Steroids. CCCIX.[1] Synthesis of new steroids with unnatural configuration

PIERRE CRABBÉ, ALICIA CRUZ, AND JOSÉ IRIARTE
Research Laboratories, Syntex, S.A., Apartado Postal 2679, Mexico

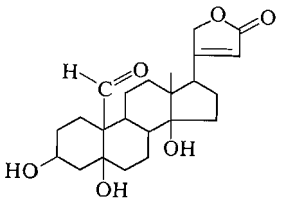
Received August 22, 1967

The preparation of several new estrane, androstane, and 19-norpregnane derivatives with unnatural configuration is discussed. A synthesis of both enantiomers (**16***b*) and (**18**) from estrone is described. The structure and configuration of the compounds reported are established on the basis of their physical properties.

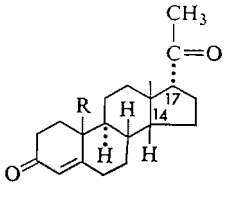
Canadian Journal of Chemistry, 46, 349 (1968)

When reporting the multistage transformation of the cardiac aglycone strophanthidin (**1**) to 14β,17α-19-norprogesterone (**2***a*), Ehrenstein (2) opened the field of steroid chemistry to new horizons. The bis-iso-19-norprogesterone (**2***a*) resembled the natural hormone progesterone (**3**) but lacked the angular methyl grouping at position-10, and the stereochemistry at C-14, as well as at C-17 was different. Because the 14β,17α-19-norprogesterone (**2***a*) was shown to exhibit higher biological activity (3) than progesterone (**3**), several research groups decided to undertake the synthesis of steroids with abnormal configuration (4). Hence, since Ehrenstein's early observation, numerous similar steroids, among which the 14β,17α-progesterone (**2***b*) and 19-norsteroids (4, 5), have been prepared. Related work was also undertaken in the Syntex Laboratories (4*d*, 6). In the present study the preparation of several other new steroids with unnatural configuration, belonging to the estrane, androstane, and 19-norpregnane series is reported.

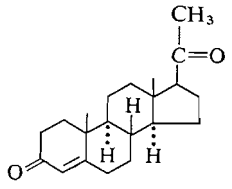
Treatment of the enol acetate (**5**) (7, 8) of estrone methyl ether (**4***a*) with bromine affords the 16α-bromo derivative, (**4***b*) (7), as the main compound. The 16α-configuration[2] is assigned to the bromine atom on the basis of the optical properties exhibited by this compound (**4***b*), since the Cotton effect associated with the 17-keto chromophore is less intense than in **4***a*, in agreement with the octant rule (10). Conversion of the bromo-ketone (**4***b*) into its cycloethylene ketal followed by dehydrobromination (7, 11) and mild acid hydrolysis provides the known Δ^{15}-17-ketone (**6***a*) (7, 11), typified by a *negative* Cotton effect in the 350 mμ region. On treatment



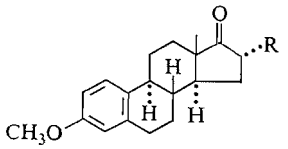
1



2*a*, R = H
b, R = CH_3



3

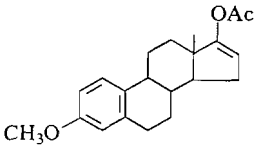


4*a*, R = H
b, R = Br

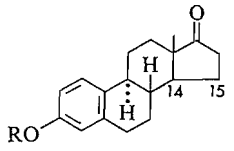
with acid, the α,β-unsaturated ketone (**6***a*) affords a mixture of three isomeric compounds separable by column chromatography. The first substance is the 14β-isomer (**6***b*) (7), characterized by its nuclear magnetic resonance (n.m.r.) spectrum which shows olefinic resonance as a doublet at 374 c.p.s. ($J_{15,16} = 6$ c.p.s.) (C-16H) and a further doublet of doublets ($J_{15,16} = 5$ c.p.s.; $J_{14,15} = 8$ c.p.s.) at 427 c.p.s. (C-15H). Its ultraviolet (u.v.) absorption spectrum and the *positive* Cotton effect for the n–π^* transition of the α,β-unsaturated ketone, at ca. 340 mμ are also characteristic of compound (**6***b*). The second isomer is the β,γ-ethylenic ketone (**6***c*) (7). Although the u.v. spectrum of this compound is reminiscent of (but less intense than) that of compound (**6***b*), its n.m.r. spectrum is characteristic in having only *one* olefinic proton (338 c.p.s.). Moreover, compound (**6***c*) exhibits a relatively strong *positive* Cotton effect in the 300 mμ region, as expected for such a chromophore (12).

[1]For Steroids. CCCVIII, see ref. 1.
[2]For the stereochemistry of enolization of 17-keto steroids, see ref. 9.

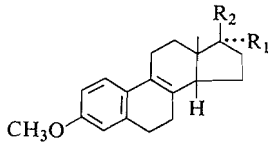
At equilibrium the isomers (**6***b*) and (**6***c*) are obtained in the 2:3 ratio, when the isomerization of **6***a* is performed under mild acidic conditions. The predominance of the β,γ-unsaturated ketone (**6***c*) in the mixture is attributable to conformational factors (13), interpretable by consideration of dihedral angles (14) at the C/D ring junction.



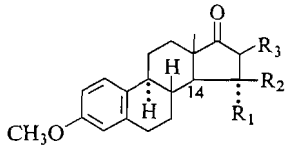
5



6*a*, R = CH_3; 14αH; Δ^{15}
b, R = CH_3; 14βH; Δ^{15}
c, R = CH_3; Δ^{14}
d, R = CH_3; 14βH
e, R = H; 14βH
f, R = THP; 14βH



7*a*, R_1, R_2 = ketone
b, R_1 = OH; R_2 = C≡CH



8*a*, 14αH; R_1 = OCH_3; R_2 = R_3 = H
b, 14αH; R_1 = R_3 = H; R_2 = OCH_3
c, 14βH; R_1 = R_3 = H; R_2 = OCH_3
d, 14βH; R_1 = H; R_2, R_3 = epoxy

The third compound isolated is the steroid (**7***a*) (7). The u.v. absorption spectrum presents the styrene chromophore at ca. 273 mμ and the n.m.r. spectrum does not show any olefinic proton. Furthermore, this compund (**7***a*) exhibits two Cotton effects. The weakly positive Cotton effect associated with the 17-ketone in the 300 mμ region is in agreement with the *cis* C/D ring junction (12); whereas the strong positive Cotton effect at ca. 270 mμ is due to the styrene chromophore (15) ($a = +601$). The steroid (**7***a*) is obtained exclusively when **6***a* is submitted to relatively vigorous acidic conditions. This is worth noting, since it is known that the double bond of a ring A aromatic Δ^8-steroid with the 14αH-stereochemistry is readily isomerized to the $\Delta^{9(11)}$-position. Although a 9,(11)-dehydro 14-iso-compound is a known product of the isomerization of equilin (16), it appears that with the 14β-configuration, the 8,9-double bond is energetically preferred over the 9(11)-position. This also can be interpreted by the dihedral angle theory (14).

Reaction of **7***a* with ethinylmagnesium bromide (17) furnishes the corresponding ethinyl derivative (**7***b*) (for stereochemistry see below).

Worth mentioning here is the earlier attempt (7) to effect a base-catalyzed isomerization of **6***a* with methanolic potassium hydroxide. When repeated, this reaction leads to the isolation of various substances, depending on the experimental conditions (18). Indeed, it has been observed that base treatment of **6***a* in methanol solution gives, besides the isomers (**6***b*) and (**6***c*), addition of methoxyl to the α,β-unsaturated chromophore.

When **6***a* is treated with methanolic potassium hydroxide, under rather mild conditions, its 14β-isomer (**6***b*) and the Δ^{14}-derivative (**6***c*) are obtained. Furthermore, two new methoxylated compounds are also isolated. To the first substance, structure (**8***a*) is assigned. The new methoxyl group gives a three proton signal at 200 c.p.s. in the n.m.r. Since the positive Cotton effect associated with the 17-carbonyl of the steroid (**8***a*) is rather intense ($a = +103$), and because of the position of the 18-methyl group is normal for a 14α-17-keto steroid, the 14αH, 15$\alpha$$OCH_3$-stereochemistry is assigned to this substance. The second methoxyl derivative appears to be the 15β-isomer (**8***b*). The Cotton effect associated with the 17-carbonyl chromophore in **8***b* is in agreement (12) with the 14α-configuration. Moreover, the β-configuration at C-15 is assigned on the basis of the chemical shift of the C-18 methyl protons in the n.m.r. (67 c.p.s.). This shift is attributed to interactions in space between the 15β-methoxyl and the 18-methyl groups.

The reversibility of the Michael addition of methoxyl to the Δ^{15}-17-keto system is deduced from the following observation. When **8***a* is heated in 2% methanolic potassium hydroxide solution, besides some starting material, ca. 50% of compound (**6***c*) and 20% of its double bond isomer (**6***b*) are obtained.

Base treatment of **6***b* under mild conditions affords mainly unchanged starting material, the Δ^{14}-17-ketone (**6***c*), and some of the 14β,15β-

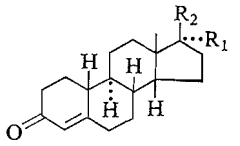
methoxylated steroid (**8***c*). The configuration at C-14 in **8***c* is assigned on the basis of the chemical shift of the C-18 methyl protons (68 c.p.s.). The resonance signal is similar to that of the 18-methyl group in 14β-compounds, eg. (**6***d*, **6***e*, **6***f*), and (**7***a*), showing some 16 c.p.s. downfield shift of the corresponding resonance in the 14α-analogue (**4***a*). Further confirmation of the 14βH-stereochemistry is obtained from the circular dichroism (c.d.) molecular ellipticity exhibited by **8***c* ($[\Theta]_{291} = +4\,720$), which is reminiscent of the Cotton effect of saturated 14β-17-keto steroids (12). Using the same reasoning as before (19), the β-configuration is assigned to the methoxyl at C-15 since addition from the hindered α-side is not favored in C/D-*cis*-β-steroids.

When the Δ^{14}-isomer (**6***c*) is submitted to similar basic reaction conditions, one recovers some unchanged product and obtains as major compound the 14β-derivative (**6***b*), as well as a small amount of the methoxylated steroid (**8***c*).

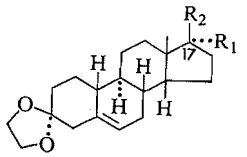
Base treatment of 15-dehydro-14β-estrone methyl ether (**6***b*) in a mixture of methanol and tetrahydrofuran (containing peroxides), in the presence of air, gave the 15,16β-oxido derivative (**8***d*). The physical properties (see Experimental) support the structure and stereochemistry assigned to this compound (**8***d*).[3]

This indicates that under acidic or basic conditions, compound (**6***a*) is isomerized into **6***b* and **6***c*, the last two ones existing in equilibrium. Furthermore, in methanolic alkaline conditions, addition of methoxyl can take place to the α,β-unsaturated system of **6***a* and **6***b*.

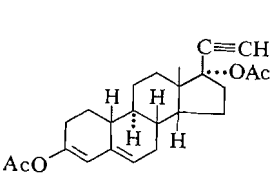
Catalytic hydrogenation of **6***b* or **6***c*, in presence of palladium on carbon, gives 14-isoestrone methyl ether (**6***d*) (7). The 14β-configuration in **6***d* is confirmed by the 18-methyl resonance signal (67 c.p.s.) and the weakly positive Cotton effect ($a = +34$), typifying the 17-keto chromophore in such a *cis*-hydrindanone system (12, 21). Treatment of the 3-methyl ether (**6***d*) with hydrogen bromide (22) affords the free phenol (**6***e*), from which the corresponding tetrahydropyranyl ether (**6***f*) is obtained by reaction with dihydropyrane (23). When **6***d* is reduced with lithium in liquid ammonia (24)[4] followed by mild acid treatment, the 14β,17α-19-nortestosterone (**9***a*) is obtained. The α-configuration of the secondary alcohol grouping at C-17 is established by Horeau's method (25).[5]



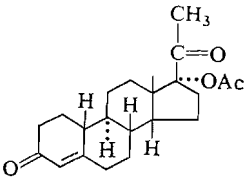
9*a*, R_1 = OH; R_2 = H
b, R_1 = OH; R_2 = C≡CH
c, R_1 = OTHP; R_2 = C≡CH
d, R_1 = —CHOH—CH_3; R_2 = H



10*a*, R_1 = OH; R_2 = H
b, R_1, R_2 = ketone
c, R_1 = OH; R_2 = C≡CH



11



12

Protection of the 3-keto group of **9***a* as the cycloethylene ketal (**10***a*), followed by oxidation (26) at C-17 provides the ketone (**10***b*). Addition of ethinylmagnesium bromide (17) at C-17, affords the 17β-ethinyl derivative (**10***c*), characterized by the resonance signal (153 c.p.s.) corresponding to an acetylenic proton. Acid hydrolysis of the ketal at C-3 and isomerization of the double bond to C-4 gives the nor-steroid (**9***b*). The structure of this compound results from its physical and spectroscopic properties, ie. the typical u.v. absorption for the Δ^4-3-keto chromophore, an hydroxyl band in the infrared (i.r.) spectrum and the acetylenic proton detected by i.r. and n.m.r. spectroscopy (see Experimental). The 17α-tetrahydropyranyl derivative (**9***c*) is also prepared (23). The β-configuration for the ethinyl side chain is deduced from the observations which follow.

