Anal. Calcd. for $C_{24}H_{36}OS_2$: C, 68.52; H, 8.62; S, 15.24. Found: C, 68.21; H, 8.72; S, 14.92.

2-Methyl-Δ^2-androsten-17β-ol (IIIb) from the Dithioketal (XIb).—To 750 ml. of liquid ammonia 6.5 g. of metallic sodium was added with 5 g. of 2-methyl-Δ^1-androsten-3-ethylene-dithioketal-17β-acetate (XIb) in solution in 350 ml. of tetrahydrofuran. Thereafter the excess of sodium was discharged by the addition of ethanol. Ammonia was evaporated overnight and the organic solvents were evaporated under reduced pressure. The organic mixture then was dissolved in chloroform, washed with water, and dried over sodium sulfate. Filtration and solvent evaporation yielded an oil which was chromatographed through activated, neutral alumina. The fractions obtained with benzene were combined and 620 mg. of IIIb was obtained, identical by mixture m.p. and infrared spectrum with a sample prepared as described above.

2-Methyl-Δ^1-androsten-17β-ol-17-acetate (XIc).—A solution of 6 g. of 2-methyl-Δ^1-androsten-3-ethylene dithioketal-17β-acetate in 1000 ml. of acetone was refluxed with stirring for 48 hr. with 75 g. of Raney nickel, which was previously deactivated by several decantations from 600 ml. of acetone. After filtration and evaporation of the solvent, the gummy mixture was filtered through neutral, activated alumina. The fractions obtained by elution with hexane were combined to furnish 2.2 g. of XIc which was recrystallized from heptane. An analytical sample had m.p. 99-101°; $[\alpha]_D$ +84°; ν_{max} 1733 (s) and 1247 cm.$^{-1}$ (s).

Anal. Calcd. for $C_{22}H_{34}O_2$: C, 79.95; H, 10.37; O, 9.68. Found: C, 79.80; H, 10.15; O, 9.44.

4α-Bromo-2α-methylandrostane-3β,17β-diol-17β-acetate (XIIb).—A solution of 3.74 g. of 4α-bromo-2α-methylandrostan-3-one-17β-ol acetate[10] in 150 ml. of tetrahydrofuran was mixed with a solution of 4 g. of sodium borohydride in 30 ml. of methanol and left overnight at room temperature. The solution was poured into water, extracted with ethyl acetate and the organic layer then was washed with water until neutral, dried with sodium sulfate, and evaporated to a crystalline mass. Four recrystallizations from methanol yielded 2.20 g. of XIIb, m.p. 213–215°; $[\alpha]_D$ −47°.

Anal. Calcd. for $C_{22}H_{35}BrO_3$: C, 61.80; H, 8.25; O, 11.21; Br, 18.70. Found: C, 61.62; H, 8.32; O, 10.60; Br, 19.33.

2α-Methyl-Δ^3-androsten-17β-ol (XIIIa).—The bromohydrin XIIb (1.18 g.) in 10 ml. of acetic acid was refluxed for 5 hr. with 4.0 g. of powdered zinc. The zinc was filtered off, and washed with hot ethanol (100 ml.). The combined ethanol and acetic acid solutions were poured into water, extracted with ethyl acetate, and the extract was washed with aqueous sodium bicarbonate and then with water until neutral. The ethyl acetate solution was evaporated to dryness, the residue dissolved in ethanol (50 ml.) containing potassium hydroxide (2 g.) and left at room temperature overnight. Working up by pouring into water, extracting into ethyl acetate, washing with water until neutral, and evaporating, chromatographing on 30 g. of alumina (activity I) and eluting with benzene yielded XIIIa, 430 mg. after four recrystallizations from hexane, m.p. 145-147°; $[\alpha]_D$ +129°; ν_{max} 3320 (s), 3030 (w), 1658 (w) and 698 cm.$^{-1}$ (s).

Anal. Calcd. for $C_{20}H_{32}O$: C, 83.27; H, 11.18; O, 5.55. Found: C, 83.71; H, 11.10; O, 5.49.

2α-Methyl-Δ^3-androsten-17β-ol Acetate (XIIIb).—Acetic anhydride-pyridine acetylation of 2α-methyl-Δ^3-androsten-17β-ol (XIIIa) at room temperature overnight led to the corresponding acetate XIIIb which was recrystallized several times from acetone, m.p. 150-152°; $[\alpha]_D$ −101°; ν_{max} 1732 (s), 1650 (w), 1250 (s) and 702 cm.$^{-1}$ (s).

Anal. Calcd. for $C_{22}H_{34}O_2$: C, 79.95; H, 10.37. Found: C, 79.50; H, 10.55.

2α,17α-Dimethylandrostan-17β-ol (XIV).—A mixture of 10 g. of 2α,17α-dimethylandrostan-3-one-17β-ol (Id) and 20 ml. of hydrazine hydrate in 500 ml. of ethylene glycol was maintained under reflux during 3 hr. Potassium hydroxide (10.0 g.) was added and the internal temperature raised to 190° by distillation and held there for 5 hr. under reflux. On addition of 500 ml. of water a precipitate formed which was extracted into ethyl acetate and washed to neutrality with water. Evaporation of the dried extracts left a residue which was chromatographed over 400 g. of alumina. Elution with benzene–ether (4:1) afforded 3.81 g. of XIV, m.p. 119-122°. Recrystallization from methanol–water yielded prisms, m.p. 127-129°; $[\alpha]_D$ −12°; ν_{max} 3480 cm.$^{-1}$ (m).

Anal. Calcd. for $C_{21}H_{34}O$: C, 82.83; H, 11.92. Found: C, 82.68; H, 11.84.

Steroids. CCVII. Ring A Modified Hormone Analogs. Part III.[1] 2-Formyl-Δ^2-androstenes and Related Compounds. A New Class of Potent Anabolic Agents[2]

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The preparation of a series of 2-formyl, 2-hydroxymethyl, 2-carboxy and 2-acetyl-Δ^2-androstenes as well as the 4α-chloro, 4α-methyl and Δ^4-analogs of 2-formyl-Δ^2-androstene-17β-ol is described. Direct acylation of Δ^2-androstene-17β-ol afforded 3-acetyl-Δ^2-androstene-17β-ol. A number of these compounds possess high myotrophic activity with a favorable myotrophic–androgenic ratio.

As a continuation of our studies of compounds with variable electron density patterns around ring A[3] and particularly those possessing a Δ^2-double bond,[1,3] it appeared that a moiety which warranted attention was the 2-formyl-Δ^2-system.

As long ago as 1941, 2-formyl-Δ^2-cholestene[4] was prepared by pyrolysis of the α-ketolactone derived from 2-oxalyl cholestan-3ζ-ol. The preferred method for the introduction of the 2-formyl-Δ^2-grouping is, however, that used in the preparation of cyclohexene aldehyde from cyclohexanone,[5] and proceeds *via* the previously described[6] 2-hydroxymethylene-3-ketones.

2-Hydroxymethyleneandrostane-17β-ol-3-one[6] (Ia) was smoothly converted into its methyl ether Ib by treatment at room temperature with methanol containing a catalytic amount of hydrochloric or perchlo-

(1) Steroids. CCVI and Part II. A. D. Cross, J. A. Edwards, J. C. Orr, B. Berköz, L. Cervantes, M. C. Calzada and A. Bowers, *J. Med. Chem.*, **6**, 162 (1963).

(2) For a preliminary account of a part of this work *cf.*, J. C. Orr, O. Halpern and A. Bowers, *ibid.*, **5**, 409 (1962).

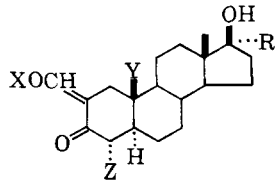
(3) For a general discussion of the considerations which govern our thinking in this work see Part I of this series: A. Bowers, A. D. Cross, J. A. Edwards, H. Carpio, M. C. Calzada and E. Denot, *ibid.*, **6**, 156 (1963).

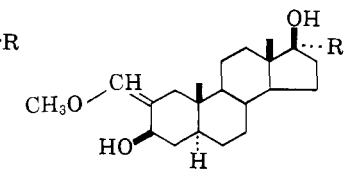
(4) P. A. Plattner and L. M. Jampolonsky, *Helv. Chim. Acta*, **24**, 1459 (1941).

(5) P. Seifert and H. Schinz, *ibid.*, **34**, 728 (1951).

(6) H. J. Ringold, E. Batres, O. Halpern and E. Necoechea, *J. Am. Chem. Soc.*, **81**, 477 (1959); see also B. Fuchs and H. J. E. Lowenthal, *Tetrahedron*, **11**, 199 (1960).

