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KALAMAZOO, MICH.

[CONTRIBUTION FROM THE WORCESTER FOUNDATION FOR EXPERIMENTAL BIOLOGY]

Degradation of Corticosteroids. IV. Preparation of 3,5-Seco-4-nor-6-androstene-5,11,17-trione-3-oic Acid and 3,5-Seco-4-nor-11β-hydroxyandrostane-5,17-dione-3-oic Acid 3,11-Lactone[1,2]

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The 3,5-seco-4-norandrostane-5,11,17-trione-3-oic acid was converted to 5-en-3,5-lactone III which on treatment with *N*-bromosuccinimide gave 3,5-seco-4-nor-6-androstene-5,11,17-trione-3-oic acid (IVa), presumably *via* an unstable 7-bromo-5-en-3,5-lactone which was not isolated. The Δ^6-acid IVa rearranges with base to the thermodynamically more stable Δ^8 isomer V. The utilization of the Δ^6-acid IVa for the degradation of ring B and isolation of carbons 5, 6 and 7 is described. Attempts to prepare the 3,5-seco-4-nor-11β-hydroxy-5-androsten-17-one-3-oic acid 3,5-lactone failed and instead the 3,5-seco-4-nor-11β-hydroxyandrostane-5,17-dione-3-oic acid 3,11-lactone (X) was obtained. The seven-membered 3,11-lactone was formed in preference to the enol lactone and must therefore be the thermodynamically more stable of the two.

As part of a broad program of studies directed toward the stepwise degradation and isolation of individual carbon atoms of corticosteroids, approaches to the cleavage of ring B were explored. Economy of biosynthetic material required development of methods leading to the isolation of a large number of atoms. The 4-nor acid II, having an exposed ring B, was considered an attractive starting material for isolation of carbons 5, 6 and 7. Additional activation, necessary for directing the chemical attack, preferentially towards ring B, was achieved by enol lactone formation. The degradation of ring B and certain reactions of the 11-keto-enol lactone III as well as observations on the course of lactone formation in the 11β-hydroxy acid IXa are the subject of this communication.

Ozonolysis of adrenosterone at −70° in ethyl acetate gave in high yield the 3,5-sec-4-nor acid II as well as a low yield of an unidentified neutral product of m.p. 180–184°. Treatment of the acid II with acetic anhydride and fused sodium acetate[4] yielded the enol lactone III. Bromination of the enol lactone with *N*-bromosuccinimide did not lead to the isolation of the 7-bromo enol lactone. When, at the completion of the bromination, the reaction mixture was processed in ethyl acetate and partitioned with sodium hydrogen carbonate, two products, an acid and a neutral substance, were obtained. The acid, m.p. 205–207°, with an analysis for a $C_{18}H_{22}O_5$ compound, absorbed ultraviolet light at 224 mμ, indicative of a β-monosubstituted α,β-unsaturated ketone[5,6] and its infrared spectrum had bands at 3600, 3100 (broad), 2750 (shoulder), 1750, 1710, 1640, 1600 (shoulder), 1170 cm.$^{-1}$ These results are consistent with the structure IVa assigned to the acid which was subsequently confirmed by degradation experiments (see below). The neutral product, m.p. 105–107°, also absorbed ultraviolet light at $\lambda_{max}^{CH_3OH}$ 224 mμ and its infrared spectrum exhibited bands at 1730, 1710, 1670, 1610, 1160 cm.$^{-1}$ The possibility of the compound being the 1-dehydro enol lactone, formed *via* bromination[7] at C-2 followed by dehydrobromination was excluded, as the product had an analysis of a $C_{26}H_{26}O_5$ substance and its infrared spectrum did not show a band in the 1680–1690-cm.$^{-1}$ region, characteristic for enol lactones.[8] Furthermore, the NMR spectrum showed only two protons on a double bond while the 1-dehydro enol lactone requires three. In addition the NMR spectrum showed a quartet and triplet of bands characteristic of an ethyl ester.[9] These results suggested that the neutral product is the ethyl ester IVc and attempts were made to saponify the substance to the acid IVa. However on treatment of the neutral product

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(2) Previous papers of this series: (a) *J. Org. Chem.*, **21**, 814 (1956). (b) *J. Org. Chem.*, **22**, 326 (1957). (c) *J. Org. Chem.*, **24**, 669 (1959).

