Steroids. CCIX.[1] Ring A Modified Hormone Analogs. Part V. 2-Methylene-3-oxygenated Androstanes

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2-N-Piperidinomethylene-17α-methylandrostane-17β-ol-3-one (Ib) is converted by sodium borohydride in methanol solution to 2-methylene-17α-methylandrostane-3β,17β-diol (IIa). Extension of this reaction to other aminomethyleneketones in the androstane and Δ⁴-androstene series showed that the products are dependent on the nature of the amino substituent. The characterization of the reduction products and their mechanism of formation are discussed.

Our interest in "non-classical" steroidal compounds was greatly stimulated by the recent observations from these laboratories that a group of simple Δ²-androstenes exhibited useful biological properties.[2a,b] In our subsequent investigations, a series of ring A modified androstane derivatives were prepared which contained the 2-methylene, 2-methyl-Δ², 2-formyl-Δ² and 2-halomethyl-Δ² moieties.[1,3] We now wish to report the results of studies leading to the preparation of 2-methylene-3-oxygenated androstanes.

Recently de Stevens and Halamandaris[4] described the reduction of 2-N-pyrrolidinomethyleneandrostane-17β-ol-3-one (Ia) to the corresponding dihydro compound, 2α-N-pyrrolidinomethylandrostane-17β-ol-3-one (IIIa), with lithium aluminum hydride. Prior to this publication we had observed that the reduction of various 2-aminomethylene-3-ketosteroids with sodium borohydride afforded a completely different type of product. Furthermore, we have found that the course of the borohydride reduction process is dependent on the nature of the amine.

Treatment of 2-N-piperidinomethylene-17α-methylandrostane-17β-ol-3-one (Ib)[5] with an excess of sodium borohydride in methanol solution led to a nitrogen-free product IIa which gave analytical results indicating the formula $C_{21}H_{34}O_2$ and which readily afforded a monoacetate IIb after treatment with acetic anhydride and pyridine at room temperature. The infrared spectra of IIa and IIb exhibited absorption bands at 895 and 1660 cm.$^{-1}$, indicating the genesis of an exocyclic methylene grouping[6] by the reduction process. On the basis of this information the borohydride reduction product was assigned the structure 2-methylene-17α-methylandrostane-3β,17β-diol (IIa).

Additional chemical proof for the 2-methylene formulation of IIa was obtained. Since secondary allylic alcohols are rearranged easily to the corresponding saturated ketones with a palladium catalyst or mineral acid,[7] the 2-methylene-17α-methylandrostane-3β,17β-diol (IIa) was expected to yield 2α,17α-dimethyldihydrotestosterone (IIIb)[8] when allowed to react under these conditions. Treatment of the 2-exomethylene-3,17-diol IIa with 5% palladized charcoal in boiling methanol afforded an oil which exhibited a maximum at 241 mμ in the ultraviolet and displayed bands at 1680 and 1715 cm.$^{-1}$ in the infrared. Paper chromatographic examination of this product showed it to be a mixture of two compounds. The faster moving component was identical in polarity with the expected 2α,17α-dimethyldihydrotestosterone (IIIb),[8] while the second component moved at the same rate as 2,17α-dimethyl-Δ¹-androstene-17β-ol-3-one (IV).[9] A mixture of IIIb and IV would account for the observed spectral properties of the rearrangement product. Alumina chromatography afforded 2α,17α-dimethyldihydrotestosterone (IIIb) (identified by comparison with an authentic sample[8]) in 20% yield. As the second component was not obtained in a pure state by chromatography, the following reaction sequence was employed for its chracterization. The crude rearrangement product was reduced with lithium aluminum hydride to a mixture of diols, which was treated without purification with 2,3-dichloro-5,6-dicyano-1,4-benzoquinone (D.D.Q.) in dioxan at room temperature, conditions known to be selective for the oxidation of allylic alcohols.[10] Chromatographic purification of the oxidation product afforded 2,17α-dimethyl-Δ¹-androstene-17β-ol-3-one (IV), identical in all respects with an authentic sample.[9] A second more polar substance obtained from the chromatogram proved to be the expected 2α,17α-dimethylandrostane-3β,17β-diol (IIIc).[9] The Δ¹-androstene IV must originate from a competing oxidation process taking place during the palladium catalyzed rearrangement reaction, since 2α,17α-dimethyldihydrotestosterone (IIIb) was recovered unchanged when treated in an analogous manner.

The above series of transformations unequivocally established the 2-exomethylene-3,17-diol structure IIa for the product from the borohydride reduction of 2-N-piperidinomethylene-17α-methyldihydrotestosterone (Ib). However the stereochemistry of the 3-hydroxyl

(1) Steroids CCVIII and Part IV, J. A. Edwards, P. G. Holton, J. C. Orr, L. C. Ibáñez, E. Necoechea, A. de la Roz, E. Segovia, R. Urquiza and A. Bowers, *J. Med. Chem.*, **6**, 174 (1963).