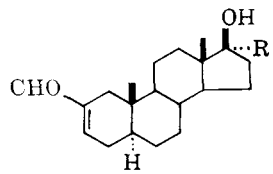
ric acid. Alternatively, but less conveniently on a large scale, Ia was methylated with ethereal diazomethane. Reduction of Ib with sodium borohydride in methanol solution gave the corresponding 3β-alcohol IIa in 75% yield. This underwent a concerted hydrolysis



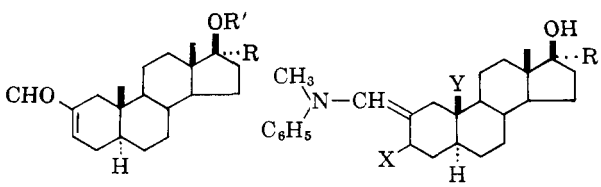


Ia, X = Z = R = H, Y = CH_3
b, X = Y = CH_3, R = Z = H
c, X = Z = H, Y = R = CH_3
d, X = Y = R = CH_3, Z = H
e, X = Y = Z = R = H
f, X = Y = Z = H, R = C≡CH
g, R = X = H, Y = Z = CH_3
h, R = H, X = Y = Z = CH_3

IIa, R = H
b, R = CH_3



I Ia, Y = CH_3, R = R′ = H
b, Y = CH_3, R′ = $COCH_3$, R = H
c, Y = CH_3, R′ = COC_2H_5, R = H
d, Y = CH_3, R′ = $COCH_2CH(CH_2)_4$, R = H
e, Y = CH_3, R′ = $CO(CH_2)_3CH_3$, R = H
f, Y = CH_3, R′ = $CO(CH_2)_4CH_3$, R = H
g, Y = CH_3, R′ = $CO(CH_2)_8CH=CH_2$, R = H
h, Y = R = CH_3, R′ = H
i, Y = CH_3, R′ = H, R = C≡CH
j, Y = R′ = R = H
k, Y = R′ = H, R = C≡CH



IVa, X = =O, Y = R = CH_3
b, X = 3α-OH, Y = R = CH_3
c, X = =O, Y = R = H
d, X = 3α-OH, Y = R = H
e, X = =O, Y = H, R = C≡CH
f, X = 3α-OH, Y = H, R = C≡CH

and elimination reaction upon treatment with hydrochloric acid in acetone solution to afford in good yield the α,β-unsaturated aldehyde IIIa. By carrying out the transformations of Ia to IIIa without isolation of the intermediates Ib and IIa, the yield of IIIa from Ia was 72%. The unsaturated aldehyde is characterized by an absorption maximum in the ultraviolet at 232 mμ (ε 13,800) and bands in the infrared at 1663 (C=O) and 1645 $cm.^{-1}$ (C=C).

In view of the interesting biological activities exhibited by IIIa (see sequel) a number of its C-17 esters were prepared, including the acetate, propionate, cyclopentylpropionate, valerate, caproate and undecenoate IIIb–IIIg. Although the lower esters were formed readily by treatment of IIIa in pyridine at room temperature with the corresponding acid anhydride, it was not possible to prepare either the caproate or the undecenoate reproducibly in this manner, since it was found that a reaction took place between the unsaturated aldehyde grouping and the higher acyl chlorides. However, good yields of these esters were obtained when the formyl group was protected as its ketal V and then treated with the higher acid chloride in benzene or tetrahydrofuran solution in the presence of pyridine.[7] Mild acid treatment then regenerated the formyl group, with preservation of the ester grouping.

In view of the effect of 17α-alkyl substituents, particularly methyl, in enhancing oral myotrophic and androgenic activities[8] in 17β-hydroxy-17α-unsubstituted androstanes, the preparation of 17α-methyl-2-formyl-Δ²-androstene-17β-ol (IIIh) was undertaken. 2-Hydroxymethylene-17α-methylandrostane-17β-ol-3-one[6] (Ic) was converted to the methyl ether Id. Sodium borohydride reduction then gave the corresponding 3β-alcohol IIb, which on acid treatment afforded the unsaturated aldehyde IIIh.

An alternative route to 2-formyl-Δ²-androstenes utilized the products of condensation of a variety of amines with 2-hydroxymethylene-3-ketones.[9] N-Methylaniline in benzene readily converted the enol Ic to the enamine IVa. Reduction of the keto group of IVa with sodium borohydride led to the 3β-alcohol IVb, which upon acid treatment readily gave the unsaturated aldehyde IIIh.[10]

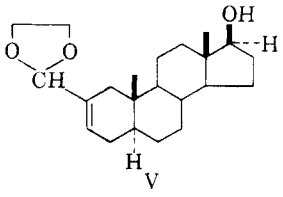
The marked progestational activity of 17α-ethynylandrostanes prompted the preparation of a member (IIIi) of this series. Treatment of the 2-formyl-Δ²-androstene-17β-ol cycloethyleneketal (V) with chromium trioxide in pyridine gave the corresponding ketone. The latter gave 2-formyl-Δ²-17α-ethynylandrostene-17β-ol (IIIi) on reaction with ethynylmagnesium bromide, followed by acid hydrolysis of the ketal.

Analogous compounds in the 19-nor series also were prepared. 19-Nordihydrotestosterone[11] in a mixture of methylene chloride and ether was condensed with ethyl formate in the presence of either sodium methoxide or sodium hydride to furnish the corresponding 2-hydroxymethylene analog Ie. This readily formed the N-methylanilinomethylene derivative IVc, which afforded the corresponding 3β-alcohol IVd upon reduction with sodium borohydride. Mild acid treatment of this β-hydroxy enamine IVd smoothly led to 2-formyl-Δ²-19-norandrostene-17β-ol (IIIj), which displayed the expected spectral characteristics in the ultraviolet and infrared.

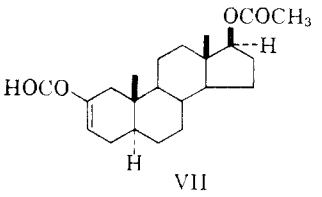
The same reaction sequence converted 2-hydroxymethylene-17α-ethynyl-19-nordihydrotestosterone (If), *via* the N-methylanilino derivative IVe and the corresponding 3β-alcohol IVf, to 2-formyl-Δ²-17α-ethynyl-19-norandrostene-17β-ol (IIIk).

Sodium borohydride reduction of the 2-formyl-Δ²-

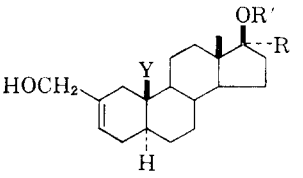
(7) A. Kuksis and J. M. R. Beveridge, *J. Org. Chem.*, **25**, 1209 (1960).
(8) F. J. Saunders and V. A. Drill, *Endocrinology*, **58**, 567 (1956).
(9) J. A. Zderic, O. Halpern, H. Carpio, A. Ruiz, D. C. Limon, L. Magaña, H. Jimenez, A. Bowers and H. J. Ringold, *Chem. Ind.* (London), 1625 (1960).
(10) This procedure was first carried out by Dr. J. A. Zderic of these Laboratories.
(11) A. Bowers, H. J. Ringold and E. Denot, *J. Am. Chem. Soc.*, **80**, 6115 (1958).



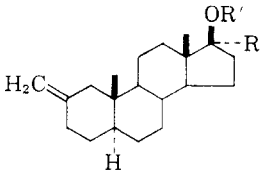
V



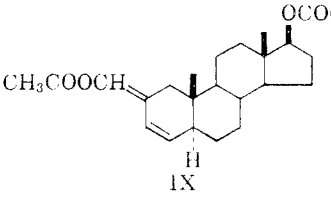
VII



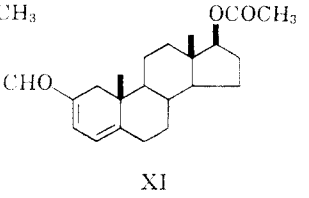
VIa, R = R′ = H, Y = CH_3
b, R = H, R′ = $COCH_3$, Y = CH_3
c, R = Y = CH_3, R′ = H
d, R = R′ = Y = H



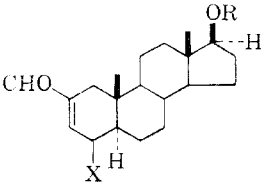
VIIIa, R = H, R′ = $COCH_3$
b, R = CH_3, R′ = H



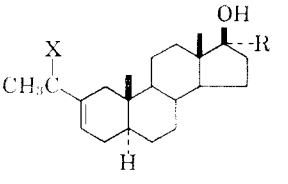
IX



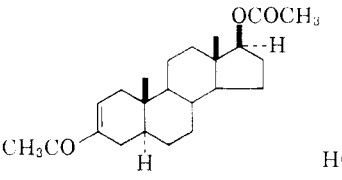
XI



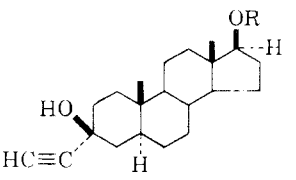
Xa, R = H, X = α-CH_3
b, R = $COCH_3$, X = α-Cl
c, R = $COCH_3$, X = β-Br
d, R = $COCH_3$, X = α-F



XIIa, R = H, X = OH, H
b, R = H, X = =O
c, R = CH_3, X = OH, H
d, R = CH_3, X = =O



XIII



XIVa, R = H
b, R = $COCH_3$

compounds IIIa, IIIb, IIIh and IIIj led to the corresponding 2-hydroxymethyl-Δ^2-analogs VIa, VIb, VIc and VId, respectively. Reoxidation of the allylic alcohol VIa with 2,3-dichloro-5,6-dicyanobenzoquinone[12] regenerated the α,β-unsaturated aldehyde IIIa in high yield. This established that the borohydride reduction of IIIa had not appreciably affected the olefinic double bond.

The unsaturated aldehyde IIIb was further characterized by oxidation with 8 *N* chromic acid[13] to afford the corresponding Δ^2-2-carboxylic acid VII.

It is of interest to note that Wolff–Kishner reduction of 2-formyl-Δ^2-androstene-17β-ol (IIIa), then acetylation, led to the exocyclic methylene compound VIIIa as the major product, together with a small amount of the 2-methyl-Δ^2-isomer which was isolated after chromatography. A similar reduction of IIIh led to VIIIb as the only isolable product, probably due to the greater difficulty of separation of the corresponding isomeric alcohols on alumina.

