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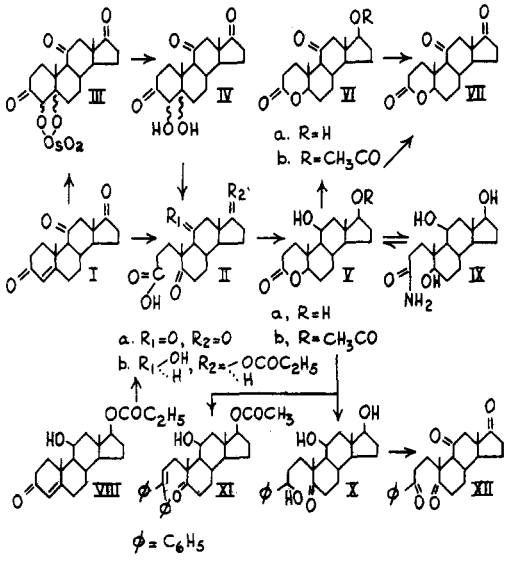
(2) Previous papers of this series: (a) *J. Org. Chem.*, 21, 814 (1956). (b) *J. Org. Chem.*, 22, 326 (1957). (c) *J. Org. Chem.*, 24, 669 (1959). (d) J. Org. Chem., 26, 3894 (1961).

the lactones must therefore have had the indicated 13α-structure. The shift of the substituted carbon-13 rather than carbon-16 is expected on both steric[3h] and electronic grounds.[7]

Relatively little information is available on 4-nor-5-hydroxy-3-oic acid 3,5-lactones,[8] and although several such compounds were prepared, attempts of assigning the configuration were made in only one case. Thus, 3-acid 5α-hydroxylactone and 3-acid 5β-hydroxylactone of the cholesterol series were assigned their configuration on the basis of rotational evidence[8a,9] and on results of hydrogenation of the 5-en-3,5-lactone (enol lactone) obtained from the 3,5-seco-4-nor-chloestane-5-keto-3-oic acid.

Ozonolysis of adrenosterone and the preparation of 11-keto-4-nor-acid IIa was described in a previous communication.[2d] The acid IIa was also prepared by an alternate route. Adrenosterone was first treated with an excess of osmium tetroxide in the presence of pyridine, then the osmate III was cleaved to what was probably a mixture of stereoisomeric *cis* glycols IV which in turn was oxidized with periodic acid to IIa. Although the osmate ester was obtained in good yield, cleavage proved to be difficult so that the yield of the glycol was not satisfactory. The oxidation of the glycol with periodic acid gave the acid IIa. Reduction of acid IIa with sodium borohydride in aqueous methanol containing sodium hydroxide[10,11] gave after dilution with water and acidification the crystalline lactone Va. The structure of the lactone (Va) was assigned to the product because of its method of preparation, its elementary composition, consistent with a $C_{18}H_{28}O_4$ compound and its insolubility in



aqueous sodium hydrogen carbonate. However the configuration of the lactone at C-5 and the hydroxy groups at C-11 and C-17 was not certain and required confirmation. In the intact steroid molecule, reduction of C-11 and C-17 ketones with lithium aluminum hydride or preferably with sodium borohydride gives predominantly the 11β and 17β-alcohols.[12,13] The specificity of the reagents to yield almost exclusively the "β" isomers was attributed to the greater accessibility of the "α" side of the molecule for the attack of the reducing agents. It was of interest to ascertain the influence of opening of ring A on the reduction of the C-5, C-11, and C-17 ketones.

Acetylation of the dihydroxylactone Va with acetic anhydride in pyridine gave the monoacetate Vb which was oxidized to the ketolactone VIb. The infrared spectrum of VIb showed a band at 1712 cm.$^{-1}$ characteristic of a ketone in a six-membered ring and the molecular rotational increment on oxidation $M_{VIb}-M_{Vb}$ was + 134°. Calculated from the data in the literature,[13a] the molecular rotational increment on oxidation of an 11β-hydroxyl was about + 180° and of an 11α-hydroxyl about + 360°. The formation of the monoacetate Vb and the oxidation of the hydroxyl to a six-membered ring ketone, together with the molecular rotational increment on oxidation + 134°, are con-