(2) (a) J. A. Edwards and A. Bowers, *Chem. Ind.* (London), 1962 (1961); (b) A. Bowers, A. D. Cross, J. A. Edwards, H. Carpio, M. C. Calzada, and E. Denot, *J. Med. Chem.*, **6**, 156 (1963).

(3) A. D. Cross, J. A. Edwards, J. C. Orr, B. Berköz, L. Cervantes, M. C. Calzada and A. Bowers, *ibid.*, **6**, 162 (1963); J. C. Orr, O. Halpern, P. G. Holton, F. Alvarez, I. Delfín, A. de la Roz, A. M. Ruiz and A. Bowers, *ibid.*, **6**, 166 (1963); see also A. D. Cross, J. A. Edwards and A. Bowers, *ibid.*, **5**, 407 (1962); J. C. Orr, O. Halpern and A. Bowers, *ibid.*, **5**, 409 (1962).

(4) G. de Stevens and A. Halamandaris, *J. Org. Chem.*, **26**, 1644 (1961).

(5) J. A. Zderic, O. Halpern, H. Carpio, A. Ruiz, D. C. Limón, L. Magaña, H. Jiménez, A. Bowers and H. J. Ringold, *Chem. Ind.* (London), 1625 (1960).

(6) *Inter alia*, see F. Sondheimer and R. Mechoulam, *J. Am. Chem. Soc.*, **79**, 5029 (1957).

(7) (a) S. Sakai, *Chem. Pharm. Bull. Japan*, **7**, 50 (1959); (b) A. S. Dreiding and J. A. Hartman, *J. Am. Chem. Soc.*, **78**, 1216 (1956); (c) C. Djerassi, C. R. Smith, A. E. Lippman, S. K. Figdor and J. Herran, *ibid.*, **77**, 4801 (1955).

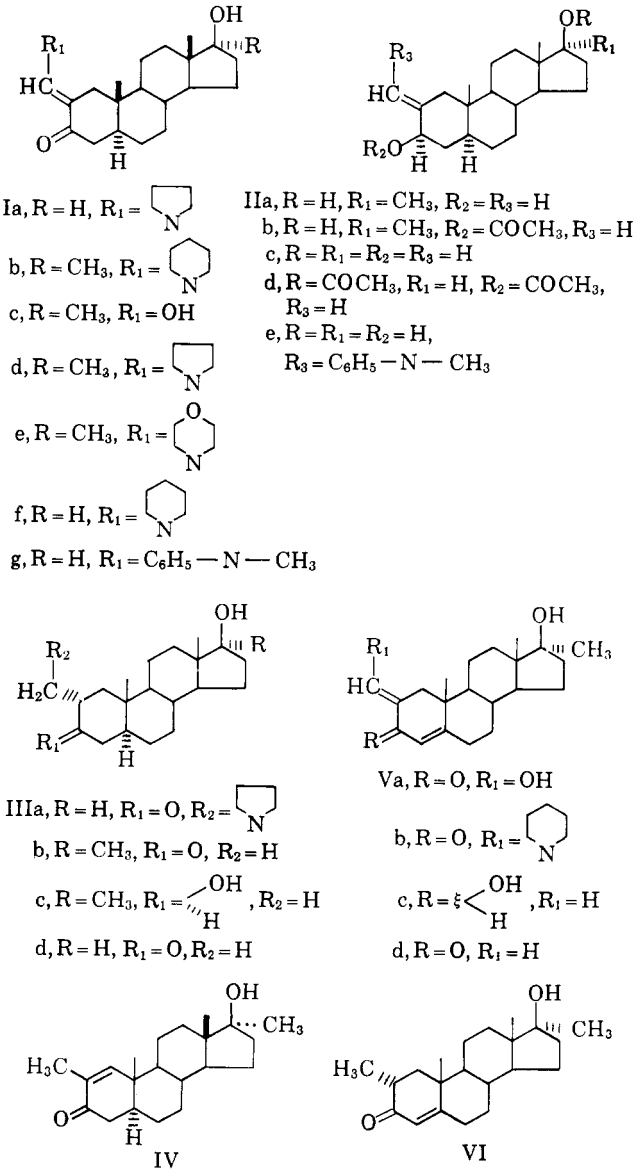
(8) H. J. Ringold, E. Batres, O. Halpern and E. Necoechea, *ibid.*, **81**, 427 (1959).

(9) R. Mauli, H. J. Ringold and C. Djerassi, *ibid.*, **82**, 5494 (1960).