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(4) R. B. Woodward, F. Sondheimer, D. Taub, K. Hensler, and M. W. MacLamore, *J. Am. Chem. Soc.*, **74**, 4223 (1952).

(5) R. B. Woodward, *J. Am. Chem. Soc.*, **63**, 1123 (1941); **64**, 76 (1942). L. F. Fieser and M. Fieser, *Steroids*, Reinhold, New York, 1959, p. 19.

(6) E. Caspi and M. M. Pechet, *J. Biol. Chem.*, **230**, 843 (1958).

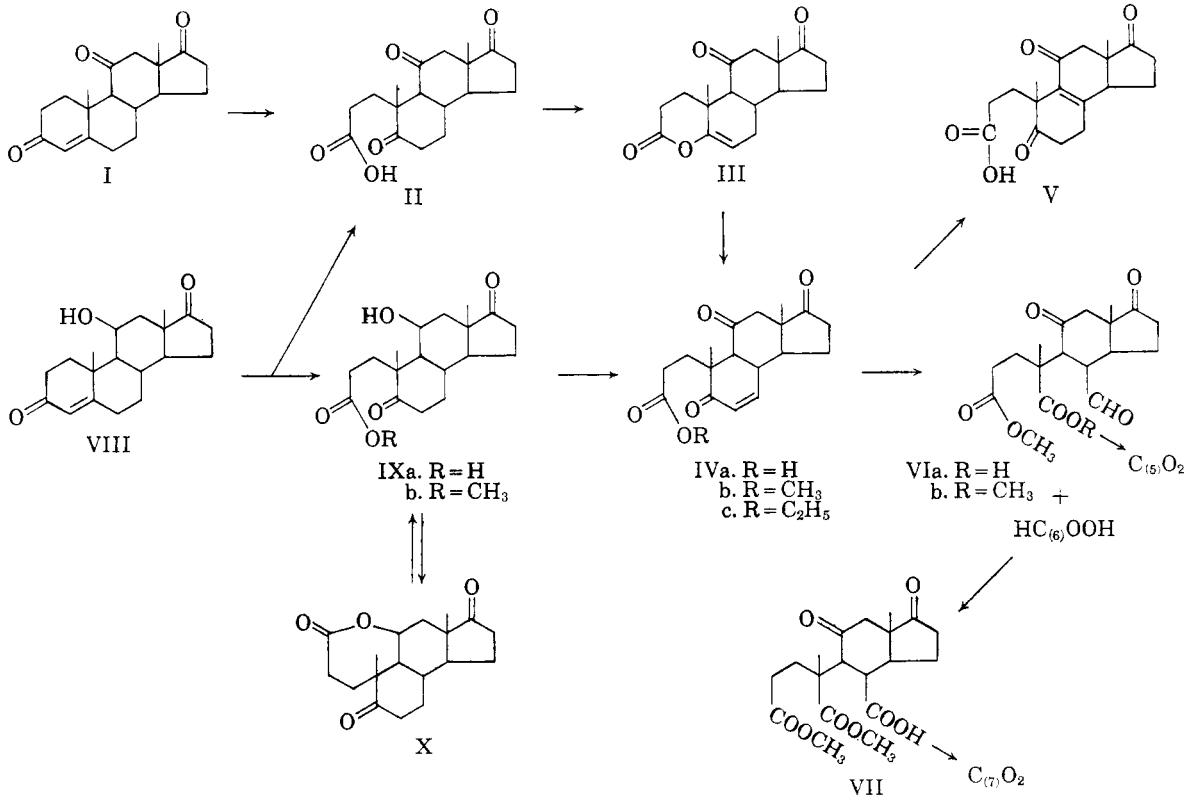
(7) C. Djerassi, *Chem. Rev.*, **43**, 271 (1948).