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TABLE I

Substance	$[M]_D$ (1)	Parent 5-keto 3-acid $[M]_D$ (2)	$\Delta[M]_D$ (1–2) (3)	$[M]_D$ (4)	$\Delta[M]_D$ (1–4) (5)
4-Oxa-5α(H)-cholestane-3-one[8a]	+312°	+137°[8a]	+175°	5α(H)-Cholestanone[a] + 165	+147
4-Oxa-5β(H)-cholestane-3-one[8a]	+ 71°	+137°[8a]	− 66°	5β(H)-Cholestanone[a] + 142	− 71
4-Oxa-5α(H)-androstane-3,11,17-trione VIII	+527°	+420°	+107°	5α(H)-Androstane-3,11,17-triones + 485	+ 42

[a] Calculated from specific rotation given in the literature.

sistent with the 11β-hydroxy configuration assigned to the lactone Va.

The assignment of the configuration at C-17 proved to be more difficult because the results of rotational analysis were inconclusive and a proof of the configuration by chemical means proved necessary. Conclusive evidence for the configuration at C-11 and C-17 was obtained by converting 11β-hydroxy-17β-propionoxy-4-androstene-3-one (VIII) to the lactone Va. Ozonolysis of the propionate VIII gave the 4-nor acid IIb, which was saponified, reduced with sodium borohydride, and then converted with mineral acid to the lactone Va thus confirming the "β" configuration of the hydroxyl group at C-11 and C-17. It seems, that although ring A was opened, the "β" side of rings C and D remained considerably shielded and the attack of the hydride ion proceeded from the more accessible "α" side.

In order to establish the configuration at C-5, the centers of asymmetry at C-11 and C-17 were eliminated by oxidizing the lactone Va to the diketo lactone VII. Axial protons show a band in the NMR spectrum[14,2d] at about τ 6.05-6.48 while equatorial at about τ 5.32–5.89. The NMR spectrum of the diketo lactone VII showed a band at τ 6.17 of an axial proton, hence the hydroxyl must have the 5β-equatorial configuration. The molecular rotational differences between the 5β(H)-lactones and their parent 5-keto 3-acids or the corresponding 5β(H)-3-ketosteroid are usually negative whereas the differences between the 5α(H)-lactones and their parent 5-keto 3-acids or 5α(H)-3-ketosteroids are positive (Table I).[9,8,15] The observed molecular rotational differences between the diketo lactone VII and the parent keto acid IIa or androstane-3,11,17-trione were + 107° and + 42° respectively, consistent with the assigned structure. The formation of the sterically favored equatorial hydroxyl is consistent with a rear attack of the reducing species on the ketone at C-5.

Inspection of models reveals that whereas the "α" side of the keto acid IIa appears to be more accessible, nevertheless the three carbon moiety at C-10 can fold back and partially obstruct the access to the C-5 ketone from the backside and force an attack of the reducing species from the top side of the molecule. Indeed, when the crude mother liquor of crystallization of the lactone Va was oxidized with chromium trioxide and the neutral product chromatographed on paper, two spots were detected with the Zimmermann reagent. It seems probable that a small amount of the isomeric 5α-hydroxy lactone was also formed, but no attempts were made to isolate the product.

The major infrared bands of the lactones in the solid state and in chloroform solutions are summarized in Table II. The frequencies of the carbonyl bands are somewhat lower than usually encountered for δ-lactones.[16,17] Similar low frequencies for δ-lactones were reported for columbin,[18] and recently for another series.[18a] The low frequencies observed for the lactones, in solution and in the solid state, might be due either to structural or solvent[16] factors. The lactones showed pronounced bands in the 1250 and 1050 cm.$^{-1}$ regions.[16] In the acetoxy compounds Vb and VIb the bands in the 1250 cm.$^{-1}$ region were merged and undistinguishable from the more intense acetate bands. The well-defined and intense band at about 1050 cm.$^{-1}$ was quite characteristic for the lactones. This is in contrast to the acid IIa or its 11β-hydroxy analog[2d] and their respective methyl esters[2d] which had less intense bands in the 1050 cm.$^{-1}$ region. The bands at about 1030 and 1015 cm.$^{-1}$ are probably due to hydroxy and acetoxy deformation and stretching vibrations. The lowering of the carbonyl band frequency in the solid state in the acetoxy lactone (Vb) (bands at 1745 and 1715 cm^{-1}), was probably the result of intermolecular hydrogen bonding in the crystal lattice.

