523° ^c	+308° (dioxane)
	+220° ^a	+517° ^c	+297° (chloroform)
	+151° ^b	+473° ^c	+322° (chloroform)

^a J.-P. Mathieu and A. Petit, "Pouvoir Rotatoire Naturel, I. Stéroïdes," Masson et Cie., Paris, 1956. ^b A. L. Wilds and N. A. Nelson, *J. Am. Chem. Soc.*, **75**, 5366 (1953). ^c See Experimental.

perimental procedure of Wettstein.¹² The resulting solution was left at room temperature for 3 hr., concentrated to about 150 ml., and filtered. Complete removal of the solvent gave a residue of 5.925 g. of crude, partly crystalline diazo ketone III, $\lambda_{\text{max}}^{\text{CHCl}_3}$ 4.75 μ , 5.78 μ , 6.10 μ , 8.03 μ .

The reaction mixture obtained by dissolving the above prepared diazo ketone III in 330 ml. of methyl alcohol with the addition of 0.80 g. of freshly precipitated silver oxide was stirred under reflux for 30 min. An additional 0.34 g. of silver oxide was added to the suspension during the next 15 min., and stirring and refluxing was continued for 30 min. Finally the reaction mixture was kept at room temperature for 2 hr.¹³ The addition of 2.3 g. of activated carbon was followed by warming on the steam bath for 20 min. The solid was removed by filtration of the hot suspension through a short column of silica gel. Evaporation of the solvent left 4.902 g. of brown oil. This was purified by chromatography on 200 g. of alumina of grade III. From the petroleum ether-benzene (1:1) eluates¹⁴ a total of 2.026 g. of crude methyl ester IV was obtained. The compound was recrystallized from petroleum ether to give 1.128 g. of the desired methyl 3-(3 β ,17 β -diacetoxy-5 α -androstan-16 β -yl)propionate (IV), m.p. 95–96°. A second crop of 0.305 g. melted at 91–93°. The over-all yield from I was 24% in this experiment.¹⁵

A sample was recrystallized for analysis, m.p. 100–101°, $[\alpha]_{\text{D}}^{25} +9^\circ$ (c, 1.13); $\lambda_{\text{max}}^{\text{CHCl}_3}$ 5.81 μ , 8.02 μ .

(12) A. Wettstein, *Helv. Chim. Acta*, **24**, 311 (1941).

(13) W. E. Bachmann, W. Cole, and A. L. Wilds, *J. Am. Chem. Soc.*, **62**, 824 (1940).

(14) The petroleum ether fraction boiling at 90–100° was used in this work.

(15) This represents one of the better yields; other experiments gave only 10–20% yield.

Anal. Calcd. for C₂₇H₄₂O₆: C, 70.10; H, 9.15. Found: C, 70.21; H, 8.97.

From the later chromatographic fractions no clean product could be obtained even after repeated chromatography.

3-(3 β ,17 β -Dihydroxy-5 α -androstan-16 β -yl)propionic Acid (V).—The mixture of 1.006 g. of IV, 1.34 g. of potassium hydroxide pellets, 50 ml. of methyl alcohol, and 5 ml. of water was refluxed for 2 hr. Distilled water (130 ml.) was added and the solution was concentrated to about 70 ml. The resulting suspension was diluted with 150 ml. of water, warmed on the steam bath, and acidified with 100 ml. of 2 *N* hydrochloric acid. The acidic suspension was warmed for 20 min. and allowed to cool. The precipitate was collected on a filter, washed with several small amounts of water and dried at 75° under reduced pressure overnight. Recrystallization of the crude acid from acetone yielded 0.591 g. (75%) of the hydroxy acid V, m.p. 199–200°, resolidification at 204–208°, second melting at 236–238°.

A sample was recrystallized for analysis, m.p. 205–206°, resolidification at 210 and second m.p. 237–239°; $[\alpha]_{\text{D}}^{25} +9^\circ$ (c, 0.677 dioxane); $\lambda_{\text{max}}^{\text{KBr}}$ 3.00 μ , 3.75–4.5 μ , 5.86 μ .