(8) H. Rosenkrantz and M. Gut, *Helv. Chim. Acta*, **36**, 1000 (1953); T. L. Jacobs and N. Takahashi, *J. Am. Chem. Soc.*, **80**, 4865 (1958).

(9) J. D. Roberts, *Nuclear Magnetic Resonance*, McGraw Hill, New York, 1959, p. 31, 67; *Catalog of NMR Spectra of Hydrogen and Hydrocarbons and Their Derivatives*, Humble Oil and Refining Co., 1959, p. 147.

with base, the acid IVa was not obtained. Instead, another acid, V, m.p. 217–219°, was isolated, which absorbed ultraviolet light at 247–248 mμ and whose infrared spectrum showed bands at 3200, 1740, 1715, 1640, 1620, 1160 cm.$^{-1}$ The ultraviolet maximum at 247–248 mμ was in good agreement with the 249-mμ wave length calculated for a $\Delta^{8-(9)}$-11-ketone[5] and the 8–9 position of the double bond was fully confirmed by the absence of protons on a double bond in the NMR spectrum of V and by the base-catalyzed rearrangement of acid IVa to the $\Delta^{8(9)}$-11-keto acid V. Attempts to rearrange acid IVa with aqueous acetic acid containing some hydrochloric acid failed and only starting material was recovered. This sequence establishes the structure of both the acid V and of the ethyl ester IVc obtained as the neutral product of bromination, which was also prepared by esterification of IVa. methylene chloride instead of ethyl acetate, only the acid IVa was obtained.

Only scant information is available on the bromination of enol esters[10–12] and the analogous reaction with enol lactones has apparently not been investigated. When C-3, or C-17 or C-20 (Δ^{17}) steroidal enol acetates were treated with *N*-bromosuccinimide, the products obtained were conjugated ketones.[10,12] Formation of the α,β-unsaturated carbonyls resulted probably from the cleavage of the enol acetates and elimination of hydrogen bromide from the resulting β-bromo ketones.[12] In the case of the reaction of the enol lactone III with *N*-bromosuccinimide, solvolysis of the products occurred probably during the reaction work-up. Several mechanisms can be visualized for the reaction and two possibilities will be mentioned. The reaction could have proceeded *via* a mechanism



It is apparent that the bromination of the enol lactone III in all probability proceeded as expected and gave the 7-bromo enol lactone, which was unstable and decomposed to yield *via* solvolysis the acid IVa and the ester IVc. When the experiment was carried out as above, but was worked up in analogous to that proposed for the enol esters, whereby the formed 7-bromo enol lactone decomposed and the intermediate underwent solvolysis during the work-up. Alternatively, the formation of free acid, IVa, and ester IVc could be interpreted as resulting from the solvolysis of the labile bromide with solvent participation at the C-3 end of the extended system of delocalizable electrons. In either case, the ethoxy group necessary to give IVc was presumably derived from ethyl acetate. However, the possibility of IVc arising through transesterification of IVa with ethyl acetate, cannot be ruled out with certainty. The available experi-

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(11) M. Rubin and B. H. Armbrecht, *J. Am. Chem. Soc.*, **75**, 3513 (1953).

(12) J. Fajkos, *Coll. Czechosl. Chem. Commun.*, **23**, 1559 (1958).

mental evidence does not permit distinction between the several possible reaction mechanisms.

Rearrangement of the unsaturated keto acid IVa to the $\Delta^{8(9)}$-11-keto acid V indicates that the latter is thermodynamically more stable. It has been reported that certain ketones may exist as β-γ rather than α-β unsaturated isomers.[13] If alkaline treatment of IVa leads to any of the $\Delta^{7(8)}$-isomer, then abstraction of the proton at C-9 followed by reprotonation at C-7 will lead to V.