The reaction of lactones with ammonia and amines has been thoroughly explored[19] and certain rules governing the course of the reaction were established as early as 1890. It has been shown that lactones of tertiary alcohols and enol lactones when

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TABLE II

MAJOR ABSORPTION BANDS OF THE INFRARED SPECTRA OF THE STEROIDAL 3,5-LACTONES[a]

Substance	Bands cm.$^{-1}$					
	(a) Solution in Chloroform		(b) Solid Incorporated in Potassium Bromide Disks			
	OH	C=O	OH	C=O		
Va	3600	1736	3464	1721	1273, 1225	1080, 1056, 1037, 1016
Vb	3625	1733, 1714 (w)(s)	3559, 3424	1745, 1715	1259 1214 (s)	1058, 1043
VIb	—	1743, 1733, 1721	—	1750, 1718	1259, 1248, 123	1049, 1027 (s)
VIa	3556 3484	1741, 1716	3474, 3344	1743, 1711	1270 (s), 1257, 1210	1053, 1038
VII	—	1751, 1733, 1716	—	1745, 1711	1249, 1229 (m), 1212 (m)	1055, 1048, 1032 (m), 1010 (m)

[a] (s) = shoulder; (w) = weak band, (m) = medium band. If not otherwise indicated the bands are of high intensity.

treated with ammonia or amines yield lactams whereas most lactones of primary, secondary, and phenolic hydroxyls give rise to δ-hydroxyamides.[19a,b] The δ-hydroxyamides under forcing conditions at elevated temperatures and pressures[15,19b,d] or catalytically at high temperature[19g] may dehydrate and form lactams. Indeed the δ-hydroxyamide IX was obtained by treating a solution of lactone Va with a concentrated aqueous solution of ammonium hydroxide or by treatment of a solution of the lactone Va in anhydrous methanol with ammonia. The substance, m.p. 261–265°, analyzed as expected for IX ($C_{18}H_{31}O_4N$) and its infrared spectrum showed bands at 1665 and 1640 cm.$^{-1}$, characteristic for amides.[20] The amide was stable to base but was hydrolyzed with dilute hydrochloric acid to the lactone Va. Attempts to prepare 2,5-seco-3,4-bisnor-5β,11β,17β-trihydroxyandrostan-2-amine from IX by the Hofmann degradation[21] method failed. Little carbon dioxide was evolved and at the completion of the reaction, lactone Va was obtained. A small amount of another product was also obtained but this was not investigated. It was apparent that rearrangement to the isocyanate did not occur. It seems possible that the electron pair of the oxygen at C-5 attacked the ketone bearing carbon at C-3 and evidently the driving force of the rearrangement could not overcome lactonization.

We then turned our attention to the possibility of using the lactone Va as starting material in a Barbier-Wieland[22] degradation of carbon-3. It was thought that upon treatment with an excess of phenylmagnesium bromide followed by dehydration of the formed tertiary alcohol 3,3-bisphenyl-3,5-seco-4-nor-5β,11β,17β-trihydroxy-2-androstene would be obtained and could then be cleaved in the conventional manner. The lactone Va was thus treated with an excess of phenylmagnesium bromide, then processed in the usual manner and a neutral substance, m.p. 223–227°, was obtained. That the reaction did not proceed as expected became apparent when a solution of the solid did not absorb ultraviolet light in the 240–250 mμ region and the product had an analysis corresponding to a $C_{24}H_{34}O_4$ compound. It became evident that instead of two phenyl residues, only one was incorporated in the molecule. The infrared spectrum of the solid showed bands at 3600 (broad) hydroxyls, 3010, 1600, 1480 aromatic ring and 1700 cm.$^{-1}$ non-conjugated carbonyl attached to a six-membered ring. The presence of the ketone in the product was surprising, because the lactone was treated for twenty-four hours with an excess of phenylmagnesium bromide at the boiling point of a mixture of benzene, ether, and tetrahydrofuran. Since it was improbable that the hydroxyl at C-11 was oxidized during the Grignard reaction it was assumed that the carbonyl is located in the immediate vicinity of the functional group involved in the reaction, *i.e.* C-3 or C-5. Since the attack of the phenyl ion had to proceed *via* the carbonyl of the lactone, the aromatic moiety must by necessity be attached at C-3. Spectroscopic evidence precluded placing of the ketone at C-3 in conjugation with the phenyl ring. It remained therefore to place the carbonyl at C-5 and the substance was identified as 3,5-seco-4-nor-3-phenyl-3,11β,17β-trihydroxyandrostan-5-one (X). Oxidation with chromium trioxide in pyridine of the alcohol X gave the neutral conjugated tetraketone XII, confirming thus the proposed structure X, and hence the location of the hydroxyl and phenyl groups at C-3 and of the ketone at C-5. This abnormal course of the Grignard reaction can be rationalized by assuming that the intermediate formed after the attack of the phenyl ion on the lactone carbonyl may undergo an intramolecular hydride ion transfer. Similar hydride ion transfers in related systems were previously proposed.[23] However, the possibility of X being