Anal. Calcd. for C₂₂H₃₆O₄: C, 72.49; H, 9.96. Found: C, 72.30; H, 10.02.

3-(3 β ,17 β -Dihydroxy-5 α -androstan-16 β -yl)propionic Acid Lactone (VI). A. **From the Dihydroxy Acid V.**—The dihydroxy acid V was sublimed at 200° \pm 10° under high vacuum. The lactone VI was recrystallized from acetone to a constant m.p. 239–240°; $[\alpha]_{\text{D}}^{25} +96^\circ$ (c, 1.024); $\lambda_{\text{max}}^{\text{Nujol}}$ 2.96 μ , 5.73 μ , 5.85 μ ; $\lambda_{\text{max}}^{\text{pyridine}}$ 5.77 μ .

Anal. Calcd. for C₂₂H₃₄O₃: C, 76.25; H, 9.90. Found: C, 76.38; H, 9.83.

B. **Without Isolation of the Dihydroxy Acid V; Using the Procedure of Wilds and Meader.**³—The solution of the crude diazo ketone III, prepared from 3.075 g. of 3 β ,17 β -diacetoxy-5 α -androstan-16 β -ylacetic acid (I) as described above, in 20 ml. of 2,4,6-trimethylpyridine and 20 ml. of benzyl alcohol in an atmosphere of nitrogen was immersed in an oil bath heated to 190°. The mixture was allowed to react for 10 min. and then left to cool. Ether was added and the solution was washed with 2 *N* hydrochloric acid and water, dried, and evaporated. The residue was dissolved in 80 ml. of methyl alcohol and 20 ml. of water and refluxed for 2 hr. with 4.0 g. of potassium hydroxide. The alkaline solution was diluted with 500 ml. of water and extracted with ether, the ether solution was extracted with several portions of 0.2 *N* sodium hydroxide solution and water and then discarded. The alkaline phase was made acidic by the addition of 10% hydrochloric acid and warmed on the steam bath for a short time. After the suspension cooled, the precipitate was collected on a filter, washed with several small amounts of water and dried at 75° under reduced pressure. Sublimation of the product at 200° \pm 10° under high vacuum and two recrystallizations from acetone gave 0.959 g. (39% based on I) of 3-(3 β ,17 β -dihydroxy-5 α -androstan-16 β -yl)propionic acid lactone (VI), m.p. 236–237°. From the mother liquors a second crop of 0.216 g., m.p. 228–230°, was obtained.

A sample was recrystallized to a constant m.p. 239–240°; $[\alpha]_{\text{D}}^{25} +96^\circ$ (c, 1.022); $\lambda_{\text{max}}^{\text{KBr}}$ 2.93 μ , 5.73 μ , 5.85 μ .

Anal. Calcd. for C₂₂H₃₄O₃: C, 76.25; H, 9.90. Found: C, 76.14; H, 10.00.

The products from preparations A and B are identical.

3-(3 β -Acetoxy-17 β -hydroxy-5 α -androstan-16 β -yl)propionic Acid Lactone (VII).—A mixture of 0.060 g. of VI, 2 ml. of acetic anhydride and 4 ml. of pyridine was allowed to stand at room temperature overnight. The solvents were evaporated under reduced pressure and an ether solution of the crystalline residue was washed with 2 *N* hydrochloric acid, 0.2 *N* sodium hydroxide solution, and water. The ether solution was dried and evaporated, and the residue was recrystallized from acetone-petroleum ether to give 0.056 g. (83%) of the acetate VII, m.p. 198–199°.

Further recrystallization gave an analytical sample, m.p. 201–202°; $[\alpha]_{\text{D}}^{25} +75^\circ$ (c, 1.023); $\lambda_{\text{max}}^{\text{CHCl}_3}$ 5.81 μ , 8.00 μ .

Anal. Calcd. for C₂₄H₃₆O₄: C, 74.19; H, 9.34. Found: C, 73.98; H, 9.32.