To investigate the effects of methyl and halogen substitution and further unsaturation γ- to the 2-formyl-Δ^2-system,[14] the 4α-methyl, 4α-chloro and Δ^4-analogs of 2-formyl-Δ^2-androstene-17β-ol (IIIa) were prepared. 4α-Methylandrostane-17β-ol-3-one[15] readily condensed with ethyl formate to afford the 2-hydroxymethylene analog Ig which was hydrogenated to give 2α,4α-dimethylandrostane-17β-ol-3-one. Conversion of 2-hydroxymethylene-4α-methylandrostane-17β-ol-3-one (Ig) to its methyl ether Ih in the usual way, then reduction with sodium borohydride and subsequent treatment with acid furnished 4α-methyl-2-formyl-Δ^2-androstene-17β-ol (Xa).

The preparation of the 4-halo analogs required a different approach since 4α-halo-3-keto-5α-androstanes are not readily available. Forcing acetylation of the unsaturated aldehyde IIIa led to the dienol acetate IX which displayed an absorption maximum in the ultraviolet at 248 mμ (ϵ 14,000) and which, on reduction with sodium borohydride in methanol, gave 2-hydroxymethyl-Δ^2-androstene-17β-ol acetate (VIb).

Treatment of the dienol acetate IX with N-chlorosuccinimide in dioxan containing perchloric acid afforded 4α-chloro-2-formyl-Δ^2-androstene-17β-ol acetate (Xb). The equatorial (4α-) configuration was assigned to the chlorine atom in Xb when it was shown that it was recovered unchanged after treatment with a saturated solution of hydrogen chloride in ethyl acetate for 5 hours at room temperature.

In a similar manner N-bromosuccinimide reacted with the dienol acetate IX to afford the 4ζ-bromo analog Xc. Dehydrobromination of Xc with calcium carbonate[16] in dimethylformamide led to 2-formyl-$\Delta^{2,4}$-androstadiene-17β-ol acetate (XI), showing a characteristic ultraviolet maximum at 321 mμ (ϵ 15,000).

In an attempt to make the 4α-fluoro analog Xd, the dienol acetate IX was treated under a wide variety of conditions with perchloryl fluoride,[17] but in no instance was a fluorine-containing product obtained. The only recognizable product, formed in low yield, was the 4α-chloro compound Xb. It is possible to rationalize this result if it be assumed that the perchlo-

(12) D. Burn, V. Petrow and G. O. Weston, *Tetrahedron Letters*, No. 9, 14 (1960).

(13) K. Bowden, I. M. Heilbron, E. R. H. Jones and B. C. L. Weedon, *J. Chem. Soc.*, 39 (1946).

(14) *Cf.* the enhancement of biological activity of certain Δ^4-3-ketones when a Δ^6-double bond or halogen atoms or methyl groups are substituted at C-6, γ- to the enone system; L. F. Fieser and M. Fieser, "Steroids," Reinhold Publishing Corp., New York, N. Y., 1959, Chapter 17.8.

(15) H. J. Ringold and E. Necoechea, unpublished work. We thank Dr. Ringold for details concerning the preparation of this compound. For constants, see ref. 2.

(16) R. Joly, J. Warnant, G. Nominé and D. Bertin, *Bull. soc. chim. France*, 366 (1958).

(17) *Cf.* the preparation of 6-fluoro-Δ^4-3-ketones from the enol acetates of Δ^4-3-ketones and perchloryl fluoride, B. M. Bloom, V. V. Bogert and R. Pinson Jr., *Chem. Ind.* (London), 1317 (1959).

ryl fluoride contains impurities which are capable of chlorinating the enol acetate.[18]

There were also prepared for biological evaluation the homologs 2-acetyl-Δ^2-androstene-17β-ol (XIIb), 2-acetyl-17α-methyl-Δ^2-androstene-17β-ol (XIId) and 3-acetyl-Δ^2-androstene-17β-ol (XIII).

Methylmagnesium bromide reacted with the unsaturated aldehyde IIIa to afford a mixture of allylic alcohols XIIa which was oxidized with 2,3-dichloro-5,6-dicyanobenzoquinone[11] in dioxan solution to the 2-acetyl-Δ^2-compound XIIb. By a similar reaction sequence, the 17α-methyl enal IIIh afforded the enone XIId *via* the allylic alcohols (XIIc).

Prior to this approach the direct acylation of Δ^2-androstene-17β-ol acetate[3] with acetic anhydride in the presence of zinc chloride was investigated. A product was obtained in low yield [λ_{max} 234 mμ (ϵ 12,600)] which was shown to be 3-acetyl-Δ^2-androstene-17β-ol acetate (XIII). Its structure was proved conclusively in the following manner: treatment of 5α-androstane-17β-ol-3-one with ethynylmagnesium bromide gave the 3-ethynylcarbinol XIVa, characterized as its acetate (XIVb). The diol XIVa underwent rearrangement[19] with formic acid to the 3-acetyl-Δ^2-compound, isolated as its 17β-acetate (XIII)[20] which proved to be identical in every respect with the product obtained from the acylation of Δ^2-androstene-17β-ol acetate.

Biological Activities.—The compounds were assayed as outlined in Part I of this series[3] and some of the results, which are of a preliminary nature, are summarized in Table I. Substitution at C-2 by hydroxymethyl or formyl groups causes a marked reduction of androgenic activity with retention of a good anabolic effect. The ratio of anabolic to androgenic activity is particularly favorable with the 2-hydroxymethyl compound. A more detailed report will appear elsewhere by Dr. R. Dorfman and his colleagues.

TABLE I

ANDROGENIC AND ANABOLIC ACTIVITIES OF 2-FORMYL- AND 2-HYDROXYMETHYLANDROSTENES (ACTIVITY OF TESTOSTERONE = 1.0)

Compound	Substitution in ring A	Assay	Androgenic	Anabolic
XI	2-CHO-$\Delta^{2,4}$-	Injection	0.1	0.1
IIIa	2-CHO-Δ^2-	Injection	0.2	1.0
VIa	2-CH_2OH-Δ^2-	Injection	0.2	2.2
VIc	2-CH_2OH-Δ^2-(17α-CH_3-17β-OH)	Oral	0.3	2.2

Experimental[21]

2-Methoxymethylene-5α-androstane-3β,17β-diol (IIa).—To 2-methoxymethylene-5α-androstane-17β-ol-3-one (Ia) (19.0 g.) dissolved in methanol (400 ml.), sodium borohydride (7.0 g.) in methanol (100 ml.) was added dropwise during 15 min., with external cooling. Five min. after the completion of addition of the borohydride, there remained in the solution no material showing selective absorption in the ultraviolet. The solution was filtered and poured slowly into a rapidly stirred 5% aqueous salt solution (3 l.) at 0°. The white precipitate was filtered off, washed with water until neutral, dried and recrystallized from acetone; yield, 14.3 g. (75%); m.p. 155-157°. A portion of this, recrystallized twice from acetone gave pure 2-methoxymethylene-androstane-3β,17β-diol (IIa), m.p. 158-160°; $[\alpha]_D$ −35° ($CHCl_3$); ultraviolet, no selective absorption; infrared, OH, no carbonyl band.

Anal. Calcd. for $C_{21}H_{34}O_3$: C, 75.40; H, 10.25; O, 14.35. Found: C, 75.52; H, 10.47; O, 14.64.

2-Formyl-Δ^2-androstene-17β-ol (IIIa).—To a suspension of 2-methoxymethyleneandrostane-3β,17β-diol (IIa) (4.0 g.) in acetone (50 ml.) was added concd. hydrochloric acid (1 drop). On shaking, the steroid dissolved completely, and after five minutes crystallization of 2-formyl-Δ^2-androstene-17β-ol (IIIa) began, and was complete within 30 min. The product was filtered off, washed with cold acetone and dried; m.p. 196–198°; yield, 2.4 g., 66%.

The pure aldehyde was obtained by twice recrystallizing from ethyl acetate, and had m.p. 209–211°; $[\alpha]_D$ +102° ($CHCl_3$); λ_{max} 232 mμ (ϵ 13,000) and 309 mμ (ϵ 44); ν_{max}^{KBr} 1663 (s), 1645 cm.$^{-1}$ (m).

Anal. Calcd. for $C_{20}H_{30}O_2$: C, 79.42; H, 10.00. Found: C, 79.13; H, 10.03.

2-Formyl-Δ^2-androstene-17β-ol Acetate (IIIb).—A solution of 2-formyl-Δ^2-androstene-17β-ol (IIIa) (4.0 g.) in pyridine (50 ml.) and acetic anhydride (20 ml.) was left overnight at room temperature. Removal of the reagents by evaporation under vacuum, and three recrystallizations of the residual crystalline solid from methanol, yielded the acetate IIIb (3.1 g., 66%); m.p. 161–163°; $[\alpha]_D$ +84° ($CHCl_3$); λ_{max} 232 mμ (ϵ 13,200) and 312 mμ (ϵ 43); ν_{max}^{KBr} 1740, 1680 and 1650 cm.$^{-1}$.

Anal. Calcd. for $C_{22}H_{32}O_3$: C, 76.70; H, 9.36; O, 13.93. Found: C, 76.43; H, 9.37; O, 14.26.

