min. the trimethylammonium perchlorate (43%) was collected on a filter. The infrared spectrum of this salt was identical with that of an authentic sample of trimethylammonium perchlorate. After another hour the filtrate was concentrated on a rotary evaporator and the residue was dissolved quickly in carbon tetrachloride. The yellow solution was then chromatographed on alumina under a nitrogen atmosphere. Evaporation of the eluate by a nitrogen stream left bright yellow needles which were stable for short periods if kept in a nitrogen atmosphere. Extraction of a carbon tetrachloride solution of 3,4-benzoheptafulvene with trifluoroacetic acid and determination of the n.m.r. spectrum gave a spectrum that was identical with that of 1-methyl-4,5-benzotropenium ion.

The infrared spectrum (carbon tetrachloride, $cm.^{-1}$) showed CH, 3030 (s) and 3060 (s); C=C, 1560; and CH out of plane bending, 858 (s). The ultraviolet spectrum (ether) showed 345 mμ (ε 965), 328 (1430), 296 sh (1495), 281 (9360), 271 (12,400), 261 (19,800), 252 (16,500), 245 sh (11,650) and 237 sh (9250).

Hydrogenation of 3,4-Benzoheptafulvene. Ether was substituted for carbon tetrachloride in the preceding preparation. After chromatographing, the eluate was concentrated by nitrogen, and the ether solution was hydrogenated with prereduced platinum oxide catalyst. The infrared spectrum of the hydrogenation product was identical with that of an authentic sample of 5-methyl-1,2-benzocycloheptene derived from 5-methyl-1,2-benzocyclohepta-1,3-diene.

5-Methyl-1,2-benzocyclohepta-1,3-diene. A solution of 6-methyl-2,3-benzocyclohept-2-enone (0.872 g., 0.05 mole) in anhydrous ether was added to a suspension of lithium aluminum hydride (0.19 g., 0.05 mole) in ether. The reaction required 30 min. The reaction mixture was then acidified with 80 ml. of 20% aqueous ammonium chloride. The ether layer was separated and the aqueous layer was further extracted with two 50-ml. portions of ether. The ether extract was then dried over anhydrous potassium carbonate. Concentration of the ether solution gave white crystals. Recrystallization from ethanol–water gave 0.73 g. (84%), of white needles, m.p. 135–137°. 6-Methyl-2,3-benzocycloheptenol (0.46 g., 0.026 mole) was dissolved in 5 ml. of absolute ethanol. Then 5 ml. of ethanol saturated with hydrochloric acid was added and the reaction mixture was refluxed for 20 min. After this period the reaction mixture was poured into 80 ml. of water and extracted with pentane. The pentane extract was dried over anhydrous magnesium sulfate and the solvent was removed on a rotary evaporator. The crude product was chromatographed on alumina giving 0.37 g. (80%) of 5-methyl-1,2-benzocyclohepta-1,3-diene. This material was hydrogenated on prereduced platinum oxide to give 5-methyl-1,2-benzocycloheptene.

Acknowledgment. The authors wish to express their indebtedness to the National Science Foundation for Research Grant GP 758 which supported this work. We also wish to thank Professor V. Boekelheide and Dr. C. D. Smith for providing us with data prior to publication of their work.

Steroids. CCLXXIII.[1] The Chemistry of Some Norcaradiene and Cycloheptatriene Analogs[2,3]

Lawrence H. Knox, Esperanza Velarde, and Alexander D. Cross

Contribution from the Syntex Research Laboratories, Mexico City, Mexico. *Received April 9, 1965*

Reaction of 19-hydroxyandrost-4-ene-3,17-dione (**2a**) *with 2-chloro-1,1,2-trifluorotriethylamine* (**1**) *affords two 5,19-cyclo steroids,* **3a** *and* **4a**. *Both products are converted by methanolic hydrochloric acid to 5β-chloromethylestrane-3,17-dione* (**8**). *Proofs of structure and further chemical transformations are described. Several steroidal cycloheptatrienes have been prepared and their properties are discussed in relation to the cycloheptatriene–norcaradiene isomerism. Removal of fluorine from nonallylic tertiary carbon by prolonged exposure to lithium aluminum hydride is reported.*

Persistent interest in methods of fluorinating alicyclic compounds led to an extensive survey of the reactions of 2-chloro-1,1,2-trifluorotriethylamine (**1**)[4] with steroidal alcohols.[5,6] Reaction led typically to fluoro steroids, chlorofluoracetate esters, and dehydration products, often following skeletal carbon–carbon bond migration as an intermediate step. Occasionally solvent intervention in the reaction was observed. The broad range of products was consistent with generation of an incipient carbonium ion followed by collapse along well-precedented paths.[5] A remarkable, and at first capricious, dependence of product composition upon the reaction conditions, especially the nature of the solvent, and the work-up procedure was observed.[7]

(1) Steroids. CCLXXII: A. D. Cross, E. Denot, H. Carpio, R. Acevedo, and P. Crabbé, *Steroids*, **5**, 557 (1965).

(2) This paper also constitutes Spectra and Stereochemistry. XXII. Part XXI: A. D. Cross and L. J. Durham, *J. Org. Chem.*, in press.