3-(17 β -Hydroxy-3-oxo-5 α -androstan-16 β -yl)propionic Acid Lactone (VIII).—To the cooled and stirred mixture of 0.86 g. of sodium dichromate, 1.2 ml. of concentrated sulfuric acid, 0.6 ml. of acetic acid, 3.7 ml. of water, and 28 ml. of benzene was added 0.578 g. of the lactone VI. The reaction mixture was kept immersed in an ice bath for 20 min. and then stirred at room temperature for 16 hr.⁴ The mixture was diluted with 200 ml. of benzene; the water layer was separated and extracted with two

200-ml. portions of benzene. The benzene extract was washed with water, dried, and evaporated to leave a residue of 0.551 g. of crystalline material. Recrystallization from acetone-petroleum ether gave 0.430 g. (75%) of the desired compound VIII, m.p. 241–243°. A second crop amounted to 0.052 g., m.p. 221–223°.

The analytical sample melted at 243–244°; $[\alpha]_D^{24} +115^\circ$ (c, 1.014); $\lambda_{\text{max}}^{\text{CHCl}_3}$ 5.80 μ , 5.85 μ .

Anal. Calcd. for $\text{C}_{22}\text{H}_{32}\text{O}_3$: C, 76.71; H, 9.37. Found: C, 76.61; H, 9.42.

3-(17 β -Hydroxy-3-oxo-1,4-androstadien-16 β -yl)propionic Acid Lactone (IX).—A solution of the lactone VIII (0.673 g.) in 20 ml. of acetic acid was treated with 1.02 g. of 30% hydrogen bromide in acetic acid and then with 0.68 g. of bromine in 3 ml. of acetic acid with swirling at about 18° for 5 min.; 3 ml. of acetic acid was added and the reaction mixture was allowed to stand at room temperature for 30 min. with occasional swirling. After the addition of 80 ml. of water, the precipitate was collected on a filter, washed with several small amounts of water, and dissolved in 200 ml. of benzene. The benzene solution was washed with water and evaporated to dryness at 40° under reduced pressure. The crude dibromide (1.086 g.) was dissolved in 23 ml. of dimethylformamide and added, with stirring, to 0.98 g. of lithium bromide and 0.98 g. of lithium carbonate at 95°, under nitrogen, and the mixture was stirred overnight.⁵ The cooled reaction mixture was diluted with 70 ml. of distilled water and 17.5 ml. of 2*N* hydrochloric acid and then extracted with three 120-ml. portions of methylene chloride. The organic phase was washed to neutrality with water, dried and evaporated to leave a residue of 0.762 g. of crude oily material, which was purified by chromatography on 45 g. of silica gel. From the benzene-ether (1:1) and ether eluates a total of 0.455 g. of IX was obtained. Recrystallization from acetone-petroleum ether gave 0.353 g. (53%) of the desired compound IX, m.p. 200–201°. After sublimation at 210° and recrystallization from acetone-petroleum ether, 0.163 g. of product, m.p. 204–205°, was isolated.

An analytical sample melted at 206–207°; $[\alpha]_D^{24} +125^\circ$ (c, 1.032); $\lambda_{\text{max}}^{\text{CH}_3\text{OH}}$ 243 m μ (ϵ 16,500); $\lambda_{\text{max}}^{\text{CHCl}_3}$ 5.79 μ , 6.02 μ , 6.16 μ , 6.23 μ .

Anal. Calcd. for $\text{C}_{22}\text{H}_{28}\text{O}_3$: C, 77.61; H, 8.29. Found: C, 77.62; H, 8.31.