2-Formyl-Δ^2-androstene-17β-ol Propionate (IIIc).—Similar treatment of the alcohol IIIa (1.01 g.) with propionic anhydride and pyridine yielded the propionate IIIc which was recrystallized twice from ethyl acetate–methanol to give 370 mg. (29%): m.p. 140–144°; $[\alpha]_D$ +74° ($CHCl_3$); λ_{max} 232 mμ (ϵ 13,500) and 310 mμ (ϵ 44); ν_{max}^{KBr} 1740, 1676 and 1724 cm.$^{-1}$.

Anal. Calcd. for $C_{23}H_{34}O_3$: C, 77.05; H, 9.56. Found: C, 76.92; H, 9.50.

2-Formyl-Δ^2-androstene-17β-ol Cyclopentylpropionate (IIId).—A solution of 2-formyl-Δ^2-androstene-17β-ol (5.0 g.) in pyridine (25 ml.) was left for 3 days at room temperature with cyclopentylpropionic anhydride (5 ml.). The solution was poured into water, extracted with ethyl acetate, and the organic phase was washed first with dilute hydrochloric acid, then with dilute sodium carbonate solution, and with water. Evaporation and chromatography on alumina gave the cyclopentylpropionate IIId, as needles from acetone, m.p. 138–141°; $[\alpha]_D$ +75° ($CHCl_3$); λ_{max} 232 mμ (ϵ 14,000) and 316 mμ (ϵ 15).

Anal. Calcd. for $C_{28}H_{42}O_3$: C, 72.82; H, 9.92; O, 11.25. Found: C, 78.60, H, 9.75; O, 11.22.

2-Formyl-Δ^2-androstene-17β-ol Valerate (IIIe).—A solution of 2-formyl-Δ^2-androstene-17β-ol (4.0 g., 13 mmoles) in benzene (160 ml.) was evaporated to 120 ml. to remove any traces of moisture. To the refluxing solution was added pyridine (1.60 ml., 19.8 mmoles, 1.5 equiv.) and valeryl chloride (2.38 ml., 19.8 mmoles, 1.5 equiv.) and reflux was continued for 45 min., during which time pyridine hydrochloride crystallized from solution. The solution was cooled and passed directly through a column of alumina (100 g., activity I). Elution with benzene yielded the valerate IIId as a non-crystalline wax (4.1 g., 79%), melting in the range 110–130°; $[\alpha]_D$ +75° ($CHCl_3$); λ_{max} 232 mμ (ϵ 12,600).

Anal. Calcd. for $C_{25}H_{38}O_3$: C, 77.67; H, 9.91. Found: C, 77.30; H, 10.02.

2-Formyl-Δ^2-androstene-17β-ol-$\Delta^{10'}$-undecenoate (IIIg).—(a)

(18) This result parallels the finding of S. Nakanishi and E. V. Jansen, *J. Org. Chem.*, **27**, 703 (1962), who treated the enol acetate of a 17-keto-steroid with perchloryl fluoride in pyridine–acetone and obtained a chloro compound. Chlorination of a phenol under similar reaction conditions was observed by A. S. Kende and P. MacGregor, *J. Am. Chem. Soc.*, **83**, 4197 (1961), and attributed to reduction of chlorate to hypochlorite by the solvent, dimethylformamide.

(19) A. W. Johnson, "Acetylenic Compounds," I. E. Arnold, London, Vol. I, 1946.

(20) After the completion of this work the preparation of XIII by the same procedure (rearrangement of XIVa) was reported by M. Dvolaitzky, H. B. Kagan and J. Jacques, *Bull. soc. chim. France*, 598 (1961).

(21) Melting points are uncorrected. Optical rotations were measured as 1% solutions in the stated solvents at 25°. Ultraviolet absorption spectra were measured in ethanol solution using a Beckman DK 2 spectrophotometer. Infrared absorption spectra were determined using a Perkin–Elmer Model 21 spectrophotometer, equipped with sodium chloride optics. Thanks are expressed to Dr. J. Matthews and his staff for these determinations. Microanalyses were performed by A. Bernhardt, Mülheim (Ruhr), W. Germany. Except where stated, alumina was neutralized before use by stirring with ethyl acetate and reactivated by heating at 120° for 72 hr. Grades of activity, where given, are those of H. Brockmann and H. Schodder (*Ber.*, **74**, 73 (1941)).

The $\Delta^{10'}$-undecenoate was prepared similarly using Δ^{10}-undecenoyl chloride. The wax had $[\alpha]_D$ +64° ($CHCl_3$); λ_{max} 232 mμ (ε 11,700).

Anal. Calcd. for $C_{31}H_{48}O_3$: C, 79.43; H, 10.32; O, 10.24. Found: C, 79.20; H, 10.42; O, 10.05.

In some runs, this esterification method gave material of λ_{max} between 222 and 232 mμ, and with lower extinction coefficients.

(b) **Preparation of the Undecenoate IIIg *via* the 2-Cycloethylene Ketal.**—A solution of 2-formyl-Δ^2-androstene-17β-ol-2-cycloethylene ketal (V) (15 g., 43 mmoles) in dry tetrahydrofuran (200 ml.) and pyridine (15 ml.) was left at room temperature overnight with undecenoyl chloride (13.2 g., 65 mmoles). Working up by addition of water and ethyl acetate, and washing the organic layer gave, on evaporation, the undecenoate 17-ketal as an oil. Treatment of the ketal with dilute aqueous methanolic hydrochloric acid for 10 hr. at room temperature, extraction, washing, evaporation to dryness and passage through a silica column in methylene chloride gave 2-formyl-Δ^2-androstene-17β-ol undecenoate (IIIg) identical with that obtained by route (a).

2-Formyl-Δ^2-androstene-17β-ol Caproate (IIIf).—2-Formyl-Δ^2-androstene-17β-ol-2′-ethylene ketal (5.0 g.) was converted by method (b), as above, to IIIf. The wax (73% yield) had $[\alpha]_D$ +69° ($CHCl_3$); λ_{max} 232 mμ (ε 11,500).

Anal. Calcd. for $C_{26}H_{40}O_3$: C, 77.95; H, 10.07; O, 11.98. Found: C, 78.34; H, 10.05; O, 11.58.

2-Formyl-Δ^2-androstene-17β-ol-2′-cycloethylene Ketal (V).—A solution of 2-formyl-Δ^2-androstene-17β-ol (IIIa) (3.0 g.) in benzene (300 ml.) and ethylene glycol (5 ml.) was stirred and refluxed through a water separator until no more water was seen to separate. Toluene-*p*-sulfonic acid (40 mg.) was added and the stirring and reflux were continued until water ceased to separate (0.5 hr.).

The solution was cooled, and excess of solid sodium bicarbonate was added. The solution was poured into water and the benzene layer was separated and washed until neutral, dried with sodium sulfate, and evaporated to give a crystalline solid. Recrystallization from hexane containing a few drops of pyridine gave the ketal (2.3 g.); m.p. 150–151°; $[\alpha]_D$ +65° ($CHCl_3$).

Anal. Calcd. for $C_{22}H_{34}O_3$: C, 76.26; H, 9.89. Found: C, 75.94; H, 9.80.

3β,17β-Dihydroxy-2-methoxymethylene-17α-methylandrostane (IIb).—A solution of 2-methoxymethylene-17α-methyldihydrotestosterone (Id) (16.5 g.) in methanol (400 ml.) was stirred while sodium borohydride (9.0 g.) was added dropwise in methanol solution during 15 min. The solution became warm during the addition and was left a total of 30 min. Pouring into water, filtration, and recrystallization from acetone yielded 3β,17β-dihydroxy-2-methoxymethylene-17α-methylandrostane (IIb), m.p. 142–144°; yield 12.3 g. (74%). A sample recrystallized four times from acetone had m.p. 146–149°; $[\alpha]_D$ −53° ($CHCl_3$).

Anal. Calcd. for $C_{22}H_{36}O_3$: C, 75.81; H, 10.41; O, 13.77. Found: C, 75.70; H, 10.50; O, 13.85.

2-Formyl-17α-methyl-Δ^2-androstene-17β-ol (IIIh).—To a stirred suspension of 3β,17β-dihydroxy-2-methoxymethylene-17α-methylandrostane (IIb) (10.0 g.) in acetone (250 ml.) was added concd. hydrochloric acid (0.1 ml.). The steroid dissolved completely within 3 min. After 10 min. water was added dropwise to the stirred solution until crystals of the aldehyde IIIh began to form. More water was added (to a total of 530 ml.), the suspension was cooled in an ice bath, and the crystals were filtered off; yield, 3.8 g. (41%). A portion recrystallized from acetone–water as plates with m.p. 148–150°; $[\alpha]_D$ +70° ($CHCl_3$); λ_{max} 232 mμ (ε 13,000); 312 mμ (ε 45). Rotatory dispersion in methanol (*c*, 0.0485): $[\alpha]_{700}$ +23°, $[\alpha]_{589}$ +76°, $[\alpha]_{350}$ +631°, $[\alpha]_{307.5}$ +60°, $[\alpha]_{265}$ +656°, $[\alpha]_{260}$ +627°. The rotatory dispersion curve is virtually unaltered on addition of a drop of hydrochloric acid.

Anal. Calcd. for $C_{21}H_{32}O_2$: C, 79.70; H, 10.19; O, 10.16. Found: C, 79.30; H, 10.36; O, 9.83.