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formed in a base-catalyzed reduction oxidation sequence, cannot be excluded with certainty.[23a] From the acetylated mother liquor of IX, another product was obtained, m.p. 153–160°. The substance was assigned structure XI because it analyzed for a $C_{32}H_{38}O_4$ compound, absorbed ultraviolet light λ_{max} 252 and its infrared spectrum showed a band for a nonconjugated carbonyl in a six-membered ring at 1700 cm.$^{-1}$.

EXPERIMENTAL[24]

4ξ,5ξ-Dihydroxyandrostane-3,11,17-trione (IV).[25] To a solution of adrenosterone (I) 300 mg. in dry dioxane, 6 ml., pyridine, 0.5 ml., and osmium tetroxide, 250 mg., were added and the mixture was stored for 96 hr. at room temperature. The first crop of the osmate III, 350 mg., was collected after 48 hr. and the second 95 mg. at the termination of the experiment. Both crops gave identical infrared spectra.

A solution of the osmate III, 150 mg., in chloroform, 60 ml., was agitated for 2 hr. with a solution of mannitol, 6 g., potassium hydroxide, 2 g., in water, 60 ml. The phases were then separated, the chloroform layer was washed, dried, and concentrated to a dark residue (60 mg.). The residue was crystallized from ethyl acetate to yield 25 mg. of slightly impure glycol IV, m.p. 242–245°. Ultraviolet; no specific absorption in the 220–240 mμ region; infrared ν_{KBr} 3680, 1745, 1710, 1020 cm.$^{-1}$

3,5-Seco-4-nor-androstane-5,11,17-trione-3-oic acid (IIa). A mixture of the glycol IV, 20 mg., methanol, 3 ml., periodic acid, 40 mg., and water, 0.5 ml., was kept for 16 hr. at room temperature. The steroid acid was recovered in the conventional manner with ethyl acetate and 15 mg. of crude acid IIa was obtained. The infrared spectrum of the acid was identical to that of the acid obtained from ozonization of adrenosterone.[2d] $[a]_D$ +131° (*c*, 1.000 chloroform) $[M]_D$ + 420°.

3,5-Seco-4-nor-11β-hydroxy-17β-propionoxyandrostane-5-one-3-oic acid (IIb). A solution of the propionate VIII, 250 mg., in ethyl acetate, 50 ml., was ozonized[2d] at −70°. Then the ozonide was decomposed by rapid distillation with water under reduced pressure. The residue was partitioned with a solution of sodium hydrogen carbonate and 178 mg. of the crude acid IIb was obtained. The acid was utilized for the preparation of the lactone Va without purification.

3,5-Seco-4-nor-5β,11β,17β-trihydroxyandrostane-3-oic-acid-3,5-lactone (Va). a. To a solution of 1.65 g. of acid I in methanol, 80 ml., 2*N* sodium hydroxide, 5 ml., water, 15 ml., a solution of sodium borohydride, 2 g., in methanol, 20 ml., was added and the mixture was refluxed for 16 hr. The volatile components were removed *in vacuo*. Water, 100 ml. was added and the mixture was extracted with three 50-ml. portions of ether. The ether solution was washed and dried and on concentration gave 35 ml. of a residue which was not investigated. The alkaline aqueous phase was diluted with about 200 ml. of water, then acidified with concentrated hydrochloric acid and was kept for 2 hr. at 4°. The crystalline lactone was collected, 722 mg., m.p. 215–225°. The filtrate was extracted with ethyl acetate, washed and dried, and on concentration gave 900 mg. of a sirup from which an additional amount of Va was obtained.

b. A mixture of the acid IIb, 147 ml., methanol, 10 ml., 2*N* sodium hydroxide, 2 ml., sodium borohydride, 500 mg., was refluxed for 4 hr., then acidified, and the lactone Va was recovered with ethyl acetate.

c. A mixture of the amide IX, 25 mg., methanol, 5 ml., and 2*N* hydrochloric acid, 1 ml., was refluxed for 1 hr., then diluted with water, 50 ml., and extracted with ethyl acetate. The extract was washed, dried, and on concentration gave the lactone Va. The lactone could not be recovered with aqueous sodium hydrogen carbonate from an ethyl acetate solution.