(10) D. Burn, V. Petrow and G. O. Weston, *Tetrahedron Letters*, **9**, 14 (1960).

group of IIa remained to be assigned. This is presumed to be β-orientated on the basis of mechanistic considerations and molecular rotation data.

The first stage in the reduction of the aminomethyleneketone is 1,4-attack by hydride on A leading to the dihydroenolate B. Intermediate B then undergoes a reverse Michael reaction (see arrows) to give the α-methyleneketone C, which is then reduced to the alcohol D.[11] The final stage of the reduction (C to D) is expected to furnish a β oriented hydroxyl function,[12] as it has been established previously that the predominating isomer formed by the borohydride reduction of steroidal 3-ketones in the 5α-series is the equatorial β-alcohol.[13] Support for this assumption is obtained by considering the change in molecular rotation ($\Delta[M]_D$ −63°) produced on acetylation at C-3 of the reduction product IIa (see Table I). This value is in agreement with the shift observed ($\Delta[M]_D$ −32°) on acetylation at C-3 of 17α-methylandrostane-3β,17β-diol (IIIc). By contrast, acetylation of 3α-hydroxyandrostanes leads to positive values for the molecular rotation differences between the acetate and the alcohol.[14,15]



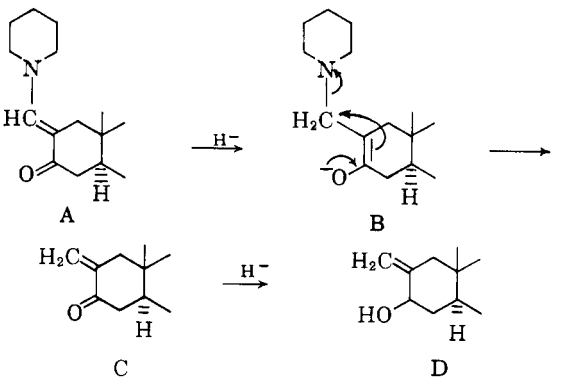


TABLE I
MOLECULAR ROTATION DIFFERENCES

Compound	$[M]_D$°	$\Delta[M]_D$° Acetate–alcohol
17α-Methylandrostane-3β,17β-diol	−33	
17α-Methylandrostane-3β,17β-diol 3-acetate	−65	−32
2-Methylene-17α-methylandrostane-3β,17β-diol (IIa)	−115	
2-Methylene-17α-methylandrostane-3β,17β-diol 3-acetate (IIb)	−178	−63
Androstane-3β,17β-diol	+12	
Androstane-3β,17β-diol 3,17-diacetate	−38	−50
2-Methyleneandrostane-3β,17β-diol (IIc)	−18	
2-Methyleneandrostane-3β,17β-diol 3,17-diacetate (IId)	−70	−52

The reduction of several other aminomethyleneandrostanes then was investigated. Both the pyrrolidine Id and morpholine Ie derivatives[16a,b] of 2-hydroxymethylene-17α-methyldihydrotestosterone (Ic) afforded the 2-methylene-3,17-diol IIa with sodium borohydride in methanol. In the 17α-hydrogen series, 2-N-piperidinomethyleneandrostane-17β-ol-3-one (If)[16b] was converted to 2-methyleneandrostane-3β,17β-diol (IIc) in the same manner. The structure proof for this substance follows from its elementary analysis, infrared bands at 895 and 1660 cm.$^{-1}$ (exocyclic methylene)[6] and conversion to 2α-methyldihydrotestosterone (IIId) with hydrochloric acid in methanol.[7b,c] The evidence supporting the 3β-hydroxyl configuration in IIc is again derived from a consideration of the reduction mechanism and molecular rotation data (see Table I).

In an accompanying paper[3] the sodium borohydride reduction of 2-N-methylanilinomethyleneandrostane-17β-ol-3-one (Ig) is described. The product from this reaction was shown to be the hydroxy enamine IIe

(11) A similar mechanism has been proposed by A. S. Dreiding and J. A. Hartman, *J. Am. Chem. Soc.*, **75**, 939 (1953), to account for the formation of 2-methylenecyclohexanol by the lithium aluminum hydride reduction of 2-hydroxymethylenecyclohexanone. See also L. H. Knox and E. Velarde, *J. Org. Chem.*, **27**, 3925 (1962), for related studies in the steroid series.

(12) A slightly less polar substance, possibly the 3α-alcohol, was detected by thin plate chromatography of the crude diol. However a single crystallization completely removed the impurity.

(13) For leading references see W. G. Dauben, E. J. Blanz, Jr., J. Jiu and R. A. Micheli, *J. Am. Chem. Soc.*, **78**, 3752 (1956).