Ozonolysis of the methyl ester IVb at −70° in ethyl acetate gave formic acid[14] derived from C-6 and the bisnor acid aldehyde VIa. The acid-aldehyde which had an analysis of a $C_{18}H_{24}O_7$ compound, did not absorb ultraviolet light in the 220–240-mμ region and its infrared spectrum was consistent with the assigned structure VIa. The acid VIa on treatment with diazomethane gave the diester aldehyde VIb, which was oxidized to the diester acid VII, m.p. 148–149°.

Several methods were considered for the isolation of C-6 and C-7 and the method of choice appeared to be electrolytic decarboxylation. It was shown that electrolytic decarboxylation can be carried out on complex multifunctional acids and that alcohols, aldehydes, ketones, and esters do not interfere with the reaction and do not contribute carbon dioxide.[15] Electrolysis[16] of the acid aldehyde VIa gave carbon dioxide and this must therefore be derived from the C-5 carboxylic group. The acid VII on electrolysis gave carbon dioxide derived from C-7.

As the 11-keto-7-bromo enol lactone proved to be unstable, it became of interest to prepare and test the stability of the 11β-hydroxy analog. It was intended to prepare the 11β-hydroxy seco acid IXa, convert the acid to the enol lactone, and brominate the lactone with *N*-bromosuccinimide. Ozonization of 11β-hydroxy-4-androstene-3,17-dione gave the 11β-hydroxy-4-nor acid IXa and a small amount of the 11-keto-4-nor acid II, arising from partial oxidation of the secondary alcohol function during ozonolysis.[17] The acid IXa gave a methyl ester IXb which was saponified back to IXa. When the acid IXa was treated with acetic anhydride and sodium acetate, under the same conditions which gave the enol lactone III, a neutral product was obtained, m.p. 196–198°. The product gave an analysis of $C_{18}H_{26}O_4$ and its infrared spectrum showed bands at 1730, 1720, 1700 cm.$^{-1}$ The absence of a hydroxyl band and of a band in the 1680–1690-cm.$^{-1}$ region suggested that the substance was not the expected enol lactone, a suspicion furthered by the complete recovery of starting material on treatment with *N*-bromosuccinimide. The possibility of the substance being the 11β-acetoxy enol lactone was excluded on the grounds of elementary analysis, infrared spectroscopy which showed no acetate band in the 1250-cm.$^{-1}$ region as well as the already mentioned bromination experiment. The NMR spectrum showed a single equatorial proton attached to an oxygen bearing carbon, most probably the 11α-hydrogen.[18] It became apparent that lactone formation occurred between the carboxyl at C-3 and the hydroxyl at C-11, and the product is assigned the structure X, which is consistent with the elementary analysis, infrared, and NMR spectrometry. Treatment of X with chromium trioxide in acetic acid led to the recovery of unchanged starting material, confirming the inclusion of the 11β-hydroxyl in the seven-membered lactone ring. The lactone was saponified with aqueous methanolic potassium bicarbonate to the acid IXa. Inspection of models indicated that the seven-membered ring lactone can be formed without difficulty and appears to be relatively strain free. The seven-membered 3,11-lactone was formed in preference to the enol lactone and must therefore be the thermodynamically more stable of the two.

EXPERIMENTAL[19]

3,5-Seco-4-nor-androstane-5,11,17-trione-3-oic acid (II). A solution of andrenosterone I, 6.8 g., in ethyl acetate, 300 ml., was cooled to −70° and treated with a stream of ozone-enriched oxygen. The course of reaction was followed by ultraviolet spectroscopy, and the reaction stopped when the band at 237 mμ had disappeared. The solution was agitated with a 25% solution of hydrogen peroxide, 50 ml., for 16 hr., then washed with water, partitioned with sodium bicarbonate to yield 5.97 g. of acid II, and 0.79 g. of a neutral syrup. The neutral syrup crystallized slowly on standing at room temperature. The second solid was not homogeneous and was partitioned with sodium bicarbonate to yield 305 mg. of acid II and 450 mg. of a neutral product, m.p. 180–184°, which has not been identified as yet.