17α-Methyl-2-N-methylanilinomethylene-5α-androstan-17β-ol-3-one (IVa).—A solution of 2-hydroxymethylene-17α-methyl-5α-androstan-17β-ol-3-one[6] (40.0 g.) in methanol (800 ml.) containing N-methylaniline (40 ml., freshly distilled) was heated under reflux (2 hr.) and then evaporated to dryness. The residue was slurried with hexane (500 ml.) and absorbed on unwashed alumina (800 g.). Elution first with hexane, then hexane–benzene (1:1) and finally benzene removed N-methylaniline. Subsequent elution with ethyl acetate–benzene (1:1) gave, after crystallization from acetone–hexane, 38.2 g. (74%) of 17α-methyl-2-N-methylanilinomethylene-5α-androstane-17β-ol-3-one (IVa), m.p. 196–198°; $[\alpha]_D$ −415° (pyridine); λ_{max} 238–240 mμ (ε 5,100) and 346 mμ (ε 29,500). The analytical sample, which was crystallized once from ether and 4 times from acetone–ether, had m.p. 198–199°; $[\alpha]_D$ −407° (pyridine); λ_{max} 238 mμ (ε 5,200) and 344–346 mμ (ε 21,400).

Anal. Calcd. for $C_{28}H_{39}NO_2$: C, 79.76; H, 9.32; O, 7.59; N, 3.32. Found: C, 79.42; H, 9.14; O, 7.99; N, 3.64.

17α-Methyl-2-N-methylanilinomethylene-5α-androstane-3β,17β-diol (IVb).—To a solution of 17α-methyl-2-N-methylanilinomethylene-5α-androstane-17β-ol-3-one (500 mg.) in methanol (20 ml.) was added sodium borohydride (600 mg.) in water (2 ml.) and the mixture was set aside at room temperature for 2.5 hr., after which it was poured into water (100 ml.) and the product was extracted into ethyl acetate (3 × 50 ml.). Evaporation of the dried extracts and crystallization of the residue from acetone gave 450 mg. of material, m.p. 159–160°. Repeated recrystallization from acetone gave a single isomer, presumably the 3β,17β-diol IVb, m.p. 163–164°; $[\alpha]_D$ −242.5° ($CHCl_3$); λ_{max} 274 mμ (ε 14,500).

Anal. Calcd. for $C_{27}H_{41}NO_2$: C, 78.78; H, 10.04; O, 7.77; N, 3.40. Found: C, 78.41; H, 10.00; O, 7.80; N, 3.02.

2-Formyl-17α-methyl-Δ^2-androstene-17β-ol (IIIh).—A solution of 17α-methyl-2-N-methylanilinomethylene-5α-androstane-3β,17β-diol (100 mg.) in methanol (2.5 ml.) was treated with three drops of concd. hydrochloric acid. After 10 min., the solution was poured into water (20 ml.) and the product was collected, washed with water and dried (74 mg., m.p. 140–144°). Recrystallization from acetone–hexane gave 2-formyl-17α-methyl-Δ^2-androstene-17β-ol, m.p. 150–151°; $[\alpha]_D$ +72° ($CHCl_3$); λ_{max} 232 mμ (ε 13,000), identical with that prepared from IIb.

When this sequence was repeated without isolation of IVb, the over-all yield from IVa to IIIh of m.p. 150–151° was 93%.

2-Formyl-Δ^2-androstene-17-one-21′-cycloethylene Ketal.—2-Formyl-Δ^2-androstene-17β-ol-2′-ethylene ketal (2.3 g.) in pyridine (10 ml.) was cooled in ice, and a suspension of chromium trioxide–pyridine complex (from chromium trioxide, 3 g.) was added. The mixture was left at room temperature for 16 hr. Ether (500 ml.) was added, and the mixture was shaken to disperse the precipitate. The granular solid was filtered off, the ether solution was washed with water until neutral, and evaporated to leave a crystalline residue. The 2′-ketal-17-ketone was recrystallized from ethyl acetate to m.p. 179–181°; $[\alpha]_D$ +120° ($CHCl_3$); λ_{max} 293 mμ (ε 35).

Anal. Calcd. for $C_{22}H_{32}O_3$: C, 76.70; H, 9.36; O, 13.93. Found: C, 76.50; H, 9.57; O, 13.82.

17α-Ethynyl-2-formyl-Δ^2-androstene-17β-ol (IIIi).—A solution of 2-formyl-Δ^2-androstene-17-one-2′-ethylene ketal (1.8 g.) in dry tetrahydrofuran (10 ml.) was added to a solution of ethynylmagnesium bromide (from 2 g. of magnesium)[22] and the mixture was left at room temperature overnight. The solution was poured into water, extracted with ether, washed, dried and evaporated to an oil. Treatment of this with hydrochloric acid (0.3 ml.) in acetone (10 ml.), dilution with water and extraction, gave (IIIi), purified by chromatography and recrystallization from benzene–acetone, to m.p. 178–180°; $[\alpha]_D$ +19° ($CHCl_3$); λ_{max} 232 mμ (ε 13,000).

Anal. Calcd. for $C_{22}H_{30}O_2$: C, 80.93; H, 9.26; O, 9.80. Found: C, 80.91; H, 9.06; O, 10.10.

2-Hydroxymethylene-19-norandrostane-17β-ol-3-one (Ie). (a) By Sodium Methoxide Condensation.—To a stirred solution of 19-norandrostane-17β-ol-3-one[10] (1.0 g.) in a mixture of methylene chloride (6.5 ml.) and ether (2.0 ml.) was added sodium methoxide (0.6 g.) and ethyl formate (1.0 ml., freshly distilled). The reaction mixture was stirred at room temperature for 4 hr., after which the precipitated sodium salt was collected, washed well with methylene chloride and dried *in vacuo*. The salt was dissolved in water (100 ml.) and the solution was acidified with dilute hydrochloric acid to precipitate the hydroxymethylene derivative Ie which was collected, washed well with water and dried *in vacuo*. The yield of crude product (m.p. 172–180°) was 1.01 g. (92%) and it was sufficiently pure for subsequent transformations.

A twice recrystallized sample had m.p. 190–192° (from acetone–hexane); $[\alpha]_D$ +119° (dioxan); λ_{max} 281 mμ (ε 8,900); ν_{max}^{KBr} 3550–3450 (s) (bonded OH), 1705 (w) (C=O) and 1635 cm.$^{-1}$ (s) (chelated C=O).

(22) L. Skattebol, E. R. H. Jones and M. C. Whiting, *Org. Syntheses*, **39**, 56.

Anal. Calcd. for $C_{19}H_{28}O_3$: C, 74.96; H, 9.27; O, 15.76. Found: C, 74.90; H, 9.30; O, 15.61.

(b) **With Sodium Hydride.**—Sodium hydride (2.9 g.) was added slowly in portions to a stirred solution of 19-norandrostane-17β-ol-3-one (7.0 g.) in dry tetrahydrofuran (87.5 ml.) containing ethyl formate (9.5 ml., freshly distilled). The mixture was allowed to stand at room temperature overnight, after which it was diluted by the slow addition of water (200 ml.). The resulting turbid solution was extracted with ether (2 × 50 ml.) and then acidified with acetic acid. The white precipitate of 2-hydroxymethylene-19-norandrostane-17β-ol-3-one (Ie) was collected, washed with water and dried (4.80 g., 62%, m.p. 180–184°). Recrystallization from acetone–hexane gave a product (m.p. 190–192°) identical with that obtained by method (a).

2-N-Methylanilinomethylene-19-norandrostane-17β-ol-3-one (IVc).—A solution of 2-hydroxymethylene-19-norandrostane-17β-ol-3-one (Ie) (4.45 g.) in a mixture of benzene (50 ml.) and methanol (50 ml.) containing N-methylaniline (5.0 ml.) was heated overnight in an apparatus equipped with a water separator. The solvents were removed *in vacuo* and the residue was digested with hexane to give the enamine as a crystalline solid. The crude product was recrystallized from acetone to give 4.05 g. (70%) of 2-N-methylanilinomethylene-19-norandrostene-17β-ol-3-one of m.p. 174–176°; $[\alpha]_D$ −262° (dioxan); λ_{max} 238 (ε 5,000) and 344 mμ (ε 19,500); ν_{max}^{KBr} 3500 (s) (OH) 1660 (s) (α,β-unsaturated C=O), 1615 (m) (conj. C=C stretching, 752 (s) and 690 cm.$^{-1}$ (s) (aromatic C–H out-of-plane deformation).

Anal. Calcd. for $C_{26}H_{35}NO_2$: C, 79.35; H, 8.96; O, 8.13; N, 3.56. Found: C, 79.27; H, 8.93; O, 8.30; N, 4.01.

2-N-Methylanilinomethylene-19-norandrostane-3β,17β-diol (IVd).—A solution of sodium borohydride (680 mg.) in water (8 ml.) was added to a solution of 2-N-methylanilinomethylene-19-norandrostane-17β-ol-3-one (IVc) (675 mg.) in a mixture of methanol (15 ml.) and dioxan (19 ml.). The mixture was stirred at room temperature for 8 hr. The precipitated diol was collected and washed with water (440 mg., m.p. 148–152°). Slow dilution of the mother liquors with water gave a further 220 mg. of material, m.p. 150–155°. The total yield was 660 mg. (97%). Both crops of material displayed only a single maximum at 272 mμ in the ultraviolet spectra, indicating that reduction was complete. Repeated recrystallizations from ethyl acetate raised the melting point to 164–166°, indicating that the crude product was a mixture, probably of alcohols epimeric at C-3. The pure isomer, isolated in 62% yield and presumably the 3β, 17β-diol IVd, had m.p. 164–166°; $[\alpha]_D$ +19° (dioxan); λ_{max} 272 mμ (ε 12,000); ν_{max}^{KBr} 3450–3400 (s) (OH), 1680 (w) (unconj. C=C), 1615 (m) (aromatic C=C, 752 (s) and 690 cm.$^{-1}$ (s) (aromatic C–H).