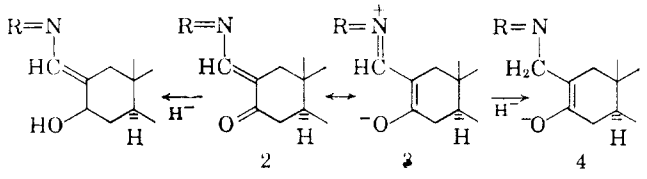
(14) See L. F. Fieser and M. Fieser, "Steroids," Reinhold Publishing Corp., New York, N. Y., 1956, p. 179.

(15) A 3α-hydroxyl formulation in IIa cannot be excluded with certainty on the basis of the above evidence since the effect of the 2-exomethylene grouping upon the rotatory contribution of the 3-alcohol and its acetate derivative is unknown.

(16) (a) R. O. Clinton, A. J. Manson, F. W. Stonner, R. L. Clarke, K. F. Jennings and P. E. Shaw, *J. Org. Chem.*, **27**, 1148 (1962); (b) J. A. Zderic and H. Carpio, forthcoming publication from these laboratories.

formed by 1,2-addition of hydride to the aromatic aminomethyleneketone Ig.[17] The striking differences observed in the reduction pathways of the alicyclic and the aromatic amino compounds with sodium borohydride must be attributed to the nature of the amino substituents. A satisfactory rationalization of these results may be made on the basis of electronic and steric considerations.

The two extreme resonance forms of the alicyclic aminomethyleneketones are represented by the expressions 2a and 3a. Hydride attack on 2a would be expected simply to reduce the 3-keto group to the enamine alcohol Ia. For the reduction of 3a, hydride attack at C-3 is prevented by the stabilized enolate and consequently reduction would proceed by attack on the C=N$^+$ linkage to produce 4a.[18] Therefore a predominance of the polarized form 3a is required for 1,4-reduction to occur. Since it has been shown experimentally that the alicyclic amino derivatives do undergo reduction by the 1,4-process, an intermediate of the type 3a may be the controlling factor in this reaction.



a —N=R = alicyclic amine
b —N=R = N-methylaniline

When the group N=R represents an aromatic substituent the concentration of the hybrid 3b would be considerably reduced due to the electron withdrawing properties of the phenyl group. Consequently 1,2 hydride attack on 2b to yield Ib would be the preferred pathway, in accord with the experimental results.

On the basis of the available evidence the control of these borohydride reductions by a steric effect cannot be excluded. Specifically the smaller alicyclic amino groups might permit 1,4-reduction while the bulkier N-methylanilino substituent could inhibit this reaction.

In view of the potential utility of the products obtained from the reduction of 2-aminomethylene-3-ketoandrostanes, it was of considerable interest to study the reduction of analogous compounds containing a Δ^4-double bond. For this purpose 2-N-piperidinomethylene-17α-methyltestosterone (Vb) was prepared in high yield by treating 2-hydroxymethylene-17α-methyltestosterone (Va)[8] with an excess of piperidine in boiling benzene solution. The initial reduction experiments with Vb were carried out in methanol solution at 0-10°. Under these conditions Vb failed to react to any appreciable extent, in contrast to the smooth reduction encountered with the androstane derivatives. However treatment of Vb with sodium borohydride in aqueous tetrahydrofuran at reflux temperature afforded a new compound, which no longer contained nitrogen. That the expected transformation to a 2-methylene steroid had indeed taken place was confirmed by the infrared spectrum which exhibited exocyclic methylene bands at 890 and 1670 cm.$^{-1}$.[6] On the basis of this information and the results encountered in the 4,5-dihydro series, the reduction product was formulated as 2-methylene-17α-methyl-Δ^4-androstene-3ξ,17β-diol (Ve). This substance was not obtained in a pure state and it was later shown to be admixed with a small amount of 2-methylene-17α-methylandrostane-3β,17β-diol (IIa).

Treatment of the impure dienol Ve with D.D.Q.[10] in dioxane, led, as expected, to rapid oxidation as evidenced by the precipitation of the corresponding hydroquinone. Chromatography of the oxidation product afforded 2-methylene-17α-methyltestosterone (Vd), λ_{max}^{EtOH} 261 mμ (log ϵ 4.18). The infrared spectrum of this dienone showed strong bands at 1620 cm.$^{-1}$ (double bond stretching) and 1670 cm.$^{-1}$ (unsaturated ketone). The high intensity exhibited by the former band is very characteristic for *cis*oid enones.[19] The nuclear magnetic resonance (n.m.r.) spectrum of the D.D.Q. oxidation product is also in complete agreement with the assigned structure.[20] Three sharp 3-proton methyl resonances occur at 54.3 (18-H), 66.9 (19-H) and 72.6 c./s. (17α-CH$_3$). The C-4 proton resonance appears at 351 c./s., broadened by long-range coupling. One of the exomethylene protons is heavily deshielded by the neighboring carbonyl group[21] and resonates at 356 c./s., while the other exomethylene proton resonance appears at 313 c./s. The difference in chemical shift between these two protons is 43 c./s. (0.71 p.p.m.), in good agreement with other related systems.[21] Both of the exomethylene proton resonance bands appear as triplets (*J*, *ca.* 2 c./s.) owing to mutual coupling and long-range coupling with the allylic protons at C-1. Reduction of the dienone Vd with lithium in liquid ammonia under controlled conditions afforded the known 2α,17α-dimethyltestosterone (VI).[8] These results furnish unequivocal proof for the 2-methylene-Δ^4-3-keto structure Vd[22] and of its precursor Ve.