Treatment of compound (**9***b*) with acetic anhydride in presence of *p*-toluenesulfonic acid

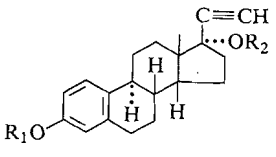
[3]For a similar example of epoxidation of Δ^{15}-17-ketone with alkaline hydrogen peroxide, see ref. 20.

[4]For a review on reduction with metal–ammonia reagents, see ref. 24*d*.

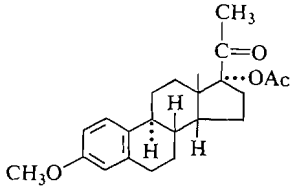
[5]We are indebted to Professor A. Horeau and Dr. H. Kagan, Collège de France, Paris, for this determination.

gives the enol acetate (**11**). This bis-acetate (**11**) is characterized by a u.v. absorption band at 234 mμ and its n.m.r. spectrum which shows two lowfield methyl signals (121 and 127 c.p.s.), ascribed to acetoxy groupings, an acetylenic proton signal (156 c.p.s.), and two olefinic proton signals (C-4: 340 and C-6: 330 c.p.s.) respectively. When the triple bond of **11** is reacted with mercuric sulfate in ethanol solution, in the presence of dilute sulfuric acid,[6] 17α-acetoxy-14β-19-norprogesterone (**12**) is obtained. The physical properties support structure (**12**) proposed for this compound. Its c.d. curve exhibits a multiple negative Cotton effect in the 330 mμ region, due to the n–π^* transition of the Δ^4-3-keto chromophore (12). Moreover, a mild positive Cotton effect appears at 285 mμ ([θ] = +2 050), which is in agreement with the 17β-stereochemistry of the methyl ketone side chain (12). The positive molecular ellipticity of the acetyl side chain in **12** is weaker than in normal 17β-acetyl steroids, such as in progesterone (3; [θ] = +11 000) (12). This is due to the *cis*-β-C/D-ring juncture (12, and see, for example 28) and the 17α-acetoxy grouping (29), both factors being known to reduce the positive Cotton effect of a 20-keto grouping (12).

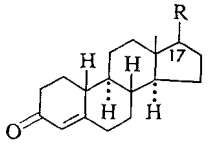
Since hydration of the triple bond in **11** occurs with retention of configuration,[6] this necessarily implies the stereochemistry for the ethinyl side chain to be β in compounds (**10***c*), (**9***b*,*c*) and (**11**), as well as in (**7***b*).



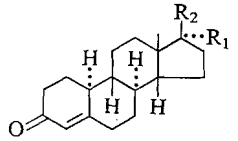
13*a*, $R_1 = CH_3$; R_2 = H
b, $R_1 = CH_3$; R_2 = Ac
c, $R_1 = R_2$ = H
d, R_1 = THP; R_2 = H
e, $R_1 = CH_3$; R_2 = THP



14



15*a*, R = ξOH
b, R = ketone
c, R = βOH



16*a*, R_1 = OH; R_2 = H
b, R_1, R_2 = ketone

[6]Private communication from Dr. J. Fried, Institute of Steroid Chemistry, Syntex Research, Palo Alto, Calif. See ref. 27.

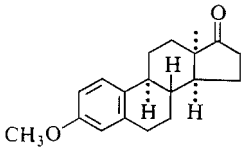
The 14-isoestrone derivative (**6***d*) is converted into the 17-substituted steroid (**14**) *via* the intermediates (**13***a*) and (**13***b*) by the above mentioned reaction sequence. The physical properties of these compounds support the proposed structure and stereochemistry. Reduction of compound (**14**) under Birch's conditions (24) simultaneously reduces ring A and the 20-ketone, with concurrent removal of the 17α-acetoxy grouping and inversion of the acetyl side chain (30). After mild acid treatment, a mixture of alcohols stereoisomeric at C-20 (**9***d*) is obtained. Chromic acid oxidation (31) of this mixture of alcohols furnishes 14β,17α-19-norprogesterone (**2***a*), the physical properties of which are identical with the reported data (2). Furthermore, the negative c.d. maximum at ca. 300 mμ clearly indicates (12) the configuration of the acetyl side chain to be α.

Lithium in ammonia reduction (24) of Δ^8-isoestrone-3-methyl ether (**7***a*) followed by subsequent acid hydrolysis leads to a mixture of compounds separated by thin-layer chromatography. To the main isomers, the 8β,9α,10β,14α (**15***a*) and 8α,9β,10α,14β (**16***a*) configuration is suggested from the data mentioned below. Since the steroid (**15***a*) could not be obtained in crystalline form (being presumably a complex mixture of 17α- and 17β-alcohols, as well as some 14β-derivative), the crude product was oxidized (31) to afford the diketone (**15***b*) which exhibited physical properties identical with those of the known compound (24*b*). The multiple Cotton effect of the Δ^4-3-keto chromophore in **15***b* is *negative*, in agreement (12) with the 9α,10β "natural" stereochemistry. Conversely, the optical rotatory dispersion (o.r.d.) and c.d. curves show that the multiple Cotton effect of the n–π^* transition of the unsaturated chromophore in the nor-steroid (**16***a*) is *positive*. This is in keeping with the "retro" configuration (9β, 10α), since Δ^4-3-keto retrosteroids are known to exhibit a positive multiple Cotton effect in the 330 mμ region (12, 32).

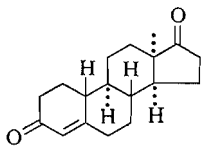
The formation of compound (**15***a*) by reduction of **7***a* implies an inversion of the configuration at C-14, presumably through double bond migration from position-8,9 to -8,14, prior to reduction.

The optical properties of compound (**16***a*) establish its stereochemistry at C-9 and C-10, but no definite conclusion can be drawn for the configuration of the hydrogen atom at C-8. If the configuration at C-8 is α, then the stereochemistry of **16***a* should be the opposite of 19-

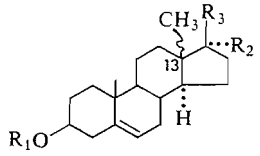
nortestosterone (**15***c*) (5a) at all asymmetric centers, with the exception of the methyl grouping at C-13. This point is confirmed as follows.



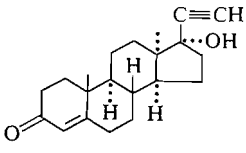
17



18



19*a*, R_1 = THP; 13βCH_3; R_2, R_3 = ketone
b, R_1 = THP; 13αCH_3; R_2, R_3 = ketone
c, R_1 = THP; 13αCH_3; R_2 = OH; R_3 = C≡CH
d, R_1 = H; 13αCH_3; R_2 = OH; R_3 = C≡CH



20

Irradiation of estrone 3-methyl ether (**4***a*) with ultraviolet light gives its 13α-isomer (**17**) (33). The *cis*-α-stereochemistry at the C/D ring junction in **17** is established by the weakly negative Cotton effect exhibited by the 17-keto chromophore ($[\theta]_{307} = -1\,980$) (12, 29, 34). The methyl ether of lumiestrone (**17**) (33, 35) is then reduced with lithium in liquid ammonia (24) and treated with acid to provide a mixture of epimers at C-17. Chromic acid oxidation (31) of this mixture of secondary alcohols affords the 19-nor diketo steroid (**18**). Similarly, the keto alcohol (**16***a*) is oxidized to the diketo steroid (**16***b*). The isomeric compounds (**16***b*) and (**18**) exhibit superimposable i.r. curves, identical n.m.r. and u.v. spectra, as well as other physical properties except for the sign of the specific rotation which is opposite (see Experimental). Worth noting is the identity of the fragmentation pattern of the antipodes (**16***b*) and (**18**) under electron impact, (see Experimental).[7]

The enantiomeric relationship characterizing these steroids is further confirmed by their o.r.d. and c.d. curves. As shown in Fig. 1, the o.r.d. and c.d. curves of **16***b* and **18** are mirror images, confirming the stereochemistry at all asymmetric centers, particularly the 8αH-configuration in **16***b* and hence in its precursor **16***a*. The o.r.d. and c.d. curves of the enantiomers (**16***b*) and (**18**) reproduced in Fig. 1 clearly show that the multiple Cotton effect at ca. 330 mμ associated with the n–π^* transition of the Δ^4-3-keto chromophore is negative in compound (**18**) and positive in **16***b*. Conversely, the π–π^* transition of the same chromophore, appearing in the 235 mμ region, is positive for **18** and negative for its enantiomer (**16***b*). The n–π^* transition of the saturated 17-keto chromophore at ca. 300 mμ is hardly observed in these curves, even in the c.d. curves. This is due to the very intense Cotton effect associated with the π–π^* transition of the unsaturated ketone (12, 37).

A 1:1 mixture of the enantiomers (**16***b*) and (**18**) provides the racemate devoid of optical activity (see Experimental).

While the 14β-estradiol derivatives (**13***c*–**13***e*) are also prepared by conventional methods (see Experimental), ultraviolet irradiation (33, 34b, 35, 38) of the 17-keto androstane derivative (**19***a*) affords the 13α-steroid (**19***b*). Nucleophilic addition of acetylene (17) to the carbonyl gives a mixture of ethinyl derivatives. The main constituent is considered (39, see also 34*b*) to be the 17β-ethinyl compound (**19***c*). Mild acid hydrolysis gives the 3-alcohol (**19***d*). Oxidation (31) then leads to the iso-ethinyl testosterone derivative (**20**).

Experimental

Microanalyses were done by Dr. A. Bernhardt, Mülheim, Germany. Melting points (m.p.) were determined in capillary tubes with a "Mel-temp" apparatus; they are corrected. Rotations were taken between 16° and 22° with a 1 dm tube at sodium D-line, in chloroform solution. Optical rotatory dispersion (o.r.d.) curves were taken with an automatic recording JASCO/UV-5 spectropolarimeter. Circular dichroism (c.d.) curves have been obtained with a Jouan dichrograph at the University of Strasbourg, through the kind cooperation of Professor G. Ourisson. The o.r.d. and c.d. curves of enantiomers (**16***b*) and (**18**) (Fig. 1) are due to the courtesy of Dr. H. Wolf, Institute für Organische Chemie der Technischen Hochschule, Braunschweig, Germany, to whom we express our sincere gratitude. Infrared spectra were taken with a Perkin–Elmer, model 21, NaCl prism in KBr pellets. Unless stated otherwise, u.v. absorption spectra were obtained in 95% ethyl alcohol, with a Beckman model DU spectrophotometer. Nuclear magnetic resonance spectra were recorded at 60 Mc.p.s. using 5–8% w/v solutions of steroid in chloroform containing tetramethylsilane (TMS) as an internal reference. Resonance frequencies, ν, are quoted as c.p.s. downfield from the TMS reference (0.0 c.p.s.) and are accurate to ±1 c.p.s. Coupling constants,

[7]A similar case has been reported recently (36).