3-(3 β ,17 β -Dihydroxy-5-androsten-16 β -yl)propionic Acid Lactone (XIII).—The acid chloride XI (4.015 g., m.p. 143–145°) was prepared from 3.90 g. of 3 β ,17 β -diacetoxy-5-androsten-16 β -ylacetic acid (X), 1.8 ml. of thionyl chloride, and 1 drop of pyridine in 100 ml. of ether.¹⁰ The crude intermediate XI was converted to the diazo ketone XII (4.19 g., m.p. 225–235° dec.; $\lambda_{\text{max}}^{\text{CHCl}_3}$ 4.76 μ , 5.79 μ , 6.10 μ , 8.04 μ) in methylene chloride solution with diazomethane according to the procedure of Wettstein.¹² A mixture of the crude diazo ketone XII, 30 ml. of 2,4,6-trimethylpyridine, and 30 ml. of benzyl alcohol was immersed into an oil bath at 200° for 10 min. according to the procedure of Wilds and Meader,³ and worked up as in the preparation of VI. The reaction product was sublimed at 220° under high vacuum and recrystallized from acetone to give 1.735 g. (56%) of 3-(3 β ,17 β -dihydroxy-5-androsten-16 β -yl) propionic acid lactone (XIII), m.p. 259–260°. A second crop of 0.409 g. of less pure product, m.p. 252–253°, was obtained from the mother liquors.

An analytical sample melted at 259–260°; $[\alpha]_D^{25} +40^\circ$ (c, 0.988); $\lambda_{\text{max}}^{\text{CHCl}_3}$ 2.77 μ , 2.90 μ , 5.81 μ .

Anal. Calcd. for $\text{C}_{22}\text{H}_{32}\text{O}_3$: C, 76.71; H, 9.37. Found: C, 76.43; H, 9.44.

3-(17 β -Hydroxy-3-oxo-4-androsten-16 β -yl)propionic Acid Lactone (XIV).—The solution of 1.88 g. of the lactone XIII in 80 ml. of glacial acetic acid was treated successively with 0.80 g. of bromine in 8 ml. of glacial acetic acid, 0.73 g. of chromic anhydride in 1.5 ml. of water and 11 ml. of acetic acid for 2 hr. Chromous chloride solution (80 ml., 1*N*) was added and the solution was allowed to stand under nitrogen for 2 hr.⁶ The reaction mixture was diluted with 700 ml. of distilled water and the precipitate was separated by filtration and washed with several small portions of water. The product was dried at 75° *in vacuo* overnight and recrystallized from acetone-petroleum ether and then from acetone to yield 0.724 g. of the desired lactone XIV, m.p. 241–242°. A second crop of 0.581 g. melted at 235–240°. The yield amounts to 70%.

A part of the first crop was sublimed and recrystallized from acetone-petroleum ether; m.p. 244–245°; $[\alpha]_D^{24} +186^\circ$ (c, 1.14); $\lambda_{\text{max}}^{\text{CH}_3\text{OH}}$ 240 m μ (ϵ 16,300); $\lambda_{\text{max}}^{\text{CHCl}_3}$ 5.81 μ , 6.01 μ , 6.18 μ .

Anal. Calcd. for $\text{C}_{22}\text{H}_{30}\text{O}_3$: C, 77.16; H, 8.83. Found: C, 77.20; H, 8.87.

3-[3,17 β -Dihydroxy-1,3,5(10)-estratrien-16 β -yl]propionic Acid Lactone (XVIII).—The acid XV (3.18 g.) was allowed to react with 1.5 ml. of thionyl chloride and 1 drop of pyridine in 150 ml. of ether¹⁰ to yield 3.40 g. of the crude acid chloride XVI, m.p. 124–126°; $\lambda_{\text{max}}^{\text{CHCl}_3}$ 5.67 μ , 5.77 μ , 6.24 μ , 6.34 μ , 6.72 μ . The 3,17 β -diacetoxy-1,3,5(10)-estratrien-16 β -ylacetic acid methylene chloride (XVI) was added to a solution of diazomethane in methylene chloride¹³ to give, after workup, 3.71 g. of the diazo ketone XVII, m.p. 126–128° dec.; $\lambda_{\text{max}}^{\text{CHCl}_3}$ 4.76 μ , 5.78 μ , 6.10 μ , 6.72 μ .