(3) A brief account of a part of this work has been published: L. H. Knox, E. Velarde, and A. D. Cross, *J. Am. Chem. Soc.*, **85**, 2533 (1963).

(4) N. N. Yarovenko and M. A. Raksha, *Zh. Obshch. Khim.*, **29**, 2159 (1959); *cf. Chem. Abstr.*, **54**, 9724*h* (1960).

(5) L. H. Knox, E. Velarde, S. Berger, D. Cuadriello, and A. D. Cross, *Tetrahedron Letters*, 1249 (1962); *J. Org. Chem.*, **29**, 2187 (1964).

(6) D. E. Ayer, *Tetrahedron Letters*, 1065 (1962).

(7) Successful solutions to these problems have been applied recently in the synthesis of 19-nor-7-fluoro-B-homosteroids: L. H. Knox, E. Velarde, S. Berger, I. Delfin, R. Grezemkovsky, and A. D. Cross, to be published.

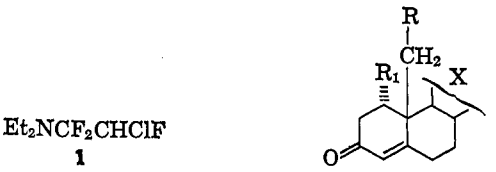
The ready availability in these laboratories of 19-hydroxy steroids[8] offered the opportunity to investigate the reaction of these neopentyl-type alcohols with the fluoramine reagent **1**. Apart from the possibility of obtaining the elusive 19-fluorosteroids for bioassay, the expectancy of neighboring group participation leading to 5,19-bridged structures constituted a further attraction[9]

Reaction of 19-hydroxyandrost-4-ene-3,17-dione (**2a**)[10] with an excess of the fluoramine **1** in acetonitrile under reflux furnished two products, separable by chromatography. Elemental analyses, physical properties, and chemical transformations led to assignment[3] of structures **3a** and **4a** to the products from the following reasoning.

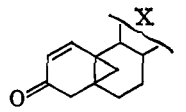
For product **3a** the infrared spectrum showed the presence of conjugated and cyclopentanone carbonyl functions ($\nu_{C=O}$ 1665 and 1742 cm.$^{-1}$), while an ultraviolet absorption maximum at 271 mμ (log ϵ 3.80) clearly indicated extension of conjugation beyond an α,β-unsaturated ketone. The n.m.r. spectrum showed the presence of C—CH=CH—CO (pair of doublets at 340 and 350, 442 and 452 c.p.s., J = 10 c.p.s., with no sign of allylic or other long-range coupling), CH_2CO (pair of doublets at 136.5, 155, 165, and 183.5 c.p.s., J = 18.5 c.p.s.), and geminal cyclopropyl protons of an otherwise fully substituted cyclopropane ring (doublets at 22 and 70.5 c.p.s., J = 4.2 c.p.s.).[11] For 5β-substituted steroidal 3-ketones we have frequently observed a well-differentiated pair of doublets in the n.m.r. for which the coupling constant is large.[12,13]

A consideration of the combined spectral data and of the reaction mechanism[3,5,6] leads to structure **3a** for the product. Hydrogenation of **3a** furnished the dihydro derivative **5a** which proved to be identical with samples prepared both by hydrogenation of the corresponding 6,7-dehydro analog (**5a**, 6,7-dehydro)[15,16] and by chromic oxide oxidation of the diol **5b** which resulted when the 19-tosylate **2b**[16] was treated with lithium in liquid ammonia.[17] The same diol **5b** was arrived at when the saturated dione **5a** was reduced with lithium aluminum hydride. Acid-catalyzed isomerization of this dione **5a** afforded androst-4-ene-3,17-dione (**2c**).

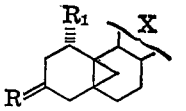
Et_2NCF_2CHClF
1



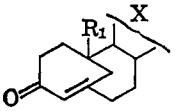
2a, R=OH; R_1=H; X=A
b, R=OTs; R_1=H; X=A
c, R=H; R_1=H; X=A
d, R=H; R_1=Me; X=B



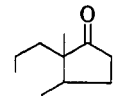
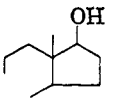
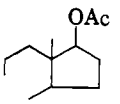
3a, X=A
b, X=B
c, X=C



5a, R=O; R_1=H; X=A
b, R=H, OH; R_1=H; X=B
c, R=H, OH; R_1=H; X=C
d, R=O; R_1=H; X=C
e, R=O; R_1=Me; X=B
f, R=Me, OH; R_1=Me; X=B
g, R=H, OAc; R_1=H; X=C