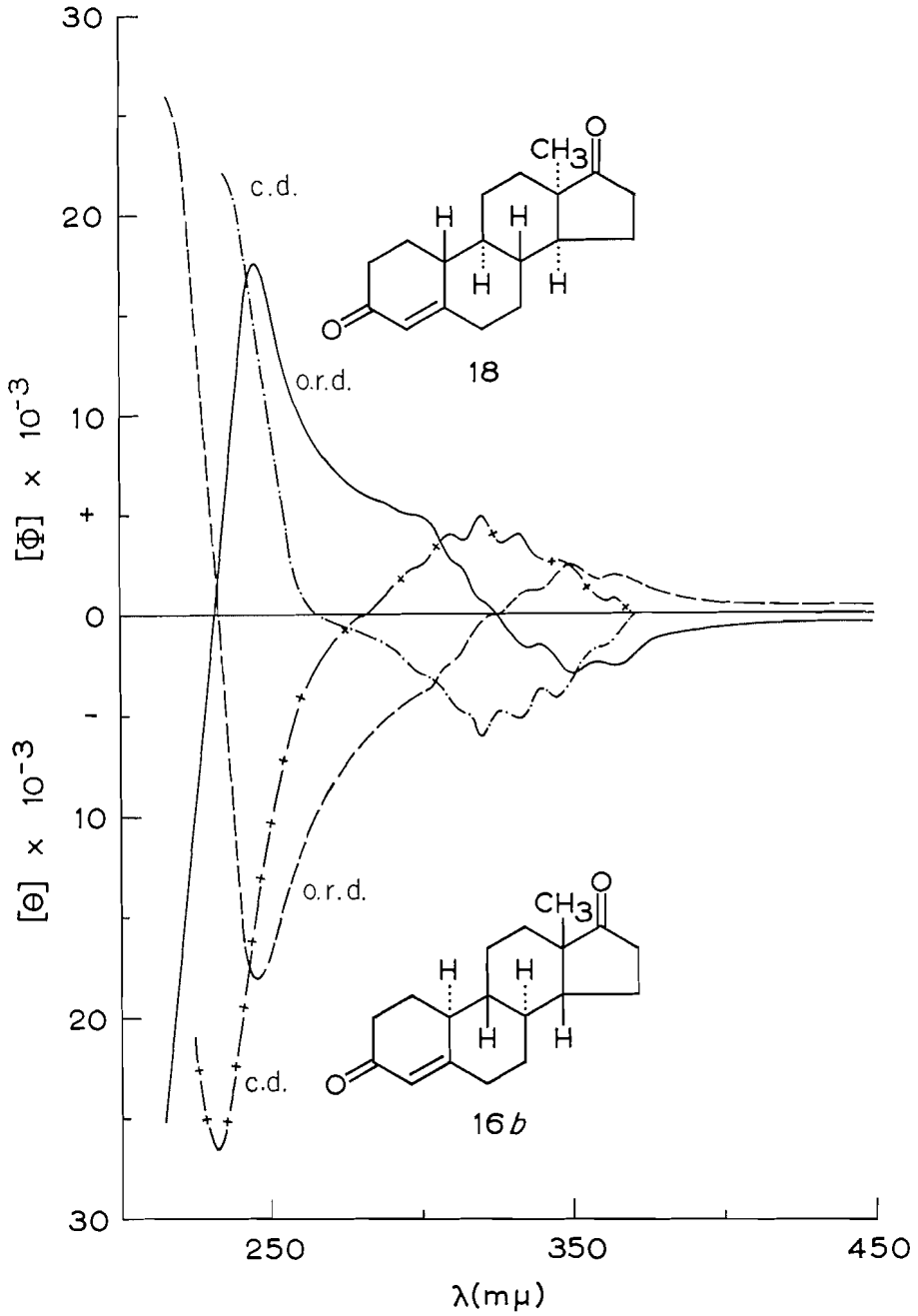


FIG. 1. Optical rotatory dispersion and circular dichroism curves of the enantiomeric steroids (**16***b*) and (**18**).

J, also expressed in c.p.s. units, are accurate to ±0.5 c.p.s. We are indebted to Dr. L. Throop and his staff, Syntex Research, Palo Alto, California, for o.r.d. and n.m.r. measurements. Silica gel G (Merck) and neutral alumina were used for preparative thin-layer and column chromatography.

Estrone 3-Methyl Ether (4a)

Optical rotatory dispersion (*c*, 0.0003; dioxane): $[\Phi]_{600}$ +539°; $[\Phi]_{350}$ +2938°; $[\Phi]_{319}$ +8814°; $[\Phi]_{297}$ ±0°; $[\Phi]_{278}$ −5190°; $[\Phi]_{246}$ ±0°; $[\Phi]_{234}$ +3526°; c.d. (*c*, 0.0003; dioxane): $[\Theta]_{332}$ ±0; $[\Theta]_{300}$ +11 080; $[\Theta]_{268-271}$ +9400.

16α-Bromo-3-hydroxyestra-1,3,5(10)-trien-17-one-3-methyl Ether (4b) (7)

Optical rotatory dispersion (*c*, 0.001; dioxane): $[\Phi]_{600}$ +436°; $[\Phi]_{380}$ +2327°; $[\Phi]_{341}$ +5743°; $[\Phi]_{314}$ ±0°; $[\Phi]_{292}$ −5080°; $[\Phi]_{258}$ +0°; $[\Phi]_{234}$ +8228°; $[\Phi]_{229}$ ±0°; $[\Phi]_{225}$ −16 333°; c.d. (*c*, 0.009; dioxane): $[\Theta]_{362}$ ±0; $[\Theta]_{317}$ +7890; $[\Theta]_{186}$ +3200.

3-Hydroxyestra-1,3,5(10),-15-tetraen-17-one-3-methyl Ether (6a) (7)

Melting point 180–181°; $[\alpha]_D$ −56°; c.d. (*c*, 0.001; dioxane): $[\Theta]_{400}$ ±0; $[\Theta]_{357}$ −1350; $[\Theta]_{298}$ −120; u.v. λ_{max} 224, 278, 287 mμ (log ε 4.16, 3.37, 3.32); i.r. ν_{max} 1720 cm^{-1}; n.m.r. 66 (18-H), 176 (benzylic H), 227 (3-methoxyl), 360, 363, 366, 369 (quartet, 16-vinyl H split by 15H, J = 6 c.p.s.) and by 14αH (J = 3 c.p.s.); 400, 404 (C-2 and C-4 aromatic H), 429, 437 (doublet J = 8, C-1 aromatic H); 456, 462 c.p.s. (15-vinyl H, doublet).

3-Hydroxy-14β-estra-1,3,5(10),15-tetraen-17-one-3-methyl Ether (6b) and 3-Hydroxyestra-1,3,5(10),14-tetraen-17-one-3-methyl Ether (6c) (7)

A mixture of 15-dehydroestrone 3-methyl ether (**6***a*) (3.5 g) and *p*-toluenesulfonic acid monohydrate (2.28 g) in 175 ml of benzene was heated under reflux for 15 min. A saturated solution of sodium bicarbonate was added, the mixture was extracted with methylene chloride, and washed with water until neutral. The solution was dried over anhydrous sodium sulfate, filtered, and evaporated to dryness *in vacuo*. The residue appeared to be a mixture of two components in the 2:3 ratio. Chromatography on silica gel followed by crystallization from methylene chloride – methanol of the fractions eluted with hexane – ethyl acetate (95:5) afforded 1.85 g of 14-dehydroestrone-3-methyl ether (**6***c*) exhibiting: m.p. 102–103°; $[\alpha]_D$ +287°; c.d. (*c*, 0.001; dioxane): $[\Theta]_{320}$ +3470; $[\Theta]_{315}$ +4650; $[\Theta]_{306}$ +6800; $[\Theta]_{297}$ +7000; u.v. λ_{max} 221–222, 280, 287 mμ (log ε 3.94, 3.31, 3.29); i.r. ν_{max} 1750, 1650, 1640, 1610 cm^{-1}; n.m.r. 70 (18-H), 180 (benzylic H), 227 (methoxyl H), 338 (15-vinyl H), 401 (C-4 aromatic H), 401, 408 (C-2 H), 430, 437 (C-1 H).

Further elution of the column with the same solvent system, followed by crystallization from methylene chloride – methanol, gave 1.04 g of 15-dehydro-14β-estrone-3-methyl ether (**6***b*) showing: m.p. 100–101°; $[\alpha]_D$ +476°; c.d. (*c*, 0.0014; dioxane): $[\Theta]_{349}$ +2840; $[\Theta]_{337}$ +3660; $[\Theta]_{326}$ +3465; u.v. λ_{max} 220–221, 277–278, 286–287 mμ (log ε 4.22, 3.40, 3.35); i.r. ν_{max} 1700, 1615, 1575 cm^{-1}; n.m.r. 70 (18-H), 172 (benzylic H), 226 (methoxyl H), 371, 377 (C-16 H, doublet J = 6), 398 (C-4 H), 398, 407, 423, 431 (C-15 H, doublet J = 8). 456, 462, c.p.s.

Anal. Calcd. for $C_{19}H_{22}O_2$: C, 80.81; H, 7.85. Found: C, 80.46; H, 7.94.

Acid Isomerization of 15-Dehydroestrone-3-methyl Ether (6a)

A solution of 50 mg of pure 15-dehydroestrone methyl ether (**6***a*) and 33 mg of *p*-toluenesulfonic acid monohydrate in 2.5 ml of anhydrous benzene was allowed to reflux for 3 min. The reaction mixture was then poured into a saturated sodium bicarbonate solution. Extraction with methylene chloride gave a residue which was purified by chromatography on silica gel. The fractions eluted with hexane – ethyl acetate (95:5) afforded 30 mg of starting material. Further elution gave 10 mg of 14-dehydroestrone methyl ether (**6***c*) with m.p. 100–101°; $[\alpha]_D$ +290°; u.v. λ_{max} 219–221, 280, 287 mμ (log ε 3.95, 3,31, 3.29), identified by thin-layer chromatography (t.l.c.) infrared spectra and mixture melting point with an authentic specimen.

Alkaline Isomerization of 15-Dehydroestrone Methyl Ether (6a)

A solution of 1 g 15-dehydroestrone methyl ether (**6***a*) in 200 ml of 2% methanolic potassium hydroxide was heated to reflux for 30 min under nitrogen. Extraction with methylene chloride, washing to neutrality with water, and evaporation of the solvent gave 970 mg of an amorphous product. This mixture was chromatographed on fluorescent, preparative silica gel chromatoplates. The following products were isolated. First, 200 mg of 14-dehydroestrone methyl ether (**6***c*); m.p. 99–100°; $[\alpha]_D$ +288°; undepressed on admixture with an authentic sample. Then a semicrystalline material with $[\alpha]_D$ +377° which after recrystallization from methylene chloride – methanol gave 295 mg of 14β-15-dehydroestrone methyl ether (**6***b*); m.p. 99–100°; $[\alpha]_D$ +470°, identified by t.l.c., i.r., and mixture m.p. (undepressed) with an authentic sample. A third compound (220 mg) was obtained. Its physical properties agree with the 15α-hydroxyestrone dimethyl ether (**8***a*) structure. Recrystallization from methylene chloride – methanol afforded the analytical sample of **8***a*: m.p. 126–127°; $[\alpha]_D$ +227°; o.r.d. (*c*, 0.0006; dioxane): $[\Phi]_{600}$ +625°; $[\Phi]_{589}$ +729°; $[\Phi]_{318}$ +8547°; $[\Phi]_{288}$ ±0°; $[\Phi]_{279}$ −1772°; $[\Phi]_{270}$ −1563°; $[\Phi]_{262}$ ±0°; $[\Phi]_{240}$ +7558°; $[\Phi]_{234}$ +9902°; $[\Phi]_{224}$ ±0; $[\Phi]_{223}$ +1954°; $[\Phi]_{222}$ ±0°; $[\Phi]_{216}$ +5081°; c.d. (*c*, 0.0005; dioxane): $[\Theta]_{326}$ +0; $[\Theta]_{299}$ +9970; $[\Theta]_{286}$ +7500; u.v. λ_{max} 219–220, 278, 287 mμ (log ε 3.94, 3.34, 3.31); i.r. ν_{max} 1745, 1613 cm^{-1}; n.m.r. 55 (18-H), 200 (15-methoxyl), 224 (3-methoxyl), ~240 (15-H), 396 (C-4 H), 404, 406 (C-2 H), 426, 434 (C-1 H) c.p.s.

Anal. Calcd. for $C_{20}H_{26}O_3$: C, 76.40; H, 8.34. Found: C, 76.91; H, 8.37.[8]

Finally chromatography of the residue on silica gel gave by elution with hexane – ethyl acetate (4:1), followed by crystallization from methanol 15β-hydroxyestrone dimethyl ether (**8***b*) (75 mg) as needles: m.p. 125–127°;

[8]This compound (**8***a*) is the 15-methyl ether of 3,15α-dihydroxyestra-1,3,5(10)-trien-17-one obtained previously by microbiological hydroxylation of estrone, followed by methylation; see ref. 40.

$[\alpha]_D$ +92°; o.r.d. (*c*, 0.0007; dioxane): $[\Phi]_{600}$ +476°; $[\Phi]_{350}$ +2474°; $[\Phi]_{321}$ +6613°; $[\Phi]_{297}$ ±0°; $[\Phi]_{275}$ −3425°; $[\Phi]_{250}$ ±0°; $[\Phi]_{237}$ +3045°; $[\Phi]_{230}$ ±0°; $[\Phi]_{223}$ −3093°; c.d. (*c*, 0.0016; dioxane): $[\Theta]_{337}$ ±0; $[\Theta]_{303}$ +8750; $[\Theta]_{299}$ +7900; u.v. λ_{max} 279, 288 mμ (log ε 3.33, 3.31); i.r. ν_{max} 1735, 1613 cm^{-1}; n.m.r. 67 (18-H), 197 (15-methoxyl), 224 (3-methoxyl), ~242 (15-H), 398 (C-4 H), 398, 405, 408 (C-2 H), 426, 436 c.p.s. (C-1 H).

Anal. Calcd. for $C_{20}H_{26}O_3$: C, 76.40; H, 8.34; O, 15.27. Found: C, 76.57; H, 8.10; O, 15.43.

Acid Isomerization of 14-Dehydroestrone-3-methyl Ether (6c)

A solution containing 50 mg of 14-dehydroestrone-3-methyl ether (**6***c*), 33 mg of *p*-toluenesulfonic acid monohydrate, and 2.5 ml of anhydrous benzene was heated at reflux temperature for 3 min. Neutralization, followed by extraction with methylene chloride and chromatography on silica gave, after elution with hexane – ethyl acetate (95:9) and crystallization from methylene chloride – methanol, 12.5 mg of starting material (m.p. 101–102°), and 7.5 mg of 15-dehydroestrone-3-methyl ether (**6***b*), with m.p. 99–100°, $[\alpha]_D$ +456°; u.v. λ_{max} 220–222, 278, 287 mμ (log ε 4.15, 3.38, 3.32), identified by direct comparison (mixture melting point, t.l.c., and infrared spectra) with an authentic specimen.