A sample was crystallized several time from ethyl acetate and showed a m.p. of 246–252° with prior softening at 242° $[\alpha]_D$ +106.6°; (*c*, 1.11 in methanol); $[M]_D$ +329° infrared ν_{KBr}; 3464, 1721, 1273, 1225, 1080, 1056, 1037, 1016 cm.$^{-1}$; ν_{CHCl_3} 3600, 1736 cm.$^{-1}$

Anal. Calcd. for $C_{18}H_{28}O_4$: C, 70.10; H, 9.15. Found: C, 70.03, H, 9.08.

3,5-Seco-4-nor-17β-acetoxy-5β,11β-dihydroxyandrostane-3-oic acid 3,5-lactone (Vb). The lactone Va, 41 mg., was dissolved in pyridine, 0.4 ml., acetic anhydride, 0.2 ml. was added, and the mixture was kept for 16 hr. at room temperature. The steroid was recovered in the usual manner and was crystallized from ethyl acetate to yield 30.8 ml. of Vb.

A sample was crystallized several times from ethyl acetate to a m.p. of 192–194°; $[\alpha]_D$ +52.2° (*c* 0.65 in methanol; $[M]_D$ +183°; infrared ν_{KBr}: 3559, 3424, 1745, 1715, 1259, 1214, 1058, 1043 cm.$^{-1}$ ν_{CHCl} 3625, 1733, 1714 (weak shoulder) cm.$^{-1}$

Anal. Calcd. for $C_{20}H_{30}O_5$:$^1/_4$ H_2O: C, 67.67; H, 8.66. Found: C, 67.43; H, 8.53.

3,5-Seco-4-nor-5β-hydroxyandrostane-11,17-dione-3-oic-acid 3,5-lactone (VII). a. To a solution of lactone Va, 100 mg., in acetic acid, 3 ml., a solution of 200 mg. of chromium trioxide in 0.2 ml. of water was added and the mixture was kept for 16 hr. at room temperature. The excess chromium trioxide was reduced with methanol, the volatile components were removed *in vacuo* and the steroid was extracted with ethyl acetate. The extract was washed with aqueous sodium bicarbonate, dried, and concentrated to yield 62.3 mg. of neutral VII. An acidic fraction (28.2 mg.) was recovered from the sodium bicarbonate solution but was not investigated.

b. A solution of the 11-ketolactone VIa in pyridine was treated with a suspension of chromium trioxide in pyridine for 4 hr. and the diketolactone was recovered with ethyl acetate.

c. A portion of the crude mother liquor of crystallization of the lactone Va was oxidized as above and the neutral steroids were recovered with ethyl acetate. A portion of the residue was chromatographed on paper in the benzene-cyclohexane (1:1) formamide system and then the paper chromatogram was treated with the Zimmermann reagent.

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(23) R. B. Woodward, F. S. Sondheimer, and Y. Mazur, *J. Am. Chem. Soc.*, **80**, 6693 (1958); P. D. Bartlett and J. D. McCollum, *J. Am. Chem. Sod.*, **78**, 1441 (1956).

(23(a) We wish to thank one of the referees for suggesting to us this alternate possibility.

(24) Melting points were determined on a microhot stage and are reported as read. Infrared spectra were taken in chloroform solutions or on solids incorporated into potassium bromide disks. Ultraviolet spectra were taken in methanol on a Cary 11-MS spectrophotometer. Rotations were determined in chloroform or methanol in a 1 dm. semimicro tube. Elementary analyses were carried out by Dr. S. M. Nagy, Cambridge, Mass., and Dr. W. Kirstein, Upsala, Sweden. The NMR spectra were taken at 60 Mc. in deuterated chloroform containing 1% by volume of tetramethyl silane on a Varian High Resolution NMR Spectrometer Model V4300B. The spectra were calibrated using a Hewlett-Packard wide range oscillator Model 200 CDR together with a Hewlett-Packard counter Model 521CR. The results are expressed in τ units. $\tau = 10.00 - \frac{\nu_{TMS} - \nu_x}{\nu_{TMS}} \times 10^6$ where TMS = tetramethylsilane.