The acid II was crystallized several times from ethyl acetate, m.p. 184–185°; (no selective absorption in the ultra-

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(19) Melting points were determined on a micro-hot stage and are reported as read. Analyses were carried out by Dr. S. M. Nagy, M.I.T., Cambridge, Mass., and by Schwarzkopf Microanalytical Laboratories, New York. Ultraviolet absorption spectra were determined by means of a Cary model 11 MS spectrophotometer on methanolic solutions. Infrared spectra were taken on solid material incorporated into potassium bromide pellets. NMR Spectra were taken at 60 mc. in deuterated chloroform containing 1% by volume of tetramethyl silane on a Varian High Resolution Spectrometer Model V4300B. The spectra were calibrated using a Hewlett-Packard wide range oscillator, Model 200CDR, together with a Hewlett-Packard electronic counter Model 521CR. The results are expressed in τ units where

$$\tau = 10.00 - \frac{\nu_{TMS} - \nu_X}{\nu_{TMS}} \cdot 10^6$$

violet); infrared ν_{max}: 3320 (broad), 2700 (shoulder), 1745, 1710, 1680, 1175 cm.$^{-1}$

Anal. Calcd. for $C_{18}H_{24}O_5$: C, 67.48; H, 7.55. Found: C, 66.96; H, 7.69.

3,5-Seco-4-nor-5-androstene-11,17-dione-3-oic acid 3,5-lactone (III). A. A solution of keto acid II, 3.4 g., was heated for 2.5 hr. in 150 ml. of boiling, freshly-distilled acetic anhydride, then freshly-fused sodium acetate, 200 mg., was added and the solution boiled for another 2 hr. Acetic anhydride was removed under reduced pressure and the residue was dissolved in ethyl acetate, washed successively with water, saturated sodium bicarbonate solution, and saturated sodium chloride solution, then dried over anhydrous sodium sulfate, and evaporated to give 2.8 g. of crystalline enol lactone III. The product was crystallized several times from ethyl acetate, m.p. 197–201°, no selective absorption in the ultraviolet; ν_{max} 1760, 1740, 1700, 1680, 1160 (doublet), 1140 cm.$^{-1}$

Anal. Calcd. for $C_{18}H_{22}O_4$: C, 71.50; H, 7.33. Found: C, 71.47; H, 7.60.

Unchanged acid II, 503 mg. was recovered from the alkaline solution.

B. A mixture of enol lactone III, 25 mg., in methanol, 5 ml., and a saturated solution of aqueous potassium bicarbonate 0.5 ml., was allowed to stand for 16 hr. at room temperature. The acid II was recovered in the usual manner.

3,5-Seco-4-nor-6-androstene-5,11,17-trione-3-oic acid (IVa). A. A sample of the enol lactone III, 2.1 g., was dried for 3 hr. at 100° at 0.01 mm. pressure and was dissolved in dry carbon tetrachloride, 200 ml. To the boiling solution, a mixture of *N*-bromosuccinimide,[20] 1.36 g., and benzoyl peroxide, 50 mg., was added and the solution was illuminated with a G. E. Photospot RSP 2 lamp for 6 min. The color of the solution changed from light yellow to light orange. The solution was cooled in ice, filtered through Celite, and the filtrate was evaporated to dryness under reduced pressure. The residue was dissolved in ethyl acetate, washed with water, and partitioned with sodium bicarbonate to give 1.15 g. of acid IVa and 1.02 g. of neutral IVc.

B. A mixture of the enol lactone III, 1. g., *N*-bromosuccinimide, 649 mg., benzoyl peroxide, 50 mg., and dry carbon tetrachloride, 150 ml., was treated exactly as described above. After cooling, the mixture was filtered, the carbon tetrachloride removed, then the residue was dissolved in methylene chloride, washed with water to yield 1.04 g. of crude acid IVa.

The acid was crystallized from a mixture of ethyl acetate and methanol, m.p. 205–207°; $\lambda_{max}^{CH_3OH}$ 224 mμ ε 9800; ν_{max} 3600, 3100 (broad), 2750 (shoulder), 1740, 1710, 1650, 1600, 1170 cm.$^{-1}$

Anal. Calcd. for $C_{18}H_{22}O_5$: C, 67.91; H, 6.97. Found: C, 68.09, 67.98; H, 7.04, 7.00.