Alkaline Isomerization of 14-Dehydroestrone-3-methyl Ether (6c)

A solution of 14-dehydroestrone methyl ether (**6***c*) (540 mg) in 100 ml of 2% methanolic potassium hydroxide was heated to reflux, under nitrogen, for 30 min. Extraction with methylene chloride, washing to neutrality, furnished an amorphous residue which was chromatographed on fluorescent silica gel chromatoplates. Two compounds were isolated besides 170 mg of unchanged starting material with: m.p. 99–100°; $[\alpha]_D$ +291°; undepressed by mixture m.p. with an authentic sample. The 14β-15-dehydroestrone derivative (**6***b*) (310 mg) was also isolated; m.p. 99–100°; $[\alpha]_D$ +434°; t.l.c., i.r., and mixture melting point identical with an authentic sample. Finally, 40 mg of an homogenous product were obtained, which provided, after crystallization from methylene chloride – methanol, pure 15β-hydroxy-14β-estrone dimethyl ether (**8***c*); m.p. 87–89°; $[\alpha]_D$ +137°; c.d. (*c*, 0.0006; dioxane): $[\Theta]_{320}$ ±0; $[\Theta]_{291}$ +4720; $[\Theta]_{286}$ +3600; u.v. λ_{max} 220–221, 278, 287 mμ (log ε 3.92, 3.28, 3.27); i.r. ν_{max} 1740, 1610 cm^{-1}; n.m.r. 68 (18-H), 197 (15-methoxyl), 225 (3-methoxyl), 242, 250 (15-H), 398 (C-4 H), 398, 405, 408 (C-2 H), 428, 435 c.p.s. (C-1 H).

Anal. Calcd. for $C_{20}H_{26}O_3$: C, 76.40; H, 8.34. Found: C, 76.44; H, 8.33.

Acid Isomerization of 15-Dehydro-14β-estrone-3-methyl Ether (6b)

A solution of 200 mg of 15-dehydro-14β-estrone-3-methyl ether (**6***b*) and 120 mg of *p*-toluenesulfonic acid monohydrate in 10 ml of anhydrous benzene, was heated under reflux for 3 min. Neutralization with a sodium bicarbonate solution followed by extraction with methylene chloride, gave a product which was chromatographed on silica gel. Elution with 5% ethyl acetate in hexane and subsequent crystallization from methylene chloride–methanol afforded 14-dehydroestrone methyl ether (**6***c*) (100 mg); m.p. 101–102°, $[\alpha]_D$ +250°, u.v. λ_{max} 220–221, 278, 287 mμ (log ε 3.96, 3.32, 3.31). A second crop gave impure starting material (**6***b*) (60 mg); m.p. 97–99°, $[\alpha]_D$ +448°; u.v. λ_{max} 220–222, 278, 287 mμ (log ε 4.2, 3.4, 3.34).

Alkaline Treatment of 3,15α-Dihydroxyestrone-3-methyl Ether (8a)

A solution containing 50 mg of **8***a*, and 50 mg of potassium hydroxide in 25 ml methanol was gently refluxed for 4 h under nitrogen. After cooling and extraction by usual procedure a crude mixture (50 mg) was obtained. Preparative thin-layer chromatography allowed the isolation of 25 mg of the 14-dehydro compound (**6***c*): m.p. 95–97°; $[\alpha]_D$ +286°, identical in every respect (t.l.c., i.r., and m.p.) with an authentic sample. Moreover, 10 mg of 15-dehydro-14β-estrone-3-methyl ether (**8***b*) were also obtained; m.p. 96–97°; $[\alpha]_D$ +408°, and shown, by usual criteria (t.l.c., mixture melting point, i.r.), to be identical with a pure sample of **6***b*.

3-Hydroxy-14β-estra-1,3,5(10), 8-tetraen-17-one-3-methyl Ether (7a)

A mixture of 15-dehydroestrone-3-methyl ether (**6***a*) (2.33 g), *p*-toluenesulfonic acid monohydrate (1.5 g) and toluene (120 ml) was heated at reflux temperature for 16 h. This solution was then washed thoroughly with saturated sodium bicarbonate solution, and with water until neutral. Removal of the solvent *in vacuo* and subsequent crystallization from methanol afforded Δ^8-14β-estrone-3-methyl ether (**7***a*) (1.4 g); m.p. 121–122°, $[\alpha]_D$ +213°; o.r.d. (*c*, 0.001; dioxane): $[\Phi]_{600}$ +590°; $[\Phi]_{500}$ +1000°; $[\Phi]_{400}$ +1290°; $[\Phi]_{321}$ +3270°; $[\Phi]_{310}$ +2440°; $[\Phi]_{299}$ +4150°; $[\Phi]_{276}$ +30 500°; $[\Phi]_{248}$ −29 600°; $[\Phi]_{228}$ −23 000°; c.d. (*c*, 0.001; dioxane): $[\Theta]_{356}$ ±0; $[\Theta]_{322}$ + 3170; $[\Theta]_{300}$ −6500; u.v. λ_{max} 273–274 mμ (log ε 4.22); i.r. ν_{max} 1730, 1650, 1610 cm^{-1}; n.m.r. 65 (18-H), 164 (benzylic H), 228 c.p.s. (methoxyl H).

Alkaline Isomerization of 15-Dehydro-14β-estrone-3-methyl Ether (6b)

A solution of 550 mg of **6***b* and 2 g of potassium hydroxide in 100 ml methanol was heated to reflux under nitrogen for 30 min. By extraction with methylene chloride, washing with water until neutral, and removal of the solvent an amorphous residue (540 mg) was obtained. By chromatography on silica gel preparative fluorescent chromatoplates there were isolated three substances. First, 170 mg of 14-dehydroestrone methyl ether (**6***c*) were obtained. Recrystallization from methylene chloride – methanol provided the pure isomer (**6***c*); m.p. 102–103°; $[\alpha]_D$ +284°, identical in all respects with an authentic sample. Moreover 310 mg of unchanged starting material (**6***b*) with m.p. 96–97°; $[\alpha]_D$ +448° were recovered. Finally, 45 mg of an homogeneous substance were obtained which crystallized from methylene chloride – methanol, to give the analytical sample of 15β-hydroxy-14β-estrone dimethyl ether (**8***c*); m.p. 87–89°; $[\alpha]_D$ +137°; u.v. λ_{max} 219–221, 278, 287 mμ (log ε 3.95, 3.31, 3.28); i.r. ν_{max} 1738, 1610 cm^{-1}, shown to be identical (mixture melting point, t.l.c., i.r.) with an authentic sample.

3-Hydroxy-15, 16β-oxido-14β-estra-1,3,5(10)-trien-17-one-3-methyl Ether (8d)

A solution of 15-dehydro-14β-estrone methyl ether (**6***b*) (880 mg) in undistilled tetrahydrofuran (10 ml) was

treated with 50 ml of a 3% solution of potassium hydroxide in aqueous methanol. The mixture was heated for 30 min at reflux temperature. Subsequent neutralization, addition into water, extraction with methylene chloride, and chromatography of the residue on fluorescent silica gel plates, gave 200 mg of unchanged starting material, as well as 286 mg of a compound with m.p. 100–101°, without defined absorption maximum around 220 mμ. Further crystallization of this product from methanol gave 205 mg of pure 15,16β-oxido-14β-estrone methyl ether (**8***d*): m.p. 100–111°; $[\alpha]_D$ +311°; c.d. (*c*, 0.001; dioxane): $[\Theta]_{350}$ ±0; $[\Theta]_{326}$ −3300; $[\Theta]_{320}$ −3470; $[\Theta]_{297}$ ±0; u.v. λ_{max} 278, 287 mμ (log ε 3.34, 3.32); i.r. ν_{max} 1740, 1610 cm^{-1}; n.m.r. 68 (18-H), 207, 209, 227, 230 (2-epoxide-H), 225 (C-3 methoxyl H), 398 (C-4 H), 398, 406, 409 (C-2 H), 421, 429 c.p.s. (C-1 H).

Anal. Calcd. for $C_{19}H_{22}O_3$: C, 76.48; H, 7.43. Found: C, 77.09; H, 7.49.

3,17α-Dihydroxy-17β-ethinyl-14β-estra-1,3,5(10),8-tetraene-3-methyl Ether (7b)

A stream of purified acetylene was bubbled through 200 ml of tetrahydrofuran for 2 h. A 3 *N* solution of methylmagnesium bromide in ether (5 ml) was then added slowly and the stream of acetylene was maintained for 5 h. A solution of dehydro-14β-estrone 3-methyl ether (**7***a*) (500 mg) in a few ml of tetrahydrofuran was added and the mixture was heated at reflux temperature for 1.5 h. The reaction mixture was then added to a cold saturated ammonium chloride solution and extracted with methylene chloride. Crystallization of the crude extract from ether–hexane afforded 125 mg (25%) of the 17β-ethinyl derivative (**7***b*); m.p. 91–92°; $[\alpha]_D$ +65°; u.v. λ_{max} 272–273 mμ (log ε 4.08); i.r. ν_{max} 3540, 3225, 1640, 1605 cm^{-1}; n.m.r. 67 (18-H), 130 (hydroxyl), 154 (—C≡CH), 226 c.p.s. (methoxyl).

Anal. Calcd. for $C_{21}H_{24}O_2 \cdot 1/2\ H_2O$: C, 79.46; H, 7.94; O, 12.60. Found: C, 79.52; H, 7.95; O, 12.34.

14β-Estrone-3-methyl Ether (6d)

(a) From 15-Dehydro-14β-estrone-3-methyl Ether (6b)

A solution of **6***b* (5.8 g) in ethyl acetate (125 ml) was shaken with 10% palladium on charcoal (1 g) in an atmosphere of hydrogen at 50 pounds per square inch (p.s.i.). Crystallization of the product from methanol afforded 5.5 g of 14β-estrone-3-methyl ether (**6***d*); m.p. 112–113°; $[\alpha]_D$ +179°; o.r.d. (*c*, 0.0004; dioxane): $[\Phi]_{600}$ +530°; $[\Phi]_{350}$ +2159°; $[\Phi]_{306}$ +4998°; $[\Phi]_{227}$ +1590°; $[\Phi]_{240}$ +7573°; $[\Phi]_{218}$ +22 421°; c.d. (*c*, 0.0003; dioxane): $[\Theta]_{320}$ ±0; $[\Theta]_{290}$ +4420; $[\Theta]_{280}$ +1400; u.v. λ_{max} 278, 287 mμ (log ε 3.33, 3.30); i.r. ν_{max} 1730, 1613 cm^{-1}; n.m.r. 67 (18-H); 223 (C-3 methoxyl); (lit. (7) m.p. 114–115°, $[\alpha]_D$ +156°).

(b) From 14-Dehydroestrone-3-methyl Ether (6c)

Hydrogenation of **6***c* (2.1 g) in ethyl acetate (100 ml) with 10% palladium on charcoal (0.5 g) at 50 p.s.i. afforded, after crystallization from methanol, 14β-estrone-3-methyl ether (**6***d*) (1.77 g); m.p. 110–111°; $[\alpha]_D$ +177°; u.v. λ_{max} 278, 287 mμ (log ε 3.33, 3.30). This compound was identical by i.r., t.l.c., and mixture melting point comparison with the product obtained in the previous experiment (*a*).

14β-Estrone (6e)

14β-Estrone 3-methyl ether (**6***d*) (1.7 g) was added to a saturated solution of hydrogen bromide in acetic acid (25 ml) (22). The mixture was left at room temperature for 16 h and then poured into ice-water to give a precipitate. The solid material was separated by filtration, washed with water, redissolved in methanol (36 ml), and heated to reflux with aqueous potassium hydroxide (10%, 6 ml) for 1 h. Addition to ice-water, acidification with 5% aqueous hydrogen chloride and extraction with methylene chloride gave a semicrystalline residue, which after crystallization from methylene chloride–methanol furnished 14β-estrone (**6***e*) (1.42 g). The analytical sample exhibited; m.p. 210–211°; $[\alpha]_D$ +183°; u.v. λ_{max} 280–281 mμ (log ε 3.30); i.r. ν_{max} 3250, 1715, 1613 cm^{-1}; n.m.r. 67 (18-H), ~ 324 (hydroxyl), ~ 396 (C-4 H), ~ 405 (C-2 H), 425, 435 (C-1 H) c.p.s.

Anal. Calcd. for $C_{18}H_{22}O_2$: C, 79.96; H, 8.20. Found: C, 79.14; H, 8.21.