In addition to 2-methylene-17α-methyltestosterone (Vd), the chromatography of the D.D.Q. oxidation product afforded 2-methylene-17α-methylandrostane-3β,17β-diol (IIa). The isolation of IIa was not unexpected, as the reduction of Δ^4-3-ketosteroids with sodium borohydride is known to produce the Δ^4-3-alcohol admixed with the saturated 3-alcohol.[23] Of greater interest is the stability of the 2-methylene-3,17-diol IIa to oxidation with D.D.Q. This substance was recovered in good yield after an 18 hour treatment with the quinone in boiling dioxan solution.[24] However chromium trioxide in pyridine[25] converted the 2-methylene-3,17-diol IIa to a new compound, m.p. 233-238°, which exhibited an absorption band in the infrared at

(17) Unpublished results from these laboratories have shown that the reduction of a number of steroidal 2-N-methylanilinomethylene-3-ketones with sodium borohydride always proceeds by 1,2-addition.

(18) For examples of the reduction of quarternary ammonium bases with sodium borohydride see B. Witkop and J. B. Patrick, *J. Am. Chem. Soc.*, **75**, 4474 (1953).

(19) *Cf.* R. L. Erskine and E. S. Waight, *J. Chem. Soc.*, 3425 (1960).

(20) The n.m.r. spectrum was taken in deuteriochloroform solution with a tetramethylsilane internal reference. Chemical shifts, Δ, are quoted as c./s. from the reference. A Varian A-60 spectrometer was used, in turn calibrated against a Varian HR 60 instrument suitably equipped for calibration by the standard side-band technique.

(21) *Cf.* L. M. Jackman, "Applications of Nuclear Magnetic Resonance Spectroscopy in Organic Chemistry," Pergamon Press, London, 1959, pp. 122–123.

(22) After the completion of this work the preparation of 2-methylenecortisone 21-acetate (containing the same chromophore as Vd) by an alternate sequence, was reported by T. R. Carrington, A. G. Long and A. F. Turner, *J. Chem. Soc.*, 1572 (1962); see also footnote 7 in ref. 22.

(23) F. Sondheimer, M. Velasco, E. Batres and G. Rosenkranz *Chem. Ind.* (London), 1482 (1954).

(24) Dr. B. Berköz of these laboratories also has observed that Δ^2-androstene-1α,17β-diol 17-acetate is resistant to oxidation with D.D.Q.

(25) G. I. Poos, G. E. Arth, R. E. Beyler and L. H. Sarett, *J. Am. Chem. Soc.*, **75**, 422 (1953).

1725 cm.$^{-1}$ corresponding to a saturated carbonyl group. This substance is presumed to be the dimer[9] derived from the initially formed 2-methylene-17α-methylandrostane-17β-ol-3-one.

Biological Data.—Androgen–anabolic assays were carried out as described previously.[2b] The introduction of the 2-methylene group into 17α-methyltestosterone did not enhance its anabolic or androgenic activity; the 2-methylene-Δ^4-3-ketone Vd had 15% and 50%, respectively, of the androgenic and anabolic activity of 17α-methyltestosterone.

The authors are indebted to Prof. F. Sondheimer and Prof. G. Stork for helpful discussions and to Dr. A. D. Cross for the n.m.r. spectra and interpretation.

Experimental[26]

2-Methylene-17α-methylandrostane-3β,17β-diol (IIa).—An ice-cold solution of sodium borohydride (15.6 g.) in methanol (460 ml.) was added to a previously cooled solution of 15.6 g. of 2-N-piperidinomethylene-17α-methyldihydrotestosterone (Ib)[5] in 460 ml. of methanol and the reaction was left for 5 hr. Addition of water (8 l.) precipitated 12 g. of product which after crystallization from acetone–hexane afforded 6.2 g. of the 2-methylene-3,17-diol IIa, m.p. 223–226°, and a second crop of 2.7 g., m.p. 224–226° (8.9 g. or 71%). The analytical sample was prepared from the same solvent pair and exhibited m.p. 233–235°; $[\alpha]_D$ −36°; ν_{max} 1660 and 895 cm.$^{-1}$.