Upon heating a solution of 25 mg. of the acid IVa in a boiling mixture of 5 ml. of acetic acid, 2 ml. of water, and 1 drop of concd. hydrochloric acid for 2 hr., only starting material was obtained.

Methyl 3,5-seco-4-nor-6-androstene-5,11,17-trione-3-oate (IVb). A. A methanolic solution of the acid IVa was treated with an excess of an ethereal solution of diazomethane and was processed in the usual manner to yield the ester IVb.

B. A mixture of 50 mg. of acid IVa, 5 ml. of methanol, and 40 mg. of concd. sulfuric acid was kept for 48 hr. at room temperature. After processing in the usual manner 49 mg. of ester IVb was obtained.

The ester was crystallized from ethyl acetate to a constant m.p. of 149–150°; $\lambda_{max}^{CH_3OH}$ 224 mμ ε 9800; ν_{max} 1745, 1690, 1655, 1600, 1175, 1160 cm.$^{-1}$

Ethyl 3,5-seco-4-nor-6-androstene-5,11,17-trione-3-oate (IVc). A. The ethyl ester IVc was prepared from acid IVa and ethanol as described in procedure B for the preparation of the methyl ester.

(20) H. J. Dauben, Jr. and L. L. McCoy, *J. Am. Chem. Soc.*, **81**, 4863 (1959).

B. The neutral product of the preparation of the acid IVa was the ethyl ester IVc. Usually this product was contaminated with traces of bromine and was dehydrobrominated by refluxing for 2 hr. with collidine. The product was recovered in the usual manner. The ester was crystallized from ethyl acetate, m.p. 105–107°; $\lambda_{max}^{CH_3OH}$ 224 mμ ε 10,100; ν_{max} 1730, 1710, 1670, 1610, 1160 cm.$^{-1}$ NMR τ 3.058, 3.233, 3.875, 4.067; quartet 5.825, 5.925, 6.042, and 6.175; triplet 8.687, 8.778, and 8.912.

Anal. Calcd. for $C_{20}H_{26}O_5$: C, 69.34; H, 7.57. Found: C, 69.37, 68.96. H, 7.47, 7.63.

3,5-Seco-4-nor-8(9)-androstene-5,11,17-trione-3-oic acid (V). A. A mixture of the ester IVc, 75 mg., in 4 ml. of methanol and 0.5 ml. of 2*N* sodium carbonate was boiled for 2 hr. The acid V was recovered from the acidified solution (65 mg.) as the sole product of reaction and was crystallized from mixtures of methanol and methylene chloride.

B. A mixture of acid IVa, 15.0 mg., methanol, 2 ml., 2*N* sodium carbonate, 0.1 ml., and water, 0.2 ml., was boiled for 2 hr. The acid V (13.2 mg.) was recovered in the usual manner.

The substance was crystallized from methanol-methylene chloride to a m.p. of 217–219°; $\lambda_{max}^{CH_3OH}$ 247–248 mμ ε 8200; ν_{max} 3200, 1740, 1715, 1640, 1620, 1160 cm.$^{-1}$ NMR did not show the presence of protons on a double bond.

Anal. Calcd. for $C_{18}H_{22}O_5$: C, 67.91; H, 6.97. Found: C, 67.87; H, 6.75.

Only unchanged starting material was recovered upon boiling for 2 hr. of a solution of the acid V, 25 mg., in acetic acid, 5 ml., containing 2 ml. of water and 1 drop of concd. hydrochloric acid.

Methyl-3,5:5,7-bisseco-4,6-bisnorandrostane-11,17-dione-7-aldehyde-5-acid 3-ester (VIa). A solution of ester IVb, 780 mg., in 100 ml. of dry ethyl acetate was cooled to −70° and treated with a stream of ozonized oxygen as previously described for the preparation of II. The solution was then agitated with 10 ml. of a 25% solution of carbon dioxide-free hydrogen peroxide for 4 hr. The aqueous phase was separated and saved. The ethyl acetate solution was distilled to dryness with three 5-ml. portions of water, then dissolved in ethyl acetate and partitioned with a solution of sodium bicarbonate to yield 198 mg. of a neutral fraction and 585 mg. of acid VIa.