14β-Estrone-3-tetrahydropyranyl Ether (6f)

A solution containing 14β-estrone (**6***e*) (1.3 g), anhydrous benzene (20 ml), anhydrous tetrahydrofuran (10 ml), dihydropyrane, and 50 mg of *p*-toluenesulfonic acid monohydrate was stirred at room temperature for 1 h (23). The reaction mixture was then poured into a saturated aqueous sodium bicarbonate solution and extracted with methylene chloride. After alumina chromatography the material eluted with hexane–ether (9:1) was crystallized from ether–methanol to give 14β-estrone tetrahydropyranyl ether (**6***f*) (800 mg); m.p. 102–103°; $[\alpha]_D$ +148°; u.v. λ_{max} 277, 284 mμ (log ε 3.18, 3.13); i.r. ν_{max} 1730, 1610 cm^{-1}; n.m.r. 65 (18-H), 172 (benzylic H), 200–250 (—CH_2—O—), 321 (—O—CH—O—), 407 (C-4 H) ~ 415 (C-2 H), 427–436 (C-1 H) c.p.s.

Anal. Calcd. for $C_{23}H_{30}O_3$: C, 77.93; H, 8.53; O, 13.54. Found: C, 78.32; H, 8.43; O, 13.40.

3,17α-Dihydroxy-17β-ethinyl-14β-estra-1,3,5(10)-triene-3-methyl Ether (13a)

Purified acetylene was bubbled through 200 ml of anhydrous tetrahydrofuran for 2 h. Without stopping the acetylene stream, 21.3 ml of 3 *N* solution of methylmagnesium bromide in ether were slowly added and the acetylene was allowed to pass through the solution for a further 5 h. 14β-Estrone-3-methyl ether (**6***d*) (1.7 g) in a few milliliters of anhydrous tetrahydrofuran was then added and the mixture was refluxed for 1.5 h. Addition of this solution to an ice-cold saturated solution of ammonium chloride in water and extraction with methylene chloride furnished a semicrystalline product which after recrystallization from methanol–hexane gave 900 mg of 17β-ethinyl-14β,17α-estradiol 3-methyl ether (**13***a*). Further purification by crystallization afforded the analytical sample; m.p. 112–113°; $[\alpha]_D$ +140°; u.v. λ_{max} 219–221, 278–279, 287 mμ (log ε 3.94, 3.30, 3.27); i.r. ν_{max} 3500, 3300, 3200, 3160, 1625, 1600 cm^{-1}; n.m.r. 70 (18-H), 153 (acetylenic H), 171 (benzylic H), 227 (methoxyl H), 399 (C-4 H), 408 (C-2 H), 432, 441 c.p.s. (C-1 H).

Anal. Calcd. for $C_{21}H_{26}O_2 \cdot 1/2\ H_2O$: C, 79.02; H, 8.52. Found: C, 79.43; H, 8.69.

3,17α-Dihydroxy-17β-ethinyl-14β-estra-1,3,5(10)-triene-3-methyl Ether 17-Tetrahydropyranyl Ether (13e)

A solution containing 17β-ethinyl-14β-estradiol-3-methyl ether (**13***a*) (300 mg), anhydrous benzene (30 ml),

dihydropyrane (0.3 ml) and *p*-toluenesulfonic acid monohydrate (15 mg), was stirred at room temperature for 1 h (23). It was then poured into a saturated aqueous sodium bicarbonate solution and extracted with methylene chloride. The amorphous residue was purified by chromatography on alumina. Concentration of the hexane – methylene chloride (9:1) eluates and subsequent crystallization from ether–methanol afforded 140 mg of the tetrahydropyranyl ether derivative (**13***e*); m.p. 89–90°; $[\alpha]_D$ +144°; u.v. λ_{max} 279, 287 mμ (log ε 3.29, 3.26); i.r. ν_{max} 3200, 2090, 1610 cm^{-1}; n.m.r. 69 (18-H), 151 (—C≡CH), 200–250 (—CH_2—O—), 223 (CH_3—O—), ~ 314 (—O—CH—O—), 395 (C-4 H), 405 (C-2 H), 428, 437 c.p.s. (C-1 H).

Anal. Calcd. for $C_{26}H_{34}O_3$: C, 79.15; H, 8.69; O, 12.17. Found: C, 79.01; H, 8.77; O, 12.13.

*3,17α-Dihydroxy-17β-ethinyl-14β-estra-1,3,5(10)-triene 3-methyl Ether 17-Acetate (**13***b*)*

The ethinyl steroid (**13***a*) (400 mg) was treated with acetic anhydride (4 ml) and *p*-toluenesulfonic acid monohydrate (120 mg) at room temperature for 20 h. The reaction mixture was poured into water and extracted with methylene chloride. This extract was washed successively with saturated aqueous sodium bicarbonate solution and water, dried, and concentrated *in vacuo* to give a residue which crystallized from methylene chloride – methanol to give the 17β-ethinyl-14β-estratriene acetate (**13***b*) (310 mg); m.p. 129–130°; $[\alpha]_D$ +110°; u.v. λ_{max} 278–279, 287 mμ (log ε 3.29, 3.26); i.r. ν_{max} 3225, 1750, 1615, 1255 cm^{-1}; n.m.r. 73 (18-H), 122 (—OAc), 154 (—C≡CH), 224 (CH_3O—), 397 (C-4 H), ~ 407 (C-2 H, C-1 H), 437, 429 c.p.s. (C-1 H).

Anal. Calcd. for $C_{23}H_{28}O_3$: C, 78.37; H, 8.01; O, 13.62. Found: C, 78.76; H, 8.04; O, 13.49.

*3,17α-Dihydroxy-17β-ethinyl-14β-estra-1,3,5(10)-triene-3-tetrahydropyranyl Ether (**13***d*)*

A solution of methylmagnesium bromide in ether (10 ml of 3 *N*) was slowly added to a saturated solution of purified acetylene in anhydrous tetrahydrofuran (200 ml). A stream of acetylene was passed through this mixture for 4 h. 14β-Estrone tetrahydropyranyl ether (**6***f*) (700 mg) in a few ml of anhydrous tetrahydrofuran was then added and the mixture was refluxed for 1.5 h. Addition to an ice-cold saturated aqueous solution of ammonium chloride and extraction with methylene chloride gave an amorphous residue which crystallized from methylene chloride – ether, to give 750 mg of 17β-ethinyl-14β, 17α-estradiol-3-tetrahydropyranyl ether (**13***d*); m.p. 147–148°. Recrystallization afforded a pure sample; m.p. 157–158.5°; $[\alpha]_D$ +72°; u.v. λ_{max} 284 mμ (log ε 3.16); i.r. ν_{max} 3200, 3150, 2075, 1610 cm^{-1}; n.m.r. 68 (18-H), 142 (hydroxyl), 151 (—C≡CH), 200–250 (—CH_2—O—), 322 (—O—CH—O—), 406 (C-4 H), 415 (C-2 H), 428, 437 c.p.s. (C-1 H).

Anal. Calcd. for $C_{25}H_{32}O_3$: C, 78.91; H, 8.48; O, 12.61. Found: C, 78.34; H, 8.37; O, 12.79.

*3,17α-Dihydroxy-17β-ethinyl-14β-estra-1,3,5(10)-triene (**13***c*)*

A solution of 800 mg of 17β-ethinyl-14β,17α-estradiol-3-monotetrahydropyranyl ether (**13***d*) in 50 ml methanol was treated with a saturated solution of oxalic acid in 50% aqueous methanol (10 ml) at room temperature for 16 h. The reaction mixture was then poured into a saturated solution of sodium bicarbonate and extracted with methylene chloride. The residue crystallized from acetone–ether to give 600 mg of 17β-ethinyl-14β,17α-estradiol (**13***c*); m.p. 184–185°; $[\alpha]_D$ +118°; u.v. λ_{max} 281 mμ (log ε 3.29); i.r. ν_{max} 3300, 3220, 2080, 1610 cm^{-1}; n.m.r. 70 (18-H), 94 (hydroxyl), 153 (—C≡CH), 278 (hydroxyl), ~ 395 (C-4 H), ~ 404 c.p.s. (C-2 H).

Anal. Calcd. for $C_{20}H_{24}O_2 \cdot 1/2\ H_2O$: C, 78.65; H, 8.25. Found: C, 78.09; H, 8.23.

*3,17α-Dihydroxy-19-norpregna-1,3,5 (10)-triene-20-one 3-methyl Ether 17-Acetate (**14**)*

The acetate (**13***b*) (1.4 g) was added to a refluxing mixture of 20% aqueous sulfuric acid (50 ml), mercuric sulfate (1.26 g) and ethanol (300 ml). The resulting solution was allowed to reflux under nitrogen for 1.5 h (27). The solution was cooled, neutralized with saturated aqueous sodium bicarbonate, and then extracted with ethyl acetate. Working-up as usual and crystallization of the residue from methylene chloride – methanol gave 750 mg of 3,17α-dihydroxy-19-norpregna-1,3,5(10)-trien-20-one 3-methyl ether 17-acetate (**14**); m.p. 140–141°; $[\alpha]_D$ +74°; c.d. (*c*, 0.0009; dioxane): $[\Theta]_{380}$ ±0; $[\Theta]_{293}$ +2360; $[\Theta]_{260}$ +100; u.v. λ_{max} 278, 287 mμ (log ε 3.33, 3.31); i.r. ν_{max} 1730, 1708, 1610, 1250 cm^{-1}; n.m.r. 58 (18-H), 125, 127 (21-H plus an acetate grouping), ~ 168 (benzylic H), ~ 224 (methoxyl), ~ 397 (C-4 H), 397, 405, 408 (C-2 H), 428, 436 c.p.s. (C-1 H).

Anal. Calcd. for $C_{20}H_{30}O_4$: C, 74.56; H, 8.16. Found: C, 74.21; H, 8.10.

*14β,17α-19-Norpregn-4-ene-3,20-dione (**2***a*)*

A solution of compound (**14**) (780 mg) in anhydrous dioxane (100 ml) was added to a stirred solution of lithium metal (1.46 g) in 300 ml liquid ammonia – anhydrous dioxane (2:1). After stirring for 2 h, methanol was carefully added until the blue color had disappeared. The ammonia was then allowed to evaporate and the mixture was poured into saturated aqueous ammonium chloride solution, extracted with methylene chloride, and washed with water to neutrality. The residue was then dissolved in a mixture of 65 ml of methanol and 5 ml of methylene chloride, 50% aqueous hydrochloric acid (31 ml) was added, and the solution was stirred at room temperature for 1 h. Extraction with methylene chloride and chromatography on silica gel afforded 380 mg of an amorphous epimeric mixture of 20-hydroxy-14β,17α-19-norpregn-4-en-3-one (**9***d*), showing: u.v. λ_{max} 240 mμ (log ε 4.18); i.r. ν_{max} 3350, 1665, 1613 cm^{-1}. One pure isomer, presumably the 20β-compound (**9***d*) exhibited; m.p. 145–146°; $[\alpha]_D$ +86°; u.v. λ_{max} 240 mμ (log ε 4.21); i.r. ν_{max} 3400, 1655, 1625, 1605 cm^{-1}; n.m.r. 66, 72 (21–H, doublet), 74 (18-H), ~ 102 (—OH), ~ 210–235 (20-H), 349 (C-4 H), This material was dissolved in acetone (4 ml) and treated with 8 *N* chromic acid (31) (0.4 ml) at 0–5° for 10 min. Ice and water were added and the mixture was extracted with methylene chloride. This extract was washed with saturated aqueous sodium bisulfite and with water, then dried and concentrated to give an amorphous residue. Crystallization of the product from methanol–water gave 14β,17α-19-norprogesterone (**2***a*) (225 mg); m.p. 87–88°; $[\alpha]_D$ +54°; c.d. (*c*, 0.001: dioxane): $[\Theta]_{376}$

±0; $[\Theta]_{356}$ −1520; $[\Theta]_{342}$ −3630; $[\Theta]_{330}$ −4620; $[\Theta]_{316}$ −4520; $[\Theta]_{304}$ −4690; $[\Theta]_{286}$ −4690; $[\Theta]_{260}$ −610; u.v. λ_{max} 240 mμ (log ε 4.22); i.r. ν_{max} 1705, 1660, 1605 cm^{-1} (in agreement with the published constants (2)); n.m.r. 77 (18-H), 128 (21-H), 348 c.p.s. (C-4 H).

17α-Hydroxy 14β-Estr-4-en-3-one (9a)

A solution of 3.2 g of 15-dehydro-14β-estrone-3-methyl ether *(6b)* in 100 ml of anhydrous dioxane was added with stirring to 4 g of lithium in 900 ml liquid ammonia – anhydrous dioxane (2:1). After stirring for 2 h, methanol was carefully added until the blue color had disappeared. After allowing the ammonia to evaporate the mixture was poured into saturated aqueous ammonium chloride solution, extracted with methylene chloride, and the extract was washed with water to neutrality. The residue after removal of solvent was dissolved in 70 ml of methanol, and stirred with 5 *N* hydrochloric acid (125 ml) at room temperature for 1.5 h. Isolation of the product with methylene chloride and chromatography of the residue on silica gel gave 1.74 g (56%) of homogeneous amorphous material. Upon crystallization from ether–pentane, 1.1 g of 14β,17α-19-nortestosterone (**9***a*) was obtained; m.p. 105–106°; $[\alpha]_D$ +69°; u.v. λ_{max} 240, 310–316 mμ (log ε 4.21, 2.0); i.r. ν_{max} 3500, 1660, 1613 cm^{-1}; n.m.r. 64 (18-H), 157 (hydroxyl), 210–240 (17β-H), ~ 349 c.p.s. (C-4 H).