Anal. Calcd. for $C_{21}H_{34}O_2$: C, 79.19; H, 10.76; O, 10.05. Found: C, 79.50; H, 10.94; O, 9.89.

Acetylation of IIa with acetic anhydride and pyridine at room temperature provided the acetate IIb, m.p. 125–127°; $[\alpha]_D$ −49; ν_{max} 1745, 1660, 1235 and 895 cm.$^{-1}$.

Anal. Calcd. for $C_{23}H_{36}O_3$: C, 76.62; H, 10.07; O, 13.31. Found: C, 76.50; H, 10.39; O, 13.22.

Rearrangement of 2-Methylene-17α-methylandrostane-3β,17β-diol (IIa) with 5% Palladium Carbon Catalyst.—A solution of 0.5 g. of IIa in 50 ml. of methanol was boiled for 8 hr. with 0.05 g. of 5% palladium-on-carbon catalyst. Removal of the catalyst and concentration afforded 0.43 g. of oil, $\lambda_{max.}$ 241 mμ; $\nu_{max.}^{CHCl_3}$ 1715 and 1680 cm.$^{-1}$. A solution of this product in hexane–benzene (3:2) was adsorbed on a column of 20 g. of alumina and the product was eluted with increasing concentrations of benzene. The crystalline fractions without maximal absorption in the ultraviolet at 241 mμ were combined and crystallized from acetone–hexane to yield 90 mg. of 2α,17α-dimethyldihydrotestosterone (IIIb), m.p. 154–156°, identical in all respects with an authentic sample.[8]

2,17α-Dimethyl-Δ^1-androstene-17β-ol-3-one (IV).—A solution of 1 g. of the palladium-on-carbon rearrangement product (prepared by treating 1 g. of the 2-methylene-3,17-diol IIa with an equal weight of catalyst as described above) in 25 ml. of dry tetrahydrofuran was added dropwise to a boiling solution of lithium aluminum hydride (1 g.) in tetrahydrofuran (25 ml.). The reaction mixture was heated under reflux for 18 hr., cooled, and the excess hydride destroyed with acetone and saturated sodium sulfate solution. The precipitated solids were collected and the filtrate was concentrated to a small volume and treated with methylene chloride. This solution was dried over sodium sulfate and reconcentrated to yield 1 g. of crystalline solid.

A solution of the reduction product in 30 ml. of dioxan was treated with a solution of 0.35 g. of 2,3-dichloro-5,6-dicyano-1,4-benzoquinone in 20 ml. of dioxan and the reaction mixture was left standing 4 days. Methylene chloride (500 ml.) was added and the solution was filtered through a column of 40 g. of alumina. The column was washed with an additional 300 ml. of solvent and the combined eluates were concentrated to dryness *in vacuo*. A benzene solution of the resulting oil (0.6 g.) was adsorbed on a column of 24 g. of alumina. Mixtures of benzene and benzene–ether (4:1) eluted 0.22 g. of oil and mixtures of benzene–ether (3:2, 2:3) eluted 0.15 g. of crystals. Acetone–hexane crystallization of the latter fraction afforded 0.08 g. of 2α,17α-dimethylandrostane-3β,17β-diol (IIIc), m.p. 132–134°, identical in all respects with an authentic sample.[9]

The less polar oil after rechromatography on alumina and crystallization (acetone–hexane) yielded 0.04 g. of crystals, m.p. 165–167°, identical with a sample of 2,17α-dimethyl-Δ^1-androstene-17β-ol-3-one (IV).[9]

2-Methylene-17α-methylandrostane-3β,17β-diol (IIa) from 2-N-Pyrrolidinomethylene-17α-methyldihydrotestosterone (Id).[16a,b]—The reduction of 0.6 g. of the pyrrolidinomethylene compound Id in 18 ml. of methanol with a solution of 0.6 g. of sodium borohydride in 18 ml. of methanol as described previously gave 0.14 g. of the 2-methylene-3,17-diol IIa, m.p. 229–232°.

IIa from 2-N-morpholinomethylene-17α-methyldihydrotestosterone (Ie).[16b]—The reduction of 0.75 g. of the morpholinomethylene compound Ie, dissolved in 22 ml. of methanol, with a solution of 0.75 g. of sodium borohydride in 22 ml. of methanol at 5° during 5 hr., provided, after isolation with methylene chloride and crystallization, 0.18 g. of the 2-methylene-3,17-diol IIa, m.p. 227–230°.