The diazo ketone XVII prepared above was treated in 22.5 ml. of 2,4,6-trimethylpyridine and 22.5 ml. of benzyl alcohol at 200° for 15 min. under nitrogen³ and worked up as described above in the case of the corresponding compounds in the androstane series. The reaction product was pyrolyzed at 200° under high vacuum for 12 hr. and purified by chromatography on 150 g. of silica gel. The eluates with benzene-ether (1:1), ether, and ether-acetone (9:1, 8:2) gave, after evaporation of the solvent, 1.289 g. of the crude lactone XVIII. After two recrystallizations from acetone 0.651 g. (26% based on XV) of the desired 3-[3,17 β -dihydroxy-1,3,5(10)-estratrien-16 β -yl]propionic acid lactone (XVIII) was isolated; this compound decomposed above 320°.

A sample was recrystallized twice more for analysis; decomposition point above 320°; $[\alpha]_D^{25} +160^\circ$ (c, 0.55 dioxane); $\lambda_{\text{max}}^{\text{CH}_3\text{OH}}$ 248 m μ (ϵ 80); $\lambda_{\text{max}}^{\text{CH}_3\text{OH}}$ 280 m μ (ϵ 2,600); $\lambda_{\text{max}}^{\text{CHCl}_3}$ 3.03 μ , 5.88 μ , 6.18 μ , 6.31 μ , 6.68 μ .

Anal. Calcd. for $\text{C}_{21}\text{H}_{26}\text{O}_3$: C, 77.27; H, 8.03. Found: C, 77.49; H, 8.06.

3-[17 β -Hydroxy-3-methoxy-1,3,5(10)-estratrien-16 β -yl]propionic Acid Lactone (XIX).—The crude hydrolysis product of the Arndt-Eistert rearrangement (2.17 g.), made from 3.15 g. of XV as indicated above, was dissolved in 58 ml. of methyl alcohol and 58 ml. of water in the presence of 1.86 g. of sodium hydroxide pellets and warmed to 50°. To this mixture was added with stirring 4 ml. of dimethyl sulfate in 4.5 ml. of methyl alcohol over a period of 15 min.⁶ The dropping funnel was rinsed with 4.5 ml. of methyl alcohol and the reaction mixture was stirred at 50° for 3 hr. The resulting suspension was stirred for 2 hr. at room temperature and was allowed to stand overnight. Sodium hydroxide pellets (0.40 g.) were added and the mixture was refluxed for 2 hr. The resulting slurry was diluted with 580 ml. of water and made acidic with 60 ml. of 5*N* sulfuric acid. The acidic mixture was warmed on the steam bath for 40 min. and allowed to cool. The solid was collected on a filter, washed with water, dried at 75° under reduced pressure, and pyrolyzed at 210° for 24 hr. The compound was purified by chromatography¹⁷ on 220 g. of silica gel. The residues from the benzene-ether (9:1) eluates gave, after sublimation at 220° under high vacuum and subsequent recrystallization from acetone-petroleum ether, 1.114 g. (43% based on XV) of the methoxylactone XIX, m.p. 224–226°.

A sample was recrystallized for analysis; m.p. 224–225°; $[\alpha]_D^{25} +152^\circ$ (c, 1.05); $\lambda_{\text{max}}^{\text{CHCl}_3}$ 5.80 μ , 6.21 μ , 6.35 μ , 6.67 μ .

Anal. Calcd. for $\text{C}_{22}\text{H}_{28}\text{O}_3$: C, 77.61; H, 8.29. Found: C, 77.51; H, 8.43.

The same compound XIX was obtained from the phenolic lactone XVIII on similar treatment.

Sodium 3-[17 β -Hydroxy-3-methoxy-1,3,5(10)-estratrien-16 β -yl]propionate (XX).—A mixture of 2.309 g. of the lactone XIX and 17 ml. of a 2*N* aqueous sodium hydroxide solution in 130 ml. of methyl alcohol was refluxed gently on the steam bath for 30 min. The solution was diluted with 140 ml. of water and concentrated under reduced pressure to about 150 ml. The suspension was warmed on the steam bath for 40 min. and allowed to cool. The crystalline compound was collected on a filter and washed with 130 ml. of ice cold water. The sodium salt XX amounted to 2.532 g. (98%), carbonization at 230–233° (capillary).