The acid was crystallized several times from ethyl acetate, m.p. 162–165°, no selective absorption in the ultraviolet; ν_{max} 3700, 3500, 3350, 2650 (small), 1740, 1730, 1700, 1200, 1150, 1010, 980 cm.$^{-1}$

Anal. Calcd. for $C_{18}H_{24}O_7$: C, 61.35; H, 6.86. Found: C, 61.02; H, 6.86.

Isolation of C-6. The aqueous phase obtained from the decomposition and washing of the ozonized solution of IVb was placed in a round-bottom flask, acidified with acetic acid and treated at the boiling point with a solution of mercuric acetate, 1.5 g., in carbon dioxide-free water, 10 ml. A stream of carbon dioxide-free nitrogen was passed through the train of apparatus to carry over evolved gases through a barium hydroxide solution. The barium carbonate obtained was filtered, reprecipitated, and 275.5 mg. (60% yield) was obtained.

Bismethyl-3,5:5,7-bisseco-4,6-bisnorandrostane-11,17-dione 7-acid 3,5-diester (VII). The diester aldehyde VIb, 143 mg., prepared by treating VIa with diazomethane, was dissolved in 5 ml. of acetic acid and was treated with a solution of 150 mg. of chromium trioxide in 0.6 ml. of water. The mixture was left overnight at room temperature. The excess chromic acid was reduced with methanol, the volatile components were removed, the residue then dissolved in ethyl acetate and partitioned with a saturated solution of sodium bicarbonate to yield a neutral fraction and the acid VII, 56 mg. The acid was crystallized several times from ethyl acetate, m.p. 148–149°, no selective absorption in the ultraviolet; ν_{max} 3600 (shoulder,) 3500, 1750, 1710 (shoulder), 1190 cm.$^{-1}$

Anal. Calcd. for $C_{19}H_{26}O_8$: C, 59.67; H, 6.85. Found: C, 59.49; H, 6.52.

Isolation of C-5. An electrolysis cell equipped with two platinum wire electrodes was charged with a mixture of the acid VIa, 36.4 mg., pyridine, 0.4 ml., water, 0.2 ml., and triethylamine, 0.02 ml. The cell was attached to a 12-volt battery, an initial current of 6.5 MA was passed and provisions were made to absorb the evolved gases in a barium hydroxide solution. The intensity of the current decreased rapidly and after 2.5 hr. the reaction was interrupted. A stream of nitrogen was passed and the barium carbonate was filtered, then reprecipitated to yield 11.7 mg. of barium carbonate (57%).

Isolation of C-7. A mixture of 22.6 mg. of acid VII, pyridine, 0.4 ml., water, 0.2 ml., and triethylamine, 0.02 ml., was electrolyzed as described for isolation of C-5. Barium carbonate (8.0 mg.) was collected (68%).

3,5-Seco-4-nor-11β-hydroxyandrostane-5,17-dione-3-oic acid (IXa). A solution of VIII, 3.14 g., in ethyl acetate, 200 ml., was ozonized at −70° and then processed as described for the preparation of II to yield 1.15 g. of a neutral syrup and 1.96 g. of an acidic fraction from which the acid IXa was crystallized. Upon chromatography on silica gel of the acidic mother liquor an additional amount of IXa and a small amount of II was obtained.

A sample of IXa was crystallized several times from ethyl acetate, m.p. 209–210°; ultraviolet: none; ν_{max} 3500 (sharp), 3200 (broad), 2650, 1730, 1710, 1690 cm.$^{-1}$

Anal. Calcd. for $C_{18}H_{26}O_5$: C, 67.06; H, 8.13. Found: C, 67.25, 67.09; H, 7.73, 8.30.