4a, R=O; R_1=F; X=A
b, R=H, OH; R_1=F; X=B
c, R=O; R_1=F; X=B
d, R=O; R_1=F; X=C
e, R=O; R_1=H; X=B
f, R=O; R_1=H; X=A

A=  B=  C= 

Evidence for structure **4a** for the second product of the reaction between the 19-alcohol **2a** and the fluoramine **1** was derived as follows. Elemental analysis indicated an over-all replacement of hydroxyl by fluorine, and an ultraviolet maximum at 241 mμ (log ϵ 4.09) showed retention of an enone chromophore. A one-proton resonance at 346 c.p.s. broadened by allylic long-range coupling[18] was typical of an olefinic C-4 proton of a Δ^4-3-ketone. Hydrogenation over palladium on charcoal furnished a dihydro derivative **6a** for which no olefinic proton resonance was detectable. Neither the initial fluorination product **4a** nor the dihydro derivative **6a** showed any resonance characteristic of proton in the environment HCF.[5] The fluorine was therefore regarded as tertiary and, from a consideration of the likely reaction mechanism,[3] the product was considered to be 10β-fluoro-5,19-cyclo-5,10-secoandrost-4-ene-3,17-dione (**4a**).[19] Chemical evidence strongly supported this formulation. Thus when the product **4a** was exposed to aqueous

(8) B. Berkoz, E. Denot, and A. Bowers, *Steroids*, **1**, 251 (1963).

(9) Reaction of the reagent **1** with Δ^5-19-hydroxysteroids follows a different path from that reported here and will be the subject of a later communication.

(10) A. S. Meyer, *Experientia*, **11**, 99 (1955).

(11) Except where stated otherwise, n.m.r. spectra were recorded for 5–10% solutions in deuteriochloroform containing a little tetramethylsilane (TMS) as an internal reference (0.0 c.p.s.). Chemical shifts are expressed as c.p.s. downfield from the reference for operation at 60 Mc.p.s. and are accurate to $\pm$1 c.p.s. Coupling constants, also expressed in c.p.s. units, are accurate to $\pm$0.5 c.p.s. The authors thank the Universidad Nacional Autónoma de México, the University of Texas, and Columbia University for time on Varian A-60 spectrometers.

(12) A. D. Cross and I. T. Harrison, *J. Am. Chem. Soc.*, **85**, 3223 (1963).

(13) The 5α isomers also show a large C-4 methylene geminal coupling but the resonance is at higher fields and is more difficult to distinguish from the surrounding resonance. Recently, Takahashi observed enhanced coupling constants for methylene in the environment CO·CH_2OR (R = H or Ac) and has discussed this "carbonyl effect."[14] We have observed with other steroids (unpublished results) larger J_{gem} values for methylene protons α to other sp^2-hybridized carbons.

(14) T. Takahashi, *Tetrahedron Letters*, 565 (1964).

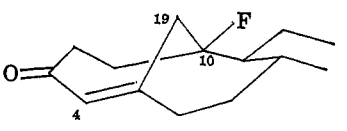
(15) J. J. Bonet, H. Wehrli, and K. Schaffner, *Helv. Chim. Acta*, **45**, 2615 (1962).

(16) O. Halpern, P. Crabbé, A. D. Cross, I. Delfin, L. Cervantes, and A. Bowers, *Steroids*, **4**, 1 (1964).

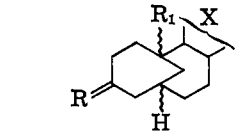
(17) *Cf.* G. Stork and J. Tsuji, *J. Am. Chem. Soc.*, **83**, 2783 (1961).

(18) T. A. Wittstruck, S. K. Malhotra, and H. J. Ringold, *ibid.*, **85**, 1699 (1963); D. J. Collins, J. J. Hobbs, and S. Sternhell, *Tetrahedron Letters*, 197 (1963).

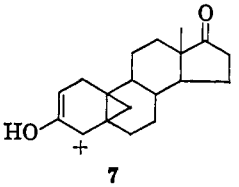
(19) Models show that for a 5,10-seco-5,19-bridged structure incoming fluorine must take up a position on the same side of the molecule as the methylene bridge. For a 5β,19-bridge the fluorine occupies a position equivalent to a 10β-equatorial orientation. Owing to the distortion of rings A and B, the bonds of the carbon atom C-10 are rotated such that the C-10–C-19 bond lies across the rings toward C-5 as in i. *Both* this bond and the C-10 fluorine bond then have such a disposition relative to the plane of the molecule that they are *both* β and pseudo-equatorial. Nomenclature employed in this paper, describing the fluorine substituent as β, is subject to the above considerations. The 10β-fluoro-5β,19-cyclo structure i is preferred over the 10α-fluoro-5α,19-cyclo isomer since in the latter several strong β-face interactions develop.



i



6a, R=O; R_1=β-F; X=A
b, R=H, OH; R_1=H; X=B
c, R=H, OAc; R_1=H; X=C
d, R=O; R_1=H; X=A
e, R=O; R_1=H; X=B
f, isomer of d
g, isomer of b
h, isomer of c



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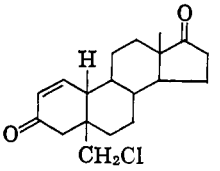

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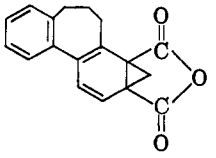

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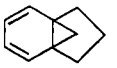

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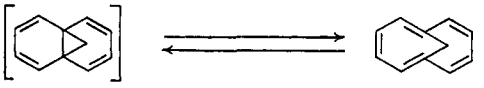