3-(17 β -Hydroxy-3-oxo-4-estren-16 β -yl)propionic Acid Lactone (XXI).—A suspension of 2.53 g. of the sodium salt XX in 40 ml. of *t*-butyl alcohol and 40 ml. of tetrahydrofuran was diluted to about 400 ml. with liquid ammonia. The reaction mixture was cooled in a Dry Ice-acetone bath and 1.62 g. of lithium wire was added in small pieces to the stirred solution over a period of 15 min.⁸ After 4 hr. 0.25 g. more of the lithium wire was added. Fifteen minutes later 7.5 ml. of anhydrous ethyl alcohol was added

(16) O. Schindler, *Helv. Chim. Acta*, **43**, 754 (1960).

(17) We express our thanks to Mr. Michael H. Evans for technical assistance in this experiment.

with stirring and continued cooling. This was followed by the addition of a second 7.5-ml. portion of ethyl alcohol 25 min. later. The cooling bath was removed and the ammonia was allowed to evaporate in a stream of nitrogen.

The reaction mixture was diluted with 450 ml. of distilled water, brought to pH 5 by the addition of 600 ml. of 1 *N* oxalic acid, and extracted with 800 ml. of ether. The water phase was separated and extracted with two successive portions of 400 ml. of ether. The ether extracts were washed with water, combined, dried, and evaporated to leave a solid residue weighing 2.55 g. A mixture of this crude Birch reduction product, 24 ml. of 2 *N* hydrochloric acid, and 12 ml. of water in 120 ml. of methyl alcohol was warmed to a gentle reflux for 40 min. After the addition of 35 ml. of 2 *N* sodium hydroxide solution the reaction mixture was warmed for an additional 15 min. under nitrogen. This was followed by the addition of 250 ml. of water and concentration of the suspension to about 200 ml. under vacuum. The slurry was made acidic by the addition of 100 ml. of 10% hydrochloric acid, warmed on the steam bath for 15 min., and allowed to cool. The precipitate was collected on a filter, washed with several small amounts of water and dried overnight at 60° under reduced pressure to leave 2.25 g. of a mixture, m.p. 166–182°. The above product was pyrolyzed at 220° under high vacuum for 60 hr. and the reaction product was purified by chromatography¹⁷ on 220 g. of silica gel. The benzene-ether (8:2) eluates gave, after evaporation of the solvent and recrystallization from acetone-petroleum ether, 0.364 g. (16%) of unreduced methoxylactone XIX, m.p. 223–225° (identified by mixed melting point determination and comparison of the infrared spectrum with that of a reference sample of XIX).

The residues from the ether and ether-acetone (9:1) eluates yielded 1.281 g. of impure 3-(17 β -hydroxy-3-oxo-4-estren-16 β -yl)-propionic acid lactone (XXI). The compound was recrystallized from acetone-petroleum ether to yield 0.669 g. of the lactone XXI, m.p. 218–220°. A second crop amounted to 0.133 g., m.p. 215–218°, bringing the yield to 37%.

A part of the first crop was sublimed under high vacuum and recrystallized from acetone-petroleum ether to a constant melting point of 223–224°. The sample had $[\alpha]_D^{25} +144^\circ$ (*c*, 1.117); $\lambda_{\text{max}}^{\text{CH}_3\text{OH}}$ 240 m μ (ϵ 17,400) $\lambda_{\text{max}}^{\text{CHCl}_3}$ 5.80 μ , 6.02 μ , 6.18 μ .

Anal. Calcd. for C₂₁H₂₈O₃: C, 76.79; H, 8.59. Found: C, 76.88; H, 8.88.