The methyl ester IXb was prepared in the usual manner with diazomethane and showed a m.p. of 135–137°; ν_{max} 3600, 1755, 1735, 1715, 1179 cm.$^{-1}$

Anal. Calcd. for $C_{19}H_{28}O_5$: C, 67.83; H, 8.39. Found: C, 67.83, 67.62. H, 8.70, 8.45.

On heating of the ester IXb with an aqueous methanolic solution of sodium carbonate the acid IXa was obtained.

3,5-Seco-4-nor-11β-hydroxyandrostane-5,17-dione-3-oic acid 3,11-lactone (X). A mixture of acid IXa, 690 mg., and 100 mg. of fused sodium acetate in acetic anhydride, 60 ml., was boiled and then worked up as described for the preparation of III to yield 520 mg. of the lactone X. A sample was crystallized from ethyl acetate and methylene chloride to a m.p. of 196–198°; $\nu_{max}^{CHCl_3}$ 1725, 1710; ν_{max}^{KBr} 1730, 1720, 1700 cm.$^{-1}$ NMR τ 5.317.

Anal. Calcd. for $C_{18}H_{24}O_4$: C, 71.02; H, 7.95. Found: C, 70.93, 70.51; H, 7.97, 7.77.

A mixture of lactone X, 25 mg., in methanol, 5 ml., and a saturated solution of aqueous potassium bicarbonate, 0.5 ml., was left for 16 hr. at room temperature. The acid IXa was recovered in the usual manner.

A solution of lactone X, 15.3 mg., in acetic acid, 4 ml., was added to a solution of chromium trioxide, 25 mg., in water, 0.5 ml., and allowed to stand for 1 hr. at room temperature. The chromium trioxide was reduced with methanol, the volatile components were removed, the residue was dissolved in ethyl acetate, washed with water, a sodium bicarbonate solution, water, then dried and concentrated to yield 15 mg. of unchanged lactone.

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[CONTRIBUTION FROM THE WORCESTER FOUNDATION FOR EXPERIMENTAL BIOLOGY]

Degradation of Corticosteroids. V. Preparation and Certain Reactions of 11-Oxygenated-3,5-seco-4-nor-5β-hydroxy-3-oic Acid 3,5-Lactones[1a,b,2]

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Several 4-nor-3,5-steroid lactones were prepared and their structures were unequivocally established. It was shown that the reduction of 3,5-seco-4-nor-androstane-5,11,17-trione-3-oic acid with sodium borohydride, proceeds mainly from the back side of the molecule to form the corresponding 5β,11β,17β-triol which dehydrates with acids to the 11β,17β-dihydroxylactone Va. The lactone Va was converted to the δ-hydroxyamide which could not be converted to an amine under the conditions of the Hofmann rearrangement. On treatment with phenylmagnesium bromide the lactone Va gave the hydroxy ketone X the formation of which was interpreted as proceeding through an intramolecular hydride ion transfer.

In pursuing our studies on the degradation of corticosteroids, 11-oxygenated-4-nor-3,5-steroid lactones were needed and the preparation and properties of several such lactones is the subject of this communication. In addition the influence of the opening of ring A on the reduction of C-5, C-11 and C-17 ketones was studied. During the investigation, an abnormal reaction of the lactones with phenylmagnesium bromide and the inability to degrade a 5-hydroxy amide to an amine by the Hofmann method were encountered and are also reported.

Lactones of ring D have been widely investigated and their preparation by chemical[3a-g,j,4] and microbiological[3h,i] means has been described. In most cases, when the lactones were prepared by chemical means, 17-ketosteroids were submitted either to the Bayer-Villiger reaction with peracids or to alkaline hydrogen peroxide to yield mainly 13α-hydroxy-17-oic acid 13,17-lactones. Since peracids cleave ketones with retention of the configuration,[5,6]

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(2) Previous papers of this series: (a) *J. Org. Chem.*, 21, 814 (1956). (b) *J. Org. Chem.*, 22, 326 (1957). (c) *J. Org. Chem.*, 24, 669 (1959). (d) J. Org. Chem., 26, 3894 (1961).