Anal. Calcd. for $C_{26}H_{37}NO_2$: C, 78.95; H, 9.43; O, 8.09; N, 3.54. Found: C, 78.84; H, 9.58; O, 8.04; N, 3.13.

2-Formyl-Δ²-19-norandrostene-17β-ol (IIIj).—A solution of the enamine alcohol IVd (2.06 g.) in methanol (75 ml.) was treated with 3 drops of concd. hydrochloric acid and allowed to stand for 30 min. Water (200 ml.) was added slowly to the stirred solution to precipitate the aldehyde as a white crystalline solid, which was collected, washed with water and dried (m.p. 160–162°). After recrystallization from acetone–hexane there was obtained 1.24 g. (81%) of IIIj, m.p. 163–165°; $[\alpha]_D$ +172° (dioxan); λ_{max} 232 mμ (ε 13,500); ν_{max}^{KBr} 3670 (s) (OH), 1690 (s) (α,β-unsaturated C=O) and 1660 cm.$^{-1}$ (m) (conj. C=C stretching).

Anal. Calcd. for $C_{19}H_{28}O_2$: C, 79.12; H, 9.78; O, 11.10. Found: C, 79.20; H, 9.85; O, 11.23.

17α-Ethynyl-2-hydroxymethylene-19-norandrostane-17β-ol-3-one (If).—To a stirred solution of 17α-ethynyl-19-norandrostane-17β-ol-3 one (1.5 g.) in a mixture of anhydrous tetrahydrofuran (14 ml.) and methylene dichloride (7.5 ml.) was added sodium methoxide (0.9 g.) and ethyl formate (1.5 ml., freshly distilled). The reaction mixture was stirred at room temperature overnight, after which the precipitated sodium salt was collected, washed with methylene dichloride and dried *in vacuo*. The salt was dissolved in water (150 ml.) and the solution was acidified with dilute hydrochloric acid to precipitate the hydroxymethylene derivative (If) which was collected, washed well with water and dried. The crude product (1.27 g., 77%) was amorphous but sufficiently pure for subsequent transformations.

A twice crystallized sample had m.p. 174–178° (from acetone–hexane); $[\alpha]_D$ −4° (dioxan); λ_{max} 280–282 mμ (ε 9,000); ν_{max}^{KBr} 3360 (m) (bonded OH), 3270 (w) (—C≡C—H), 1710 (w) (C=O), 1642–1600 cm.$^{-1}$ (chelated C=O).

Anal. Calcd. for $C_{21}H_{28}O_3$: C, 76.79; H, 8.59; O, 14,61. Found: C, 76.47; H, 8.61; O, 14.88.

17α-Ethynyl-2-N-methylanilinomethylene-19-norandrostane-17β-ol-3-one (IVe).—A solution of 17α-ethynyl-2-hydroxymethylene-19-norandrostane-17β-ol-3-one (If) (880 mg.) in a mixture of benzene (13.2 ml.) and methanol (13.2 ml.) containing N-methylaniline (0.95 ml.) was heated overnight in an apparatus equipped with a water separator. The solvents were removed *in vacuo* and the residual oil was taken up in hot acetone, treated with carbon, and diluted with hexane to give the enamine (781 mg., 70%), m.p. 198–206°. After recrystallization from acetone–hexane, IVe had m.p. 209–211°; $[\alpha]_D$ −326° (dioxan); λ_{max} 238–240 mμ (ε 6,000) and 344 mμ (ε 17,000); ν_{max}^{KBr} 3590 (m) (OH), 3270 (m) (C≡CH), 1640 (s) (α,β-unsaturated C=O), 1608 (w) (conj. C=C), 1530 (s) and 1500 cm.$^{-1}$ (s) (aromatic C=C).

Anal. Calcd. for $C_{28}H_{35}NO_2$: C, 80.54; H, 8.45; O, 7.66; N, 3.35. Found: C, 80.33; H, 8.53; O, 7.56; N, 3.40.

17α-Ethynyl-2-N-methylanilinomethylene-19-norandrostane-3β,17β-diol (IVf).—A solution of sodium borohydride (110 mg.) in water was added to a solution of 17α-ethynyl-2-N-methylanilinomethylene-19-norandrostane-17β-ol-3-one (IVe) (106 mg.) in a mixture of methanol (2.3 ml.) and dioxan (3.0 ml.). The mixture was stirred at room temperature overnight. The precipitate of diol was collected, washed with water and dried (52 mg., m.p. 119–131°). Slow dilution of the mother liquors with water gave a further 52 mg., m.p. 142–155°. The total yield was 104 mg. (95%). The mixture of epimers could be converted directly to the aldehyde (IIIk). Fractional crystallization from acetone–hexane gave a single isomer, presumably the 3β,17β-diol IVf of m.p. 158–160°; $[\alpha]_D$ −7° (dioxan); λ_{max} 272 mμ (ε 12,000); ν_{max}^{KBr} 3570 (m) (OH), 3270 (w) (—C≡CH), 1606 (s) and 1510 cm.$^{-1}$ (s) (aromatic C=C).

Anal. Calcd. for $C_{28}H_{37}NO_2$: C, 80.14; H, 8.88; O, 7.62. Found: C, 79.56; H, 9.74; O, 6.95.

17α-Ethynyl-2-formyl-19-norandrost-2-en-17β-ol (IIIk).—A solution of the enamine alcohol IVf (100 mg.) in methanol (2.3 ml.) was treated with one drop of concd. hydrochloric acid and allowed to stand for 30 min. Water (15 ml.) was slowly added and the white precipitate was collected, washed with water and dried (62 mg., 83.5%), m.p. 146–150°. A pure sample had m.p. 157–159° (from ether–hexane); $[\alpha]_D$ +73° (dioxan); λ_{max} 232 mμ (ε 14,000); ν_{max}^{KBr} 3570 (m) (OH), 3280 (m) (C≡ CH), 1680 (s) (α,β-unsaturated C=O) and 1650 cm.$^{-1}$ (w) (conj. C=C).

Anal. Calcd. for $C_{21}H_{28}O_2$: C, 80.72; H, 9.03; O, 10.24. Found: C, 80.76; H, 9.21; O, 10.44.

2-Hydroxymethyl-Δ²-androstene-17β-ol (VIa).—To a slurry of 2-formyl-Δ²-androstene-17β-ol (IIIa) (5.0 g.) in methanol (50 ml.) was added sodium borohydride (5 g.) in methanol (30 ml.). The aldehyde dissolved completely within 3 min. with mild generation of heat. The solution was left overnight at room temperature, and worked up by pouring into water, extraction into ethyl acetate, washing, drying and evaporation to give a crystalline mass. Chromatography on alumina (150 g., activity I) and elution with ether yielded VIa, m.p. 190–191° (4.41 g., 88% yield) unchanged on further recrystallization from ethanol; $[\alpha]_D$ +58° ($CHCl_3$).

Anal. Calcd. for $C_{20}H_{32}O_2$: C, 78.89; H, 10.59; O, 10.51. Found: C, 78.73; H, 10.65; O, 10.56.

Reoxidation to the Unsaturated Aldehyde IIIa.—2-Hydroxymethyl-Δ²-androstene-17β-ol (1.05 g.) in dioxan (30 ml.) with 2,3-dichloro-5,6-dicyanobenzoquinone (950 mg.) was left at room temperature overnight. Pouring into methylene chloride, filtration through alumina, and crystallization from ethyl acetate gave the conjugated aldehyde IIIa identical with authentic material.

2-Hydroxymethyl-Δ²-androstene-17β-ol 17-Acetate (VIb).—A solution of 2-formyl-17β-acetoxy-Δ²-androstene (IIIb) (8.0 g.) in dioxan (100 ml.) was mixed with a solution of sodium borohydride (5.0 g.) in water (100 ml.) and dioxan (30 ml.) and stirred at room temperature for 2.5 hr. Dilution with water, filtration, washing to neutrality, drying and recrystallization from aqueous methanol yielded VIb (7.73 g., 96%); m.p. 133–136°; $[\alpha]_D$ +46° ($CHCl_3$); infrared bands of OH, OAc, no other carbonyl band.

Anal. Calcd. for $C_{22}H_{34}O_2$: C, 76.26; H, 9.89; O, 13.85. Found: C, 75.94; H, 9.94; O, 14.44.

2-Hydroxymethyl-17α-methyl-Δ²-androstene-17β-ol (VIc).—A solution of 2-formyl-17α-methyl-Δ²-androstene-17β-ol (IIIh) (1.0 g.) in methanol (30 ml.) was left overnight at room tempera-

ture with sodium borohydride (1.0 g.). The solution was poured into water, and the precipitate was filtered off and washed until the filtrate was neutral. Chromatography of the product on alumina (30 g., activity I), and elution with ether gave VIc (320 mg., 32% yield). A portion of this, twice recrystallized from acetone, had m.p. 167–169°; $[\alpha]_D$ +26° ($CHCl_3$); ultraviolet no maximum in the region 215 to 330 mμ.

Anal. Calcd. for $C_{21}H_{34}O_2$: C, 79.19; H, 10.76. Found: C, 78.92; H, 10.75.