(25) The preparation of the glycol IV and its oxidation to the acid II was carried out by Dr. Y. W. Chang during his tenure of a postdoctoral fellowship in this laboratory in 1956–57.

Two spots were detected on the paper. The slower moving substance had a mobility identical to that of lactone VII.

A sample was crystallized from ethyl acetate and showed a m.p. 246–249° $[\alpha]_D$ +173° (*c* 0.70 chloroform) $[M]_D$ + 527°; infrared ν_{KBr}: 1745, 1711, 1249, 1229, 1212, 1055, 1048, 1032, 1010 cm.$^{-1}$. ν_{CHCl_3} 1751, 1733, 1716 cm.$^{-1}$ N.M.R. τ 6.17.

Anal. Calcd. for $C_{18}H_{24}O_4$: C, 71.02; H, 7.95. Found: C, 71.11; H, 7.72.

3,5-Seco-4-nor-17β-acetoxyandrostan-11-one-3-oic acid 3,5-lactone (VIb). A solution of the 17β-acetoxy lactone Vb, 99 mg., in pyridine, 1.0 ml., was added to a suspension of chromium trioxide, 100 mg., in pyridine, 1.0 ml., and the mixture was left for 4 hr. at room temperature.[26] The mixture was processed as previously described[27] to yield 63 mg. of VIb.

A sample was crystallized from ethanol and showed a m.p. 155–160° with prior softening at 150°. $[\alpha]_D$ +91° (*c* 0.64 in methanol); $[M]_D$ +317° infrared ν_{KBr}: 1750, 1718, 1259, 1248, 1237, 1049, 1027 cm.$^{-1}$. ν_{CHCl_3} 1743, 1733, 1721 cm.$^{-1}$

Anal. Calcd. for $C_{18}H_{28}O_5 \cdot {}^1/_4\ H_2O$: C, 68.05; H, 8.14. Found: C, 68.19; H, 8.04.

3,5-Seco-4-nor-5β,17β-dihydroxyandrostan-11-one-3-oic-acid-3,5-lactone (VIa). To a solution of VIb, 45 mg. in methanol 10 ml., water, 2 ml., and 2*N* sodium carbonate, 0.5 ml., was added. The air was displaced by nitrogen and the mixture was left for 16 hr. at room temperature. Then the solution was acidified with dilute hydrochloric acid, most of the methanol was removed *in vacuo* and the residue extracted with ethyl acetate. The extract was washed, dried, and on concentration yielded VIa.

A sample was crystallized from ethyl acetate and showed a m.p. of 200–205° then resolidified and melted again at 215–220° $[\alpha]_D$ +29.9° (*c* 0.5 in methanol), $[M]_D$ +92°; infrared ν_{KBr}: 3474, 3344, 1743, 1711, 1270, 1257, 1210, 1053, 1038 cm.$^{-1}$. ν_{CHCl_3} 3556, 3484, 1741, 1716 cm.$^{-1}$

Anal. Calcd. for $C_{18}H_{26}O_4 \cdot {}^1/_4\ H_2O$: C, 69.54; H, 8.59. Found: C, 69.88; H, 8.57.

3,5-Seco-4-nor-5β,11β,17β-trihydroxyandrostane-3-amide (IX). a. To a solution of the lactone Va, 250 mg. in purified dioxane, 20 ml., a concentrated solution of ammonium hydroxide, 10 ml., was added and the mixture was left for 16 hr. at room temperature. Removal of the volatile components left a residue which crystallized on trituration with methanol.

b. A solution of the lactone Va, 139 mg. in methanol, 20 ml. was saturated at room temperature with dry ammonia then was tightly closed and left for 16 hr. The volatile components were evaporated under nitrogen at room temperature and the crystalline amide IX was obtained.

A sample was crystallized from a mixture of methanol-acetone and ether and showed a m.p. 261–265.5; infrared ν_{KBr}: 3600 (shoulder), 3550, 3450 (shoulder), 1665, 1640, 1080, 1050, 1035 cm.$^{-1}$

Anal. Calcd. for $C_{18}H_{31}O_4N$: C, 66.43; H, 9.60; N, 4.30. Found: C, 66.43; H, 9.54; N, 4.24.

To a stirred and cooled suspension of the amide, 50 mg., in water, 2 ml. and purified tetrahydrofuran, 5 ml., 1*N* sodium hydroxide, 1 ml. was added and the mixture was kept for 30 min. in an ice bath. The suspension was then kept for 10 min. at room temperature and finally for 2 min. at 80°. After rapid cooling in an ice bath, water was added and the mixture was extracted with ethyl acetate. The extract was washed, dried, and on concentration unchanged amide was obtained.