Potassium Carbonate Hydrolysis of 3-(3 β ,17 β -Dihydroxy-5 α -androstane-16 β -yl)propionic Acid Lactone (VI).¹⁷—A mixture of 0.346 g. of the lactone VI, 0.26 g. of potassium carbonate, 2.6 ml. of water, and 21 ml. of methyl alcohol was swirled to obtain a solution and allowed to stand at room temperature for 60 hr. The addition of 25 ml. of water was followed by concentration of the suspension to about 25 ml. under reduced pressure at room temperature. The resulting slurry was made acidic with 30 ml. of 10% hydrochloric acid; the precipitate was collected on a filter, washed with several small amounts of water, and dried at 60° under reduced pressure overnight. The compound was recrystallized from acetone to give 0.273 g. (75%) of the dihydroxy acid V, m.p. 196–197°, resolidification at 200°, and second melting at 224–227°.

A sample was recrystallized to a constant melting point of 202–203°, resolidification at 208–210°, and second melting point at 235–238°. The compound dried at 65° had $[\alpha]_D^{25} +8^\circ$ (*c*, 0.588 dioxane); $\lambda_{\text{max}}^{\text{KBr}}$ 3.00 μ , 3.75–4.5 μ , 5.86 μ .

Anal. Calcd. for C₂₂H₃₆O₄: C, 72.49; H, 9.96. Found: C, 72.33; H, 9.78.

The above compound was identical to a reference sample of 3-(3 β ,17 β -dihydroxy-5 α -androstane-16 β -yl)propionic acid (V).

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The Kinetics of the Silver Metal-catalyzed Cannizzaro Reaction¹

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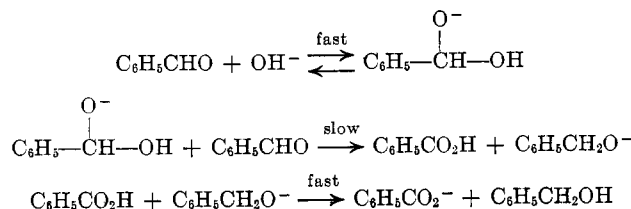
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The kinetics of the silver metal-catalyzed Cannizzaro reaction of benzaldehyde and sodium hydroxide in 50% aqueous ethanol has been measured, and it has been found that the order of the reaction varies from initially first order in benzaldehyde to zero order in the latter stages of the reaction, that the reaction is linearly dependent on the amount of silver metal catalyst used, is zero order in sodium hydroxide, and apparently takes place on the catalyst surface. The rate constant for the first 7–12% of reaction at 30° was found to be $4.9 \pm 0.3 \times 10^{-3} \text{ min.}^{-1}$ on the basis of 20 mg. of silver per 100 ml. of solution, and a k_H/k_D rate factor of 6.8 ± 0.5 measured with benzaldehyde- α -*d*₁. Benzyl benzoate could not be detected among the reaction products, although it was shown that the ester is saponified at a slower rate than the rate of formation of products from the reaction. A mechanism has been proposed which is consistent with the results and all known facts.

The Cannizzaro reaction is the disproportionation of two aldehyde molecules to form the corresponding carboxylate anion and alcohol in the presence of alkali. It has been previously reported that the rate for this reaction with benzaldehyde, as well as with many of its derivatives, was second order in aldehyde and first order in base.³ Strong evidence has been furnished that a hydride transfer occurs between two aldehyde groups and that a hydrogen transfer from solvent to

aldehyde is not involved.^{4,5} Thus, when a Cannizzaro reaction was carried out with benzaldehyde in deuterium oxide solution, it was found that the resulting benzyl alcohol contained no deuterium atom bonded to carbon.^{4,5} Furthermore, when benzaldehyde- α -*d*₁ was caused to dismutate in the presence of base, benzyl alcohol- α , α -*d*₂ (C₆H₅CD₂OH) was formed. Evidence that the hydride transfer takes place in the rate-determining step is that a k_H/k_D value of 1.8 has been found for the disproportionation of benzaldehyde.⁶ A reaction scheme frequently proposed is



(1) From the Ph.D. thesis of D. R. L., University of Connecticut, 1962. The complete compilation of the experiments can be found in this thesis. Presented at the 142nd National Meeting of the American Chemical Society, Atlantic City, N. J., September, 1962, p. 20Q.

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