2-Methyleneandrostane-3β,17β-diol (IIc).—A solution of 0.4 g. of 2-N-piperidinomethylenedihydrotestosterone (If)[16b] in methanol (12 ml.) was cooled in ice and treated with 0.4 g. of sodium borohydride dissolved in cold methanol (12 ml.). The reaction was stirred for 5 hr. at 5°, when diluted with 250 ml. of water and the product isolated with methylene chloride. Crystallization from acetone–hexane yielded 0.3 g. of solvated crystals, m.p. 116–120°, resolidifying and melting again at 174–179°. Four more crystallizations from the same solvent mixture gave the analytical specimen 196–198°; $[\alpha]_D$ −6°; ν_{max} 1660 and 895 cm.$^{-1}$.

Anal. Calcd. for $C_{20}H_{32}O_2$: C, 78.89; H, 10.59; O, 10.51. Found: C, 78.42; H, 10.62; O, 10.97.

Treatment of IIc with acetic anhydride–pyridine mixture at room temperature afforded the diacetate IId, m.p. 116–118°; $[\alpha]_D$ −18°; $\nu_{max}^{CCl_4}$ 1740, 1660, 1240 and 897 cm.$^{-1}$.

Anal. Calcd. for $C_{24}H_{36}O_4$: C, 74.19; H, 19.34. Found: C, 74.48; H, 9.51.

2-N-Piperidinomethylene-17α-methyltestosterone (Vb).—2-Hydroxymethylene-17α-methyltestosterone[7] (10 g.) was dissolved in benzene (260 ml.) and piperidine (10 ml.) and heated under reflux for 15 min. Removal of the benzene and filtration gave 9.5 g. of Vb. Recrystallization of this material from benzene–hexane yielded 9.2 g. of amino steroid, m.p. 217–220°. The melting point was unchanged after several additional crystallizations from the same solvent pair, $[\alpha]_D$ −261°; λ_{max} 250 and 275 mμ, log ϵ 4.19 and 4.13; ν_{max} 1640 and 1535 cm.$^{-1}$.

Anal. Calcd. for $C_{26}H_{39}NO_2$: C, 78.54; H, 9.89; N, 3.52. Found: C, 78.95; H, 9.67; N, 3.49.

Sodium Borohydride Reduction of 2-N-Piperidinomethylene-17α-methyltestosterone (Vb).—Sodium borohydride (51 g.) was added to a solution of 51 g. of 2-N-piperidinomethylene-17α-methyltestosterone (Vb) in 1 l. of tetrahydrofuran and 120 ml. of water. The reaction mixture was boiled under reflux for 10 hr. and then left standing at room temperature for 18 hr. Addition of water precipitated 36.5 g. of a crystalline solid which was crystallized from acetone–hexane to yield 13.5 g. of product, m.p. 182–185°; ν_{max} 1670 and 890 cm.$^{-1}$; and a second crop of 2.5 g., m.p. 173–176°.

2-Methylene-17α-methyltestosterone (Vd).—A solution of 13 g. of product from the preceding experiment in 1 l. of dioxan was treated with 10.4 g. of 2,3-dichloro-5,6-dicyano-1,4-benzoquinone and left for 18 hr. The reaction mixture was diluted with 6 l. of methylene chloride and filtered through a column of 780 g. of alumina. The column was washed with an additional 5 l. of solvent and the combined eluates were concentrated to yield 11 g. of crystals. This product was dissolved in 250 ml. of hexane–benzene (1:1) and chromatographed on a column of 440 g. of acetic acid-washed alumina. The chromatogram was developed with mixtures of hexane–benzene (2:3, 1:4 and 1:9). The fractions eluted with benzene and benzene–ether (9:1, 4:1) were combined (8.5 g.) and crystallized from acetone–hexane to yield 3.8 g. of 2-methylene-17α-methyltestosterone (VId), m.p. 187–190°. A second crop of 1.1 g., m.p. 184–186°, was obtained from the concentrated mother liquors. The analytical sample prepared from acetone–hexane exhibited m.p. 199–201°; $[\alpha]_D$ +160°; λ_{max} 261 mμ, log ϵ 4.18; ν_{max} 1670, 1620 and 895 cm.$^{-1}$.

Anal. Calcd. for $C_{21}H_{30}O_2$: C, 80.21; H, 9.62; O, 10.18. Found: C, 80.17; H, 9.73; O, 10.03.

(26) All melting points are uncorrected. Rotations were measured in chloroform, ultraviolet spectra in 95% ethanol and infrared spectra in potassium bromide disks unless otherwise stated. The infrared spectra were obtained with a Perkin–Elmer Model-21 spectrophotometer with a sodium chloride prism. Alumina was prepared as described in ref. 2b, footnote 42.

Benzene–ether (1:1, 1:4), pure ether and ether–methylene chloride (1:1) eluted an additional 1.4 g. of crystals. Acetone–hexane crystallization afforded 1 g. of 2-methylene-17α-methylandrostane-3β,17β-diol (IIa), m.p. 222–225°.