3,5-Seco-4-nor-3-phenyl-3,11β,17β-trihydroxyandrostane-5-one (X). Phenylmagnesium bromide reagent was prepared from 2 g. of activated magnesium, and 2 ml. of bromobenzene in dry ether 10 ml. To the boiling reagent a solution of the lactone, 1 g. in a mixture of ether-benzene and tetrahydrofuran was added dropwise within 15 min. The mixture was kept under reflux for 24 hr. Then a saturated solution of ammonium chloride was added and the precipitated solid was filtered. The filtrate was concentrated to a residue, steam distilled under reduced pressure, then dissolved in ethyl acetate, washed to neutral, dried, and concentrated. The resulting sirup was dissolved in methanol, 2*N* sodium hydroxide, 5 ml. was added and the mixture was refluxed for 1 hr. The methanolic solution was diluted with water, the steroid extracted with ethyl acetate which was then washed, dried, and concentrated. The residue was dissolved in acetic acid, 10 ml., the mixture was refluxed for 2.5 hr. then the acid was removed *in vacuo*. The dark sirup was dissolved in ethyl acetate, washed, dried, concentrated, and the residue 1.04 g. was chromatographed on a silica gel column prepared with benzene petroleum ether 1:1. Eluates of 2% methanol in chloroform through 25% of methanol in chloroform gave 972 mg. of a partially acetylated sirup. A portion of the combined eluates, 900 mg., was dissolved in ethanol, sodium hydroxide 2*N*, 30 ml., was added and the solution was refluxed for 3 hr. and then left for 16 hr. at room temperature. The ethanol was removed *in vacuo*, water was added, and the aqueous phase was extracted with ethyl acetate. The ethyl acetate extract was washed, dried, and on concentration gave 576 mg. of a sirup which crystallized on trituration with ethyl acetate.

A sample was crystallized from ethyl acetate–methanol and showed a m.p. 223–227°. Ultraviolet $\lambda_{max}^{CH_3OH}$ 260 mμ ε 520; infrared ν_{KBr}: 3600, 3010, 1700, 1600, 1480, 1045 (strong) cm.$^{-1}$

Anal. Calcd. for $C_{24}H_{34}O_4$: C, 74.57; H, 8.87. Found: C, 74.05; H, 8.49; C, 73.92; H, 8.70.

3,5-Seco-4-nor-3-phenylandrostane-3,5,11,17-tetraone (XII). A solution of X, 31 mg., in pyridine 1.0 ml., was added to a mixture of chromium trioxide, 70 mg., in pyridine 0.7 ml. and was left for 16 hr. at room temperature. After processing in the usual manner 32 mg. of a crude residue was obtained. The residue was crystallized from ethyl acetate to give 11 mg. of XII in two crops. Ultraviolet $\lambda_{max}^{CH_3OH}$ 244 and 280 mμ; ϵ_{244}, 9500, ϵ_{280}, 810; infrared ν_{KBr}: 3050, 1745, 1700, 1680, 1600, 1580 cm.$^{-1}$

Anal. Calcd. for $C_{24}H_{28}O_4$: C, 75.76; H, 7.42. Found: C, 75.61; H, 7.10; C, 75.71; H, 6.70.

3,5-Seco-4-nor-3,3-diphenyl-11β-hydroxy-17-acetoxy-2-androsten-5-one (XI). A portion of the mother liquor obtained after the isolation of X, 141 mg., was acetylated in the usual manner and the product was recovered with ether. The acetylated residue was chromatographed on a silica gel column prepared with hexane benzene 1:1. Eluates obtained with mixtures of benzene chloroform (99:1) were rechromatographed on a short aluminum oxide column then crystallized from a mixture of acetone and petrolum ether. A small amount of crystalline XI was obtained which showed a m.p. 153–160°; ultraviolet $\lambda_{max}^{CH_3OH}$ 252 mμ ε 10500; infrared ν_{KBr} 3550, 1730, 1700 (shoulder), 1650, 1610, 1220 cm.$^{-1}$

Anal. Calcd. for $C_{32}H_{38}O_4$: C, 78.98; H, 7.87. Found: C, 78,64; H, 7.72; C, 78.64: H, 7.88.

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