2-Hydroxymethyl-19-nor-Δ²-androstene-17β-ol (VId).—A solution of sodium borohydride (400 mg.) in water (15 ml.) was added to a solution of 2-formyl-19-nor-Δ²-androstene-17β-ol (IIIj) (400 mg.) in methanol (5 ml.). After 1.5 hr., the reaction mixture was diluted slowly with water (15 ml.) and the white crystalline product was collected, washed with water, and dried (402 mg., m.p. 172–175°). Recrystallization from acetone–hexane gave 362 mg. (90%) of VId, m.p. 185–186°; $[\alpha]_D$ +104° (dioxan); ν_{max}^{KBr} 3450 cm.$^{-1}$ (s) (OH).

Anal. Calcd. for $C_{19}H_{30}O_2$: C, 78.57; H, 10.42; O, 11.02. Found: C, 78.55; H, 10.57; O, 11.22.

2-Carboxy-Δ²-androstene-17β-ol Acetate (VII).—A solution of 2-formyl-Δ²-androstene-17β-ol acetate (IIIb) (11.0 g.) in acetone (125 ml.) was treated at 0° during 3 hr. with a solution of chromium trioxide (8 *N*) in dilute sulfuric acid (20 ml.). The product precipitated on pouring the solution into water. Filtration, drying, and recrystallization from acetone gave the pure acid VII (6.8 g., 60%) m.p. 267–268°; $[\alpha]_D$ +67° ($CHCl_3$); λ_{max} 218 mμ (ε 9,100).

Anal. Calcd. for $C_{22}H_{32}O_4$: C, 73.30; H, 8.95; O, 17.75. Found: C, 73.62; H, 8.68; O, 17.20.

2-Methyleneandrostane-17β-ol Acetate (VIIIa).—A solution of 2-formyl-Δ²-androstene-17β-ol (IIIa) (3.0 g.) in ethanol (15 ml.) with potassium hydroxide (2 g.) and anhydrous hydrazine (5 ml.) was heated to 130° for 23 hr. in a sealed tube. The product was poured into water and extracted with ethyl acetate. The organic layer was washed until neutral, dried, and evaporated to give a crystalline solid. The total product was acetylated with pyridine (15 ml.) and acetic anhydride (10 ml.) overnight at room temperature. Evaporation under reduced pressure and chromatography of the product on alumina yielded, in the first fractions, 2-methyl-Δ²-androstene-17β-ol acetate, m.p. 124–126°. The infrared spectrum was identical with that of authentic material.[1] Further elution gave VIIIa which crystallized from methanol as needles (1.7 g., 52%), m.p. 140–142°; $[\alpha]_D$ −34° ($CHCl_3$); ultraviolet no maximum above 215 mμ. The melting point did not go down on admixture with material obtained[1] by the Wittig reaction with 2-keto-androstane-17β-ol and subsequent acetylation; the melting points and infrared spectra of the two products were identical.

2-Methylene-17α-methylandrostane-17β-ol (VIIIg).—A solution of 2-formyl-17α-methyl-Δ²-androstene-17β-ol (10.0 g.) in ethanol (70 ml.) with potassium hydroxide (8 g.) and anhydrous hydrazine (10 ml.) in a sealed tube was kept at 130° for 24 hr. The mixture was poured into water, acidified with oxalic acid and extracted with ethyl acetate. Evaporation of the organic layer to dryness and chromatography on alumina gave VIIIb (3.9 g., 41%) as needles from methanol, m.p. 156–158°; $[\alpha]_D$ −24° ($CHCl_3$); ν_{max}^{KBr} 3040, 1650 and 889 cm.$^{-1}$ (C=CH_2). The melting point was undepressed on mixing with a sample of 2-methylene-17α-methylandrostane-17β-ol obtained[1] by the Wittig reaction with the 2-ketone. The infrared spectra of the two products were identical.

2-Methoxymethylene-4α-methylandrostane-17β-ol-3-one (Ih).—A solution of 4α-methylandrostane-17β-ol-3-one[15] (2 g.) in benzene (120 ml.) was stirred for 5 hr. with ethyl formate (8 ml.) and sodium hydride (4 g., 50% mineral oil dispersion). The mixture was poured into water, and the material insoluble in aqueous alkali was removed by washing with ether. Acidification of the aqueous alkaline solution, and extraction with ethyl acetate yielded, on evaporation, 2.4 g. of material Ig which was dissolved directly in methanol (10 ml.) and treated with perchloric acid (3 drops, 72%). 2-Methoxymethylene-4α-methylandrostane-17β-ol-3-one (Ih) (1.74 g.), m.p. 214–216° separated from the solution on cooling and was recrystallized from methanol to m.p. 218–218.5°; $[\alpha]_D$ +45° ($CHCl_3$); λ_{max} 276 mμ (ε 12,000).

Anal. Calcd. for $C_{22}H_{34}O_2$: C, 76.26; H, 9.89. Found: C, 76.04; H, 9.64.

2-Formyl-Δ²-4α-methylandrostene-17β-ol (Xa).—To a suspension of 2-methoxymethylene-4α-methylandrostane-17β-ol-3-one (Ih) (1.54 g.) in methanol (50 ml.) was added sodium borohydride in small quantities until all the steroid had dissolved. The solution then showed no selective ultraviolet absorption. Acidification with dilute hydrochloric acid followed by precipitation in water and recrystallization from ethyl acetate gave Xa (800 mg.), m.p. 196–200°; $[\alpha]_D$ +19° (dioxan); λ_{max} 234 mμ (ε 11,500).

Anal. Calcd. for $C_{21}H_{32}O_2$: C, 79.70; H, 10.19. Found: C, 79.48; H, 10.19.

2α,4α-Dimethylandrostane-17β-ol-3-one.—A solution of 2-hydroxymethylene-4α-methylandrostane-17β-ol-3-one (Ig) (2.0 g.) in ethanol (30 ml.) was hydrogenated in the presence of water (2.1 ml.) and concd. hydrochloric acid (0.1 ml.) with palladium on charcoal (600 mg., 5% w./w.) at 2.1 kg./cm.² for 24 hr. Filtration, dilution with water, extraction and evaporation gave an oil. Chromatography on alumina and crystallization from acetone–hexane gave 2α,4α-dimethylandrostane-17β-ol-3-one, m.p. 181–185°; $[\alpha]_D$ +10° ($CHCl_3$).

Anal. Calcd. for $C_{21}H_{34}O_2$: C, 79.19; H, 10.76; O, 10.05. Found: C, 79.23; H, 10.55; O, 10.22.

2-Acetoxymethylene-Δ³-androstene-17β-ol Acetate (IX).—A solution of 2-formyl-Δ²-androstene-17β-ol (IIIa) (14 g.) in acetic anhydride (140 ml.), acetyl chloride (56 ml.) and pyridine (6.3 ml.) was refluxed under nitrogen for 2.5 hr. The reagents were removed in vacuum and the residue was recrystallized from aqueous methanol containing a small amount of pyridine to give the dienol diacetate IX (13.2 g.), m.p. 93–110°. A sample was recrystallized to m.p. 113–116°; $[\alpha]_D$ +41° ($CHCl_3$); λ_{max} 248 mμ (ε 14,000).

Anal. Calcd. for $C_{24}H_{34}O_4$: C, 74.57; H, 8.87; O, 16.56. Found: C, 74.65; H, 8.95; O, 16.40.

2-Hydroxymethyl-Δ²-androstene-17β-ol Acetate (IVb).—The enol diacetate IX (2.9 g.) in methanol (290 ml.) was mixed with sodium borohydride (4.3 g.) in water (43 ml.) at 10°, and left to warm to room temperature overnight. The solution was acidified with acetic acid, diluted with water and extracted with ethyl acetate. The organic layer was washed, dried and evaporated to dryness, and the residue was filtered through alumina in benzene. Crystallization from acetone–hexane gave VIb (1.45 g.), m.p. 141–143° and a second crop (670 mg.), m.p. 125–138°. Recrystallization gave m.p. 142.5–144°; $[\alpha]_D$ +43° ($CHCl_3$).

Anal. Calcd. for $C_{23}H_{34}O_3$: C, 76.26; H, 9.89; O, 13.85. Found: C, 75.79; H, 10.05; O, 14.16.

4α-Chloro-2-formyl-Δ²-androstene-17β-ol Acetate (Xb).—2-Acetoxymethylene-Δ³-androstene-17β-ol acetate (IX) (2 g.) in dioxan (40 ml.) at +13° was mixed with aqueous perchloric acid (3 ml., 0.5 *N*) and N-chlorosuccinimide (1 g.). The reaction was allowed to proceed for 2 hr., after which the solution was diluted with water and extracted with ethyl acetate, and the extract was evaporated to dryness. Recrystallization from acetone–hexane yielded Xb, m.p. 206–207°; $[\alpha]_D$ −24° ($CHCl_3$); λ_{max} 231 mμ (ε 12,000).

Anal. Calcd. for $C_{22}H_{31}O_3Cl$: C, 69.77; H, 8.24; Cl, 9.36; Found: C, 69.45; H, 8.37; Cl, 9.42.

This product was recovered unchanged in high yield after treatment with a saturated solution of hydrogen chloride in ethyl acetate for 5 hours at room temperature.