Anal. Calcd. for $C_{18}H_{26}O_2$: C, 78.79; H, 9.55; O, 11.66. Found: C, 78.75; H, 9.44; O, 11.91.

17α-Hydroxy-14β-estr-5-en-3-one Cycloethylene Ketal (10a)

A solution of 1.1 g of **9***a*, 375 mg of *p*-toluenesulfonic acid, 73 ml ethylene glycol, and 500 ml of benzene was allowed to reflux for 19 h. After cooling, the reaction mixture was poured into a saturated solution of sodium bicarbonate, and extracted with benzene. The organic layer was washed, dried, and evaporated *in vacuo*, furnishing 1.19 g of the crude ketal (**10***a*). Crystallization from ether afforded the analytical sample; m.p. 136–138°; $[\alpha]_D$ +98°; i.r. ν_{max} 3475 cm^{-1}; n.m.r. 61 (18-H), 134 (OH), ~ 225 (17β-H), 237 (—O—CH—), 328 c.p.s. (C-6 vinyl H).

Anal. Calcd. for $C_{20}H_{30}O_3$: C, 75.43; H, 9.50; O, 15.07. Found: C, 75.02; H, 9.58; O, 15.16.

14β-Estr-5-ene-3,17-dione 3-Cycloethylene Ketal (10b)

14β,17α-19-Nortestosterone cycloethylene ketal (**10***a*) (1.27 g) in 65 ml of pyridine was added to a cold pyridinium chromate solution, (prepared from 1.3 g of chromium trioxide and 65 ml anhydrous pyridine) (26). After stirring for 15 h at room temperature, ethyl acetate was added and the suspension was filtered through alumina. The filtrate was evaporated to dryness under vacuum to give a residue which crystallized from ether, to yield 1.0 g of 14β-estr-5-ene-3,17-dione 3-cycloethyleneketal (**10***b*); m.p. 114–115°; $[\alpha]_D$ +17°; i.r. ν_{max} 1735 cm^{-1}; n.m.r. 64 (18-H), 237 c.p.s. (cycloethylene ketal H).

Anal. Calcd. for $C_{20}H_{28}O_3$: C, 75.91; H, 8.92; O, 15.17. Found: C, 75.75; H, 8.97; O, 15.50.

17β-Ethinyl 17α-Hydroxy-14β-estr-5-en-3-one Cycloethylene Ketal (10c)

A stream of purified acetylene was bubbled through 200 ml of anhydrous tetrahydrofuran until complete saturation was achieved. A 3 *N* solution of methylmagnesium bromide in ether (10 ml) was added slowly and the stream of acetylene was maintained during 4 h. A solution of 750 mg of 14β-estr-5-ene-3,17-dione 3-cycloethylene ketal (**10***b*) in 150 ml of anhydrous tetrahydrofuran was then added and the mixture was heated at reflux temperature for 1.5 h. The product was isolated after addition of the reaction mixture to an ice-cold saturated aqueous solution of ammonium chloride, followed by extraction with methylene chloride, and washing with water to neutrality. The colored extract was dissolved in ethyl acetate, treated with charcoal, and filtered through alumina. Evaporation of the solvent and crystallization from ether gave 635 mg of 17β-ethinyl-14β,17α-19-nortestosterone cycloethylene ketal (**10***c*) the analytical sample of which exhibited; m.p. 177–179°; $[\alpha]_D$ +127°; i.r. ν_{max} 3450, 3400, 3250 cm^{-1}; n.m.r. 68 (18-H), 152 (ethinyl H), 239 c.p.s. (cycloethylene ketal H).

Anal. Calcd. for $C_{22}H_{30}O_3$: C, 77.15; H, 8.83. Found: C, 76.98; H, 8.79.

17β-Ethinyl 17α-Hydroxy-14β-estr-4-en-3-one (9b)

Perchloric acid (3 *N*, 28.2 ml) was added to a solution of the 17β-ethinyl derivative (**10***c*) (2.35 g) in tetrahydrofuran (33 ml), and the mixture was stirred at room temperature for 48 h. After addition of ice-water and extraction with methylene chloride, the organic layer was washed with sodium bicarbonate, then with water. Crystallization of the residue from methylene chloride – methanol furnished 826 mg of **9***b*. The mother liquors gave 610 mg of additional impure material. Recrystallization from the same solvents afforded the analytical sample of **9***b*; m.p. 214–215°; $[\alpha]_D$ +59°; c.d. (*c*, 0.001; dioxane): $[\Theta]_{356}$ −1620; $[\Theta]_{343}$ −4060; $[\Theta]_{330}$ −5050; $[\Theta]_{320}$ −4060; $[\Theta]_{308}$ −2670; u.v. λ_{max} 240–241 mμ (log ε 4.24); i.r. ν_{max} 3370, 3200, 2070, 1660, 1610 cm^{-1}; n.m.r. 70 (18-H), 153 (ethinyl H), 351 c.p.s. (C-4 H).

Anal. Calcd. for $C_{20}H_{26}O_2$: C, 80.49; H, 8.78. Found: C, 80.64; H, 8.76.

17β-Ethinyl 17α-Hydroxy-14β-estr-4-en-3-one Tetrahydropyranyl Ether (9c)

17β-Ethinyl-14β,17α-19-nortestosterone (**9***b*) (290 mg), 20 ml of anhydrous benzene, 0.2 ml of dihydropyrane, and 5 mg of *p*-toluenesulfonic acid monohydrate were stirred at room temperature for 1 h. The reaction mixture was then poured into a saturated aqueous solution of sodium bicarbonate and the product was isolated by extraction with methylene chloride. The organic extracts were washed until neutral, dried, and evaporated to give an amorphous residue which was crystallized from methylene chloride – methanol to yield 200 mg of 17β-ethinyl-14β,17α-19-nortestosterone tetrahydropyranyl ether (**9***c*); m.p. 160–161°; $[\alpha]_D$ +102°; u.v. λ_{max} 238 mμ (log ε 4.22); i.r. ν_{max} 3150, 2070, 1670, 1620 cm^{-1}; n.m.r. 69 (18-H), 153 (ethinyl H), 200–245 (—CH_2—O—), ~312 (—O—CH—O—); 350 c.p.s. (C-4 H).

Anal. Calcd. for $C_{25}H_{36}O_3$: C, 78.08; H, 9.44. Found: C, 78.09; H, 8.89.

3,17α-Dihydroxy 17β-Ethinyl-14β-estra-3,5-diene Diacetate (11)

A solution of 400 mg of the 19-nortestosterone derivative (**9***b*) and *p*-toluenesulfonic acid monohydrate (120

mg) in acetic anhydride (4 ml) was left at room temperature for 16 h. This solution was poured into ice-water and extracted with methylene chloride. The organic phase was first washed with sodium bicarbonate and then with water until neutral. The amorphous residue obtained after evaporation of the solvent, crystallized from methanol, to yield 200 mg of diacetate (**11**); m.p. 166–168°; $[\alpha]_D$ −39°; u.v. λ_{max} 234 mμ (log ε 4.23); i.r. ν_{max} 3200, 2125, 1755, 1745, 1660, 1630, 1245, 1205 cm^{-1}; n.m.r. 72 (18-H), 121, 127 (2-acetate methyls), 156 (ethinyl H), 330 (C-6 H), ~ 340 c.p.s. (C-4 H).

Anal. Calcd. for $C_{24}H_{30}O_4 \cdot 1/2\,H_2O$: C, 73.67; H, 7.98; O, 18.35. Found: C, 74.31; H, 7.80; O, 17.89.

17α-Hydroxy-14β-19-norpregn-4-ene-3,20-dione Acetate (12)

Mercuric sulfate (390 mg) and 15.4 ml of aqueous 20% sulfuric acid were added to a refluxing solution of 3,17α-dihydroxy 17β-ethinyl-14β-estra-3,5-diene diacetate (**11**) (440 mg) in ethanol (92.4 ml), and the mixture was heated at reflux temperature under nitrogen for 1.5 h. The cooled solution was poured into ice-water, extracted with ethyl acetate, washed with sodium bicarbonate solution, and finally with water until neutral. The residue appeared practically homogeneous on a chromatoplate. Crystallization from ether afforded the pure sample of 17α-hydroxy-14β-19-norprogesterone acetate (**12**) (250 mg); m.p. 159–161°; $[\alpha]_D$ +43°; c.d. (*c*, 0.001; dioxane): $[\Theta]_{370}$ ±0; $[\Theta]_{359}$ −1490; $[\Theta]_{343}$ −3930; $[\Theta]_{331}$ −4880; $[\Theta]_{321}$ −3660; $[\Theta]_{289}$ +1910; $[\Theta]_{285}$ +2050; $[\Theta]_{260}$ +520; u.v. λ_{max} 240 mμ (log ε 4.33); i.r. ν_{max} 1735, 1710, 1670, 1625, 1258 cm^{-1}; n.m.r. 60 (18-H); 125, 126 (21-H and 17α-acetate), ~ 349 c.p.s. (C-4 vinylic H).

Anal. Calcd. for $C_{22}H_{30}O_4$: C, 73.71; H, 8.44; O, 17.85. Found: C, 73.62; H, 8.74; O, 17.74.

13α-Estrone 3-Methyl Ether (17)

A solution of estrone methyl ether (**4***a*) (10 g) in 500 ml of tetrahydrofuran was irradiated, under nitrogen, with a Hanau Q-81 high pressure ultraviolet lamp for 12 h in a centrally illuminating apparatus, provided with a water cooled quartz filter and magnetic stirring. Evaporation of the solvent left a residue which was chromatographed on silica gel to give 2.71 g of lumiestrone methyl ether (**17**) from the hexane eluates. A pure sample, obtained by crystallization from methanol, showed; m.p. 126–128°; $[\alpha]_D$ −30°; c.d. (*c*, 0.001; dioxane): $[\Theta]_{340}$ ±0; $[\Theta]_{319}$ −1520; $[\Theta]_{307}$ −1980; $[\Theta]_{298-300}$ −1155; $[\Theta]_{285}$ −300; u.v. λ_{max} 278, 287 mμ (log ε 3.31, 3.28); i.r. ν_{max} 1725, 1613 cm^{-1}; n.m.r. 61 (18-H), 224 (methoxyl H), 397 (C-4 H), ~ 406 (C-2 H), ~ 436, ~ 427 c.p.s. (C-1 H) (in agreement with the published data).

13α-Estr-4-ene-3,17-dione (18)

A solution of pure 13α-estrone methyl ether (**17**) (1.08 g) in anhydrous dioxane (100 ml) was added with vigorous stirring to a mixture of lithium (2 g) in liquid ammonia and anhydrous dioxane (2:1, 300 ml). The reaction mixture was stirred for 2 h and then methanol was carefully added until the blue color had disappeared. The ammonia was allowed to evaporate, an excess of cold saturated ammonium chloride solution was added, and the product was extracted with methylene chloride. The amorphous residue thus obtained was dissolved in methanol (50 ml) and stirred with 50% aqueous hydrochloric acid (45 ml) for 1 h at room temperature. The product was again extracted with methylene chloride and purified by chromatography on silica. An amorphous fraction, corresponding to the mixture of alcohols at C-17 (39): u.v. λ_{max} 240 (log ε 3.94); i.r. ν_{max} 3400, 1715, 1645, 1620 cm^{-1}, was obtained by elution with hexane–ethyl acetate (4:1). This material was dissolved in 3 ml acetone and oxidized by treatment with 8 *N* chromic acid (31) (0.25 ml) for 10 min at 0–5°. Isolation of the product by addition of water and extraction with methylene chloride, followed by washing with sodium bisulfite solution gave an homogeneous material. Recrystallization from methanol furnished the analytical sample of 13α-estr-4-ene-3,17-dione (**18**); m.p. 160–162°; $[\alpha]_D$ −45°; o.r.d. (*c*, 0.001; dioxane): $[\Phi]_{600}$ −326°; $[\Phi]_{363}$ −2550°; $[\Phi]_{358}$ −2400°; $[\Phi]_{350}$ −2950°; $[\Phi]_{340}$ −1500°; $[\Phi]_{336}$ −1600° $[\Phi]_{326}$ ±0°; $[\Phi]_{324}$ +200°; $[\Phi]_{300}$ +4900°; $[\Phi]_{285}$ +5700°; $[\Phi]_{246}$ +17 500°; $[\Phi]_{232}$ ±0°; $[\Phi]_{215}$ +25 250°; c.d. (*c*, 0.001; dioxane): $[\Theta]_{372}$ ±0; $[\Theta]_{360}$ −1650; $[\Theta]_{346}$ −4100; $[\Theta]_{340}$ −3700; $[\Theta]_{333}$ −5050; $[\Theta]_{327}$ −4800; $[\Theta]_{321}$ −6000; $[\Theta]_{315}$ −4900; $[\Theta]_{301}$ −2900; $[\Theta]_{274}$ ±0; $[\Theta]_{261}$ ±0; $[\Theta]_{234}$ +24 500; u.v. λ_{max} 240 mμ (log ε 4.23); i.r. ν_{max} 1740, 1670, 1615 cm^{-1}; n.m.r. 60 (18-H), 352 c.p.s. (C-4 H).