2α,17α-Dimethyltestosterone (VI).—A solution of 0.5 g. of 2-methylene-17α-methyltestosterone (Vd) in 25 ml. of mixture of dry ether–dioxan (4:1) was added rapidly to a stirred solution of lithium (0.2 g.) in liquid ammonia (150 ml.). Ammonium chloride (5 g.) was added immediately to the reaction and the ammonia was permitted to evaporate. The residue was treated with water and the resulting mixture extracted with methylene chloride. The organic extracts were washed with 5% hydrochloric acid and 5% sodium bicarbonate solution and finally with water. Concentration of the sodium sulfate-dried extracts afforded 0.55 g. of oil which was dissolved in hexane–benzene (1:1) and adsorbed on a column of 20 g. of alumina. Elution with mixtures of hexane–benzene (2:3 and 1:2) and with pure benzene provided 0.24 g. of crystals. Crystallization from acetone–hexane gave 0.14 g. of 2α,17α-dimethyltestosterone (VI), m.p. 152–154°, identical in all respects with an authentic sample.[7]

Chromium Trioxide-Pyridine Oxidation of 2-Methylene-17α-methylandrostane-3β,17β-diol (IIa).—A solution of 1 g. of 2-methylene-17α-methylandrostane-3β,17β-diol (IIa) in 20 ml. of pyridine was added to a suspension of chromium trioxide (1 g.) in pyridine (20 ml.). The reaction mixture, after standing for 24 hr., was diluted with ethyl acetate and the solids were removed by filtration through Celite. The filtrate was washed with 5% hydrochloric acid and 5% sodium bicarbonate solution and finally with water. Removal of the solvent afforded 0.66 g. of product which was dissolved in benzene and adsorbed on a column of 25 g. of alumina. The product obtained by elution with ether and ether–acetone (9:1, 4:1 and 1:1) was crystallized from acetone to yield 0.4 g. of dimer, m.p. 215–225°, and raised to 233–238° after 2 additional crystallizations: $[\alpha]_D$ +34°; ν_{max} 1725 cm.$^{-1}$.

Anal. Calcd. for $C_{42}H_{64}O_4$: C, 79.70; H, 10.19. Found: C, 80.38; H, 10.32.

Steroids. CCX.[1] Ring A Modified Hormone Analogs. Part VI. Δ²- and 2-Formyl-Δ²-17β-ol-17α-propionic Acid Spirolactones

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The preparation of Δ²-androstene-17β-ol-17α-propionic acid lactone (VII) and 2-formyl-Δ²-androstene-17β-ol-17α-propionic acid lactone (X) is described.

Some pharmacological agents are capable of evoking renal modulation of electrolyte and water balance. Among these drugs, the diuretics, the action of which is dependent upon a functionally active kidney, act upon this organ in increasing the flow of urine.[3]

The synthesis of steroidal aldosterone antagonists has recently been described.[4–9]

These compounds, which are 17-spirolactones of the androstane series, are active biologically in that they are antagonists of the renal tubular action of aldosterone.[10a] Recently, anti-inflammatory properties also have been found for these 17-spirolactones.[10b]

The original studied[4,5] of the Searle group with 3-(Δ⁴-androstene-17β-ol-3-one-17α-yl)-propionic acid γ-lactone (Ia) and its 19-nor analog Ib were extended to various substituted homologs in attempts to increase their oral and aldosterone-blocking activities. The effect of methyl substitution at C-2, C-4, C-6, C-7 and C-16[8] and the introduction of Δ¹- and Δ⁶-double bonds[6] was examined. One of the more successful modifications of the Δ⁴-3-ketone 17-spirolactone I was the corresponding 7α-acetylthio analog.[6] All of these compounds however had the "classical" Δ⁴-3-keto chromophore in ring A.

Following the general considerations developed in the first paper of this series,[11] it was of interest to prepare some "non-classical" 3-desoxy-17-spirolactones in which the electron density requirements of ring A were met by a Δ²-double bond[11] or a 2-formyl-Δ²-grouping.[12]

A suitable starting material for the preparation of these "non-classical" spirolactones VII and X, was androstane-3β-ol-17-one (II),[13] which on reaction with ethynylmagnesium bromide[14] readily afforded 17α-ethynylandrostane-3β,17β-diol (IIIa).[15] Attempts to prepare the carboxylic acid IV by an exchange reaction with methymagnesium bromide and the 17α-ethynyl compound IIIa, then carboxylation, were unsuccessful, presumably due to the immediate precipitation of an insoluble complex formed by the interaction of the methylmagnesium bromide with the 3β-hydroxyl group of IIIa. This problem was overcome by conversion of the 3β-alcohol IIIa into its 3-(2′-tetrahydropyranyl)-ether IIIb.[16] The latter IIIb smoothly

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(2) This work constitutes part of the undergraduate thesis submitted by J. R. to the University of Mexico.

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