4ξ-Bromo-2-formyl-Δ²-androstene-17β-ol Acetate (Xc).—A solution of 2-acetoxymethylene-Δ³-androstene-17β-ol acetate (IX) (1.0 g.) in acetone (50 ml.) containing one drop of pyridine was mixed with sodium acetate (0.71 g.) in water (7.1 ml.) and cooled in ice. A solution of N-bromoacetamide (0.57 g.) in acetic anhydride (5.7 ml.) was added, and the mixture was stirred in an ice-bath for one hour. Pouring into water, extraction, and crystallization from acetone–hexane yielded the 4ξ-bromo unsaturated aldehyde 17-acetate Xc (540 mg.) of m.p. 179–183° (dec.); $[\alpha]_D$ −32° ($CHCl_3$); λ_{max} 236 mμ (ε 13,000).

Anal. Calcd. for $C_{22}H_{31}O_3Br$: Br, 18.80. Found: Br, 18.50.

2-Formyl-Δ²,⁴-androstadiene-17β-ol Acetate (XI).—The bromo aldehyde acetate Xc (450 mg.) was refluxed for 1 hr. with dimethylformamide (9 ml.) and finely powdered calcium carbonate (1.35 g.) in a nitrogen atmosphere. The suspension was poured into water, extracted with ethyl acetate, washed first with dilute hydrochloric acid, then with aqueous sodium bicarbonate, and finally with water. Evaporation, filtration through alumina, and crystallization from acetone–hexane gave XI (245 mg.), m.p. 169–170° (sublimes); $[\alpha]_D$ +129° ($CHCl_3$); λ_{max} 320–322 mμ (ε 15,000).

Anal. Calcd. for $C_{22}H_{30}O_3 \cdot 0.5C_3H_6O$: 75.97; H, 8.95; O, 15.08. Found: C, 76.18; H, 8.72; O, 15.10.

Reaction of the Enol Acetate IX with Perchloryl Fluoride.—Perchloryl fluorde was passed in a slow stream into a solution of 2-acetoxymethylene-Δ^3-androstene-17β-ol acetate (IX) (2.0 g.) in dioxan (75 ml.) and water (25 ml.) for 5 hr. The solution was diluted with aqueous sodium chloride and the product was extracted into ethyl acetate, washed, dried and evaporated to dryness. Chromatography of the residue on alumina and crystallization from acetone–hexane gave 4α-chloro-2-formyl-Δ^2-androstene-17β-ol acetate (Xb), m.p. 207–208°; $[\alpha]_D$ −15° ($CHCl_3$); λ_{max} 213 mμ (ϵ 12,000) identical with the product obtained by reaction of IX with N-chlorosuccinimide.

2-(1′-Hydroxyethyl)-Δ^2-androstene-17β-ol (XIIa).—A solution of 2-formyl-Δ^2-androstene-17β-ol (IIIa) (5.0 g.) in benzene (400 ml., thiophene-free) was evaporated to 300 ml. Methylmagnesium bromide in ether (100 ml., 4 *N*) then was added dropwise to the refluxing solution during 20 min. Reflux was continued at 60–65° during 6 hr., after which the solution was cooled and ethyl acetate and dilute hydrochloric acid were added. The organic layer was washed until neutral, evaporated and recrystallized from ethyl acetate 4 times. The melting points after each successive crystallization rose by about 3°, showing the product to be a mixture. Chromatography on alumina did not separate the 1′-isomeric alcohols XIIa. After four recrystallizations from ethyl acetate the product had m.p. 169–171°; $[\alpha]_D$ +79° ($CHCl_3$).

Anal. Calcd. for $C_{21}H_{34}O_2$: C, 79.19; H, 10.76; O, 10.05. Found: C, 78.83; H, 10.31; O, 10.29.

2-Acetyl-Δ^2-androstene-17β-ol (XIIb).—A solution of 2-hydroxymethyl-Δ^2-androstene-17β-ol (XIIa) (1.0 g., 3.04 mmoles) in dioxan (30 ml.) was mixed with 2,3-dichloro-5,6-dicyanobenzoquinone (800 mg., 3.35 mmoles, 1.08 equiv.) in dioxan (20 ml.). After 3.5 hr. at room temperature, crystallization of the hydroquinone appeared to be complete. The solution was diluted with methylene chloride (200 ml.) and filtered through alumina (60 g., activity III) in methylene chloride to give XIIb, which was recrystallized 3 times from methanol to m.p. 213–215°; $[\alpha]_D$ +110° ($CHCl_3$); λ_{max} 234 mμ (ϵ 15,000) and 307 mμ (ϵ 53); ν_{max}^{KBr} 1651 cm.$^{-1}$.

Anal. Calcd. for $C_{21}H_{32}O_2$: C, 79.70; H, 10.19; O, 10.11. Found: C, 79.09; H, 10.20; O, 9.97.

2-Acetyl-17α-methyl-Δ^2-androstene-17β-ol (XIId).—A solution of 2-formyl-17α-methyl-Δ^2-androstene-17β-ol (IIIh) (4.57 g.) in benzene (500 ml.) was evaporated to 300 ml. to remove water. To the refluxing solution, methylmagnesium bromide solution (100 ml., 4 *N* in ether) was added during 30 min. The solution was distilled until all ether had been removed, then reflux was continued for 18 hr., during which time a gel formed. The solution and gel were shaken with dilute hydrochloric acid (4 *N*) until all the material was in solution. The benzene layer was diluted with ethyl acetate, and washed with water until neutral. The solution was evaporated to yield a light brown oil. Chromatography of the oil on silica and elution with 25% ether in benzene increasing gradually to pure ether yielded an oil (2.38 g.) which showed no selective absorption in the ultraviolet.

The oily diol (XIIc) (1.0 g., 3.1 mmoles) in dioxan (10 ml.) was mixed with a solution of 2,3-dichloro-5,6-dicyanobenzoquinone (800 mg., 3.50 mmoles, 1.13 equiv.) in dioxan (5 ml.). After 30 min. at room temperature, the hydroquinone started to crystallize from solution and after 3.5 hr. crystallization appeared to be complete. The dioxan solution was diluted with methylene dichloride (100 ml.) and the solution was filtered through a column of alumina (60 g., activity I) in methylene chloride. Evaporation of the eluate and two recrystallizations from ethanol yielded XIId (560 mg., 48% yield), m.p. 191–193°; $[\alpha]_D$ +88° ($CHCl_3$); λ_{max} 234 mμ (ϵ 11,200) and 308 mμ (ϵ 55); ν_{max}^{KBr} 1653 cm.$^{-1}$.

Anal. Calcd. for $C_{22}H_{34}O_2$: C, 79.95; H, 10.37; O, 9.68. Found: C, 79.57; H, 10.19; O, 10.19.

3-Acetyl-Δ^2-androstene-17β-ol Acetate (XIII).—To Δ^2-androstene-17β-ol acetate (2 g.) in acetic anhydride (6 ml.) was added zinc chloride (2.5 g.), and the mixture was kept at 48° during 20 hr. The solution was poured into water and extracted with ether. The ether was washed with aqueous potassium hydroxide, then with water until neutral, dried, and evaporated. Chromatography on alumina yielded XIII (120 mg.), m.p. 129–132°. Recrystallization from acetone–hexane gave m.p. 135–137°; $[\alpha]_D$ +82° ($CHCl_3$); λ_{max} 234 mμ (ϵ 12,500).

Anal. Calcd. for $C_{23}H_{34}O_3$: C, 77.05; H, 9.56; O, 13.39. Found: C, 77.04; H, 9.46; O, 13.95.

3α-Ethynylandrostane-3β,17β-diol (XIVa).—Acetylene was passed into a stirred mixture of tetrahydrofuran (1 l.) and methylmagnesium bromide (250 ml., 4 *N* in ether) for 3 hr. To the solution was added androstane-17β-ol-3-one (5.0 g.) in tetrahydrofuran (500 ml.) and the mixture refluxed for 20 hr. The solution was poured into aqueous ammonium chloride and extracted with ethyl acetate. The extract was washed, dried and evaporated to give a residue which on chromatography yielded XIVa (2.75 g.), m.p. 172–176°. Crystallization from acetone–hexane gave m.p. 196–197°; $[\alpha]_D$ +11° ($CHCl_3$).

Anal. Calcd. for $C_{21}H_{32}O_2 \cdot C_3H_6O$: C, 76.96; H, 10.23; O, 12.82. Found: C, 77.53; H, 10.24; O, 12.41.

3α-Ethynylandrostane-3β,17β-diol 17-monoacetate (XIVb).—Acetylation of XIVa with acetic anhydride and pyridine at 90° for 1 hr. yielded the 17-monoacetate XIVb, m.p. 209–210° from acetone–hexane; $[\alpha]_D$ +17° ($CHCl_3$).

Anal. Calcd. for $C_{23}H_{34}O_3$: C, 77.05; H, 9.56; O, 13.39. Found: C, 77.47; H, 9.30; O, 13.74.

Rearrangement of 3α-Ethynylandrostane-3β,17β-diol.—3α-Ethynyl-5α-androstane-3β,17β-diol (680 mg.) was heated on the steam bath for 1.5 hr. with formic acid (35 ml., 90%). Pouring into water, extraction into ethyl acetate, washing and evaporation gave a residue (780 mg.) which was hydrolyzed with methanolic potassium hydroxide (25 ml., 5%). The free 17-alcohol was extracted with ethyl acetate and the solvent was evaporated to give a residue which was acetylated with acetic anhydride and pyridine overnight at room temperature. Pouring into water, extraction and chromatography on alumina gave 3-acetyl-Δ^2-androstene-17β-ol acetate (XIII) which was recrystallized from hexane–benzene to m.p. 135–137°; $[\alpha]_D$ +82° ($CHCl_3$); λ_{max} 234 mμ (ϵ 13,000) identical with that prepared by C-acylation of IIIb.