Anal. Calcd. for $C_{18}H_{24}O_2$: C, 79.37; H, 8.88. Found: C, 79.33; H, 9.00.

Birch Reduction of 3-Hydroxy-14β-estra-1,3,5(10),8-tetraen-17-one 3-Methyl Ether (7a)

The 8(9)-dehydro steroid (**7***a*) (1.87 g) was added to a stirred solution of 2.5 g lithium in 200 ml liquid ammonia and 200 ml anhydrous dioxane (24). After stirring for 2 h, methanol was carefully dropped into the mixture until the blue color had disappeared. The ammonia was allowed to evaporate, and excess of an ice cold saturated ammonium chloride solution was added. The product was extracted with methylene chloride. The amorphous residue obtained (1.75 g) was treated with 75 ml of methanol and 75 ml of 50% aqueous hydrochloric acid and stirred for 1 h at room temperature. The product was isolated by extraction with methylene chloride and the residue [λ_{max} 240 mμ (log ε 3.97)], was chromatographed on fluorescent silica gel preparative chromatoplates. Development with hexane–ethyl acetate (4:1) and elution of zones with ethyl acetate furnished starting material (490 mg) (λ_{max} 272, log ε 3.79), an amorphous by-product without specific u.v. absorption (60 mg), the retrosteroid (**16***a*): m.p. 138–140° (150 mg), and an epimeric mixture of 17ζ-19-nortestosterone (**15***a*) (350 mg) which could not be induced to crystallize. An analytical sample of the retrosteroid (**16***a*) ,was prepared by recrystallization from ether; m.p. 140–141°; $[\alpha]_D$ −46°, o.r.d. (*c*, 0.001; dioxane): $[\Phi]_{700}$ −119°; $[\Phi]_{400}$ −260°; $[\Phi]_{390}$ −61°; $[\Phi]_{385}$ +39°; $[\Phi]_{380}$ +182°; $[\Phi]_{360}$ +1379°; $[\Phi]_{355}$ +1233°; $[\Phi]_{348}$ +1625°; $[\Phi]_{345}$ +1030°; $[\Phi]_{343}$ +284°; $[\Phi]_{340}$ −171°; $[\Phi]_{330}$ −1295°; $[\Phi]_{325}$ −2760°; $[\Phi]_{315}$ −4000°; $[\Phi]_{313}$ −4150°; c.d. (*c*, 0.001; dioxane): $[\Theta]_{370}$ ±0; $[\Theta]_{357}$ +1350; $[\Theta]_{342}$ +3630; $[\Theta]_{329}$ +4360; $[\Theta]_{318}$ +3300; $[\Theta]_{280}$ ±0; u.v. λ_{max} 242 mμ (log ε 4.2); i.r. ν_{max} 3400, 1660, 1615 cm^{-1}; n.m.r. 51 (18-H), ~ 139 (—OH), 227, 231 (17β-H), ~ 350 c.p.s. (C-4 H).

Anal. Calcd. for $C_{18}H_{26}O_2$: C, 78.79; H, 9.55; O, 11.66. Found: C, 78.85; H, 9.50; O, 12.04.

Estr-4-ene-3,17-dione (15b)

The C-17 epimeric mixture (**15a**) (235 mg) obtained in the above experiment was dissolved in 20 ml acetone and treated with 8 *N* chromic acid (0.23 ml) at 0–5° with stirring for 12 min (31). Addition to a saturated sodium bisulfite solution and extraction with methylene chloride gave 220 mg of a crystalline residue which was purified by recrystallization from methanol–ether and identified, by mixture melting point, t.l.c., and i.r. spectra, as the known estr-4-ene-3,17-dione (**15b**) (24*b*); m.p. 160–162°; $[\alpha]_D$ +140°; u.v. λ_{max} 240 mμ (log ε 4.24); i.r. ν_{max} 1740, 1670, 1620 cm^{-1}; n.m.r. 57 (18-H), 352 c.p.s. (C-4 H).

Anal. Calcd. for $C_{18}H_{24}O_2$: C, 78.33; H, 9.00. Found: C, 78.80; H, 8.59.

8α,9β,10α,14β-Estr-4-ene-3,17-dione (16b)

A solution of the retrosteroid (**16a**) (99 mg) in acetone (10 ml) was treated with 8 *N* chromic acid at 0–5° (0.1 ml) with stirring, for 10 min (31). The reaction mixture was added to ice-water, extracted with ethyl acetate, and the extract was washed with sodium bisulfite solution and then with water until neutral. The residue (88 mg) appeared homogeneous on a chromatoplate and was crystallized readily from ether to furnish a pure sample of the diketone (**16b**); m.p. 160–161°; $[\alpha]_D$ +44°; o.r.d. (*c*, 0.001; dioxane): $[\Phi]_{600}$ +169°; $[\Phi]_{450}$ +300°; $[\Phi]_{363}$ +2000°; $[\Phi]_{358}$ +1900°; $[\Phi]_{350}$ +2450°; $[\Phi]_{340}$ +1200°; $[\Phi]_{335}$ +1200°; $[\Phi]_{324}$ ±0°; $[\Phi]_{312}$ −2200°; $[\Phi]_{310}$ −2400°; $[\Phi]_{302}$ −3800°; $[\Phi]_{244}$ −1855°; $[\Phi]_{233}$ ±0°; $[\Phi]_{217}$ +26 000°; c.d. (*c*, 0.001; dioxane: $[\Theta]_{371}$ ±0; $[\Theta]_{365}$ +800; $[\Theta]_{361}$ +750; $[\Theta]_{348}$ +2600; $[\Theta]_{338}$ +2800; $[\Theta]_{333}$ +4000; $[\Theta]_{327}$ +3700; $[\Theta]_{320}$ +4900; $[\Theta]_{315}$ +3800; $[\Theta]_{310}$ +4000; $[\Theta]_{300}$ +2400; $[\Theta]_{282}$ ±0; $[\Theta]_{259}$ ±0; $[\Theta]_{232}$ −26 500; $[\Theta]_{225}$ −21 000; u.v. λ_{max} 240 mμ (log ε 4.24); i.r. ν_{max} 1740, 1670, 1615 cm^{-1}; n.m.r. 60 (18-H), 352 c.p.s. (C-4 H).

Anal. Calcd. for $C_{18}H_{24}O_2$: C, 79.37; H, 8.88. Found: C, 79.14; H, 8.76.

D,L-13-Isoestr-4-ene-3,17-dione (18 + 16b)

A mixture of 10 mg **18** and 10 mg **16***b* was recrystallized from acetone–ether to afford sharp melting crystals: m.p. 149–150°; $[\alpha]_D$ ±0°, with u.v. and i.r. spectra identical with these of the enantiomers (**18**) and (**16***b*).

3β-Hydroxy-13α-androst-5-en-17-one Tetrahydropyranyl Ether (19b)

A solution of 3β-hydroxy-androst-5-en-17-one tetrahydropyranyl ether (**19***a*) (m.p. 171–174°) (23.5 g) in anhydrous tetrahydrofuran (1 550 ml) was irradiated with a Hanau Q-81 high pressure ultraviolet lamp, under nitrogen, for 9 h, in an apparatus designed for central illumination, water cooled quartz filtering and magnetic stirring. Evaporation of the solvent and chromatography of the residue on neutral alumina gave by elution with hexane–benzene (7:3) and crystallization from methanol 3β-hydroxy-13α-androst-5-en-17-one tetrahydropyranyl ether (**19***b*) (7.5 g). The analytical sample was obtained by recrystallization from ether and showed; m.p. 133–135°; $[\alpha]_D$ −124°; o.r.d. (*c*, 0.005; dioxane): $[\Phi]_{600}$ −597°; $[\Phi]_{340}$ −2420°; $[\Phi]_{325}$ −3871°; $[\Phi]_{317}$ −2821°; $[\Phi]_{313}$ −3023°; $[\Phi]_{304}$ −1705°; $[\Phi]_{300}$ −1976°; $[\Phi]_{295}$ −1570°; $[\Phi]_{240}$ −6588°; $[\Phi]_{213}$ −13 098°; c.d. (*c*, 0.001; dioxane): $[\Theta]_{340}$ ±0; $[\Theta]_{318}$ −2010; $[\Theta]_{309}$ −2570; $[\Theta]_{298-302}$ −1680; $[\Theta]_{280}$ ±0; i.r. ν_{max} 1735 cm^{-1}; n.m.r. 51 (18-H), 59 (19-H), ~ 210–230 (—CH_2—O—), 286(—O—CH—O—), 325 c.p.s. (C-5 H).

Anal. Calcd. for $C_{24}H_{35}O_3$: C, 77.58; H, 9.49. Found: C, 77.51; H, 9.80.

3β,17α-Dihydroxy-17β-ethinyl-13α-androst-5-ene (19d)

A stream of purified acetylene was bubbled through 1250 ml of anhydrous tetrahydrofuran at room temperature for 1 h. Without interrupting the acetylene stream, methylmagnesium bromide in ether (3 *N*, 55 ml) was then slowly added and the passage of acetylene was continued for 5 h. A solution of pure 3β-hydroxy-13α-androst-5-en-17-one tetrahydropyranyl ether (**19***b*) (7.5 g) in anhydrous tetrahydrofuran (250 ml) was added and the mixture was heated at reflux temperature for 6.5 h. The product was isolated by addition to a cold saturated aqueous ammonium chloride solution, followed by extraction with methylene chloride, and chromatography of the residue on silica. Elution with hexane–ethyl acetate (9:1) provided 1.5 g of an homogeneous amorphous material (**19***c*) which was redissolved in 50 ml of aqueous methanol. Oxalic acid (3 g) in methanol (50 ml) was added and this acid solution (pH 3) was stirred at room temperature for 16 h. Addition to a saturated sodium bicarbonate solution and extraction with methylene chloride gave 3β,17α-dihydroxy-17β-ethinyl-13α-androst-5-ene (**19***d*) (1.2 g), which after crystallization from ether gave the pure sample; m.p. 239–241°; $[\alpha]_D$ −143°; i.r. ν_{max} 3400, 3220 cm^{-1}; n.m.r. (DMSO solution) 44 (18-H), 58 (19-H), 194 (ethinyl H), 188–202 (3α-H), 242 (doublet, J = 3 c.p.s., secondary —OH) 313 (tertiary OH), 325 c.p.s. (vinyl H).

Anal. Calcd. for $C_{21}H_{30}O_2$: C, 80.21; H, 9.62. Found: C, 80.14; H, 9.68.

17β-Ethinyl 17α-Hydroxy-13α-androst-4-en-3-one (20)

A solution of 3β,17α-dihydroxy-17β-ethinyl-13α-androst-5-ene (**19***d*) (1 g), 2 g of aluminium isopropoxide and 50 ml cyclohexanone in 300 ml toluene was heated to boiling until about 100 ml of solvent had distilled off. Then the reaction mixture was refluxed for 3 h. The solution was cooled and a saturated solution of sodium–potassium tartrate (excess) was added. The volatile materials were removed by steam distillation and the residue was extracted with ethyl acetate. The amorphous extract thus obtained (0.7 g) showed; λ_{max} 242 mμ (log ε 3.89). Preparative thin-layer chromatography allowed to divide the mixture into three fractions of different polarity. The intermediate fraction (0.3 g) was further purified on fluorescent silica gel chromatoplates until an homogeneous product (110 mg, λ_{max} 240 mμ, (log ε 4.10) was obtained. Recrystallization from methylene chloride – methanol furnished a pure sample of compound (**20**); m.p. 188–189°; $[\alpha]_D$ +117°; u.v. λ_{max} 242 mμ (log ε 4.29); i.r. λ_{max} 3300, 3200, 2160, 1660, 1610 cm^{-1}; n.m.r. 60 (18-H), 68 (19-H), 142 (hydroxyl), 154 (ethinyl H), 344 (C-4 H) c.p.s.

Anal. Calcd. for $C_{21}H_{28}O_2$: C, 80.73; H, 9.03; O, 10.24. Found: C, 80.72; H, 9.06; O, 10.45.

Acknowledgments

We should like to thank Prof. M. Ehrenstein, Prof. F. Sondheimer, and Prof. G. Stork for

their interest in this work, as well as for valuable suggestions.

1. G. TARZIA, N. H. DYSON, I. T. HARRISON, J. A. EDWARDS, and J. H. FRIED. Steroids **9**, 487 (1967).
2. M. EHRENSTEIN. J. Org. Chem. **9**, 435 (1944).
3. (*a*) W. M. ALLEN and M. EHRENSTEIN. Science, **100**, 251 (1944).
   (*b*) G. W. BARBER and M. EHRENSTEIN. Ann. Chem. **603**, 89 (1957).
   (*c*) C. DJERASSI, M. EHRENSTEIN, and G. W. BARBER. Ann. Chem. **612**, 93 (1958).
   (*d*) M. EHRENSTEIN, G. W. BARBER, and R. HERTZ. Endocrinology, **60**, 681 (1957).
4. [9] (*a*) L. F. FIESER and M. FIESER. Steroids. Reinhold Publ. Co., New York. 1959.
   (*b*) L. F. FIESER and M. FIESER. Topics in organic chemistry. Reinhold Publ. Co., New York. 1963.
   (*c*) P. A. PLATTNER, H. HEUSSER, and A. SEGRE. Helv. Chim. Acta, **31**, 249 (1948), and related papers.
   (*d*) C. DJERASSI, G. ROSENKRANZ, J. IRIARTE, J. BERLIN, and J. ROMO. J. Am. Chem. Soc. **73**, 1523 (1951); L. MIRAMONTES, G. ROSENKRANZ, and C. DJERASSI. J. Am. Chem. Soc. **73**, 3540 (1951); C. DJERASSI, L. MIRAMONTES, and G. ROSENKRANZ. J. Am. Chem. Soc. **75**, 4440 (1953).
   (*e*) L. VELLUZ, J. MATHIEU, and G. NOMINÉ. Tetrahedron, Suppl. 8, Part II, 495 (1966), and references therein.
5. [9] (*a*) A. J. BIRCH. J. Chem. Soc. 367 (1950).
   (*b*) A. J. BIRCH. Ann. Rept. Progr. Chem. Chem. Soc. London, **47**, 210 (1950).
   (*c*) C. DJERASSI, R. RINIKER, and B. RINIKER. J. Am. Chem. Soc. **78**, 6362 (1956).
   (*d*) E. FARKAS, J. M. OWEN, M. DEBONO, R. M. MOLLOY, and M. M. MARSH. Tetrahedron Letters, No. 10, 1023 (1966).
   (*e*) R. BUCOURT, J. TESSIER, and G. NOMINÉ. Bull. Soc. Chim. France, 1923 (1963).
   (*f*) H. SMITH. Trans. N.Y. Acad. Sci. **27**, 546 (1965).
   (*g*) C. DJERASSI. Science, **151**, 1055 (1966), and references cited therein.
   (*h*) J. A. WATERS and B. WITKOP. J. Am. Chem. Soc. **89**, 1022 (1967).
6. (*a*) J. A. EDWARDS, P. CRABBÉ, and A. BOWERS. J. Am. Chem. Soc. **85**, 3313 (1963).
   (*b*) J. A. EDWARDS, H. CARPIO, and A. D. CROSS. Tetrahedron Letters, No. 45, 3299 (1964).
   (*c*) R. GINSIG and A. D. CROSS. J. Am. Chem. Soc. **87**, 4629 (1965).
   (*d*) R. GINSIG and A. D. CROSS. J. Org. Chem. **31**, 1761 (1966).
   (*e*) J. P. TURNBULL and J. H. FRIED. Tetrahedron Letters No. 8, 801 (1966).
7. W. S. JOHNSON and W. F. JOHNS. J. Am. Chem. Soc. **79**, 2005 (1957), and references cited therein; see also W. S. JOHNSON, R. G. CHRISTIANSEN, and R. E. IRELAND. J. Am. Chem. Soc. **79**, 1995 (1957).
8. F. S. ALVAREZ and M. ARREGUIN. Chem. Ind., London, 720 (1960).
9. J. FISHMAN. J. Org. Chem. **31**, 520 (1966).
10. W. MOFFITT, R. B. WOODWARD, A. MOSCOWITZ, W. KLYNE, and C. DJERASSI. J. Am. Chem. Soc. **83**, 4013 (1961).
11. F. SONDHEIMER, S. BURSTEIN, and R. MECHOULAM. J. Am. Chem. Soc. **82**, 3209 (1960).
12. P. CRABBÉ. Applications de la dispersion rotatoire optique et du dichroisme circulaire optique en chimie organique. Gauthier–Villars, Paris, 1968.
13. M. FÉTIZON and M. GOLFIER. Bull. Soc. Chim. France, 859 (1966).
14. [9] (*a*) J. S. E. HOLKER and W. B. WHALLEY. Proc. Chem. Soc. 464 (1961).
   (*b*) M. J. T. ROBINSON and W. B. WHALLEY. Tetrahedron, **19**, 2123 (1963).
   (*c*) W. D. COTTERILL and M. J. T. ROBINSON. Tetrahedron, **20**, 765, 777 (1964).
   (*d*) R. BUCOURT and G. NOMINÉ. Bull. Soc. Chim. France, 1537 (1966); and earlier work by Bucourt *et al.* cited therein.
   (*e*) H. CHRISTOL and Y. PIETRASANTA. Bull. Soc. Chim. France, 1034 (1967); and earlier papers.
15. P. CRABBÉ and W. KLYNE. Tetrahedron, **23**, 3449 (1967).
16. (*a*) H. HIRSCHMANN and O. WINTERSTEINER. J. Biol. Chem. **126**, 737 (1938).
   (*b*) D. BANES, J. CAROL, and E. O. HAENNI. J. Biol. Chem. **187**, 557 (1950).
   (*c*) D. BANES and J. CAROL. J. Biol. Chem. **204**, 509 (1953).
17. (*a*) E. R. H. JONES, L. SKATTEBÖL, and M. C. WHITING. J. Chem. Soc. 4765 (1956).
   (*b*) H. E. STAVELY. J. Am. Chem. Soc. **61**, 79 (1939).
18. J. FAJKŐS. Collection Czech. Chem. Commun. **23**, 2155 (1958).
19. (*a*) D. K. FUKUSHIMA and T. F. GALLAGHER. J. Am. Chem. Soc. **73**, 196 (1951).
   (*b*) H. HIRSCHMANN, F. B. HIRSCHMANN, and M. A. DAUS. J. Am. Chem. Soc. **74**, 539 (1952).
   (*c*) P. CRABBÉ, L. M. GUERRERO, J. ROMO, and F. SÁNCHEZ-VIESCA. Tetrahedron, **19**, 25 (1963); and references therein.
20. C. DJERASSI, G. VON MUTZENBECHER, J. FAJKŐS, D. H. WILLIAMS and H. BUDZIKIEWICZ. J. Am. Chem. Soc. **87**, 817 (1965).
21. (*a*) W. KLYNE. Anales. Real. Soc. Espan. Fis. Quim. Madrid, Ser. B, **62**, 371 (1966).
   (*b*) A. R. VAN HORN and C. DJERASSI. J. Am. Chem. Soc. **89**, 651 (1967); and references cited.
22. [9] (*a*) E. C. KORNFELD. J. Am. Chem. Soc, **70**, 1373 (1948).
   (*b*) J. LEVINE, T. E. EBLE, and H. FISCHBACH. J. Am. Chem. Soc. **70**, 1930 (1948).
   (*c*) G. STORK, S. D. DARLING, I. T. HARRISON, and P. S. WHARTON. J. Am. Chem. Soc. **84**, 2018 (1962).
23. A. D. CROSS, E. DENOT, H. CARPIO, R. ACEVEDO, and P. CRABBÉ. Steroids, **5**, 557 (1965).
24. (*a*) A. J. BIRCH. Quart. Rev. London, **4**, 69 (1950); see also ref. 5*a*.
   (*b*) A. L. WILDS and N. A. NELSON. J. Am. Chem. Soc. **75**, 5366 (1963).
   (*c*) W. HÜCKEL, S. GUPTÉ, and M. WARTINI. Chem. Ber. **99**, 1388 (1966); and references cited.
   (*d*) H. SMITH. Organic reactions in liquid ammonia. *In* Chemistry in nonaqueous ionizing solvents. *Edited by* G. Jander. Vol. I. Part 2. Interscience Publ., New York. 1963.
25. A. HOREAU. Tetrahedron Letters, No. 15, 506 (1961); No. 21, 965 (1962); A. HOREAU and H. B. KAGAN. Tetrahedron, **20**, 2431 (1964); A. MARQUET and A. HOREAU. Bull. Soc. Chim. France, 124 (1967).
26. G. I. POOS, G. E. ARTH, R. E. BEYLER, and L. H. SARETT. J. Am. Chem. Soc. **75**, 422 (1953).
27. D. GREEN, J. P. TURNBULL, and J. H. FRIED. Intern. Congr. on Hormonal Steroids. 2nd Intern. Congr. Ser. No. 111, 124 Excerpta Med, (1966).
28. [9] (*a*) H. MITSUHASHI and T. NOMURA. Steroids, **3**, 271 (1964).
   (*b*) H. MITSUHASHI, T. NOMURA, and M. FUKUOKA. Steroids, **4**, 483 (1964).

[9]This reference should not be considered as representing *all* the pertinent literature.

(*c*) H. MITSUHASHI, T. SATO, T. NOMURA, and I. TAKEMORI. Chem. Pharm. Bull. Tokyo, **12**, 981, 1523 (1964).
(*d*) R. TSCHESCHE, G. BRUGMANN, and G. SNATZKE. Tetrahedron Letters, No. 9, 473 (1964).
(*e*) M. MITSUHASHI and T. NOMURA. Chem. Pharm. Bull. Tokyo, **13**, 274, 1332 (1965).
(*f*) H. MITSUHASHI, T. NOMURA, and M. FUKUOKA. Chem. Pharm. Bull. Tokyo, **14**, 726 (1966).
(*g*) H. MISUHASHI and M. FUKUOKA. Chem. Pharm. Bull. Tokyo, **14**, 809 (1966).
(*h*) U. EPPENBERGER, W. VETTER, and T. REICHSTEIN Helv. Chim. Acta, **49**, 1505 (1966).
(*i*) H. H. SAUER, E. WEISS, and T. REICHSTEIN. Helv. Chim. Acta, **49**, 1632 (1966).
(*j*) N. DANIELI, Y. MAZUR, and F. SONDHEIMER. Tetrahedron, **22**, 3189 (1966); and **23**, 715 (1967).
(*k*) T. TSCHESCHE, M. BAUMGARTH, and P. WELZEL. Tetrahedron, **23**, 249 (1967).
(*l*) T. TSCHESCHE and E. SCHWINUM. Chem. Ber. **100**, 464 (1967).
29. L. VELLUZ, M. LEGRAND, and M. GROSJEAN. Optical circular dichroism, principles, measurements, and applications. Verlag Chemie, Weinheim 1965. pp. 105–110.
30. (*a*) J. S. MILLS, H. J. RINGOLD, and C. DJERASSI. J. Am. Chem. Soc. **80**, 6118 (1958); and references therein.
(*b*) M. J. WEISS, R. E. SCHAUB, G. R. ALLEN, J. F. POLETTO, C. PIDACKS, R. B. CONROW, and C. J. COSCIA. Tetrahedron, **20**, 357 (1964).
31. K. BOWDEN, I. M. HEILBRON, E. R. H. JONES, and B. C. L. WEEDON. J. Chem. Soc. 39 (1946).
32. P. CRABBÉ and A. BOWERS. J. Org. Chem. **32**, 2921 (1967).
33. (*a*) A. BUTENANDT, A. WOLFF, and P. KARLSON. Chem. Ber. **74**, 1308 (1941).
(*b*) A. BUTENANDT, W. FRIEDRICH, and L. POSCHMANN. Chem. Ber. **75**, 1931 (1942).
(*c*) A. BUTENANDT and L. POSCHMANN. Chem. Ber. **77**, 392, 394 (1944).
(*d*) A. WOLFF. Angew. Chem. **52**, 514 (1939).
(*e*) H. WEHRLI and K. SCHAFFNER. Helv. Chim. Acta, **45**, 385 (1962).
34. (*a*) J. D. CHANLEY, T. MEZZETTI, and H. SOBOTKA. Tetrahedron, **22**, 1857 (1966).
(*b*) M. FÉTIZON and J. C. GRAMAIN. Bull. Soc. Chim. France, 1003 (1967).
35. (*a*) J. HEER and K. MIESCHER. Helv. Chim. Acta, **29**, 1895 (1946).
(*b*) H. GIBIAN, K. KIESLICH, H. J. KOCH, H. KOSMOL, C. RUFER, E. SCHRÖDER, and R. VÖSSING. Tetrahedron Letters, No. 21, 2321 (1966).
(*c*) H. KOSMOL, K. KIESLICH, R. VÖSSING, H. J. KOCH, K. PETZOLDT, and H. GIBIAN. Ann. Chem. **701**, 198, 206 (1967).
36. E. SANTOS, J. PADILLA, and P. CRABBÉ. Can. J. Chem. **45**, 2275 (1967).
37. (*a*) C. DJERASSI, R. RECORDS, E. BUNNENBERG, K. MISLOW, and A. MOSCOWITZ. J. Am. Chem. Soc. **84**, 870 (1962).
(*b*) L. VELLUZ, M. LEGRAND, and R. VIENNET. Compt. Rend. **261**, 1687 (1965).
38. J. P. L. BOTS. Rec. Trav. Chim. **77**, 1010 (1958).
39. L. J. CHINN. J. Org. Chem. **40**, 4165 (1965).
40. P. CRABBÉ and C. CASAS-CAMPILLO. J. Org. Chem. **29**, 2731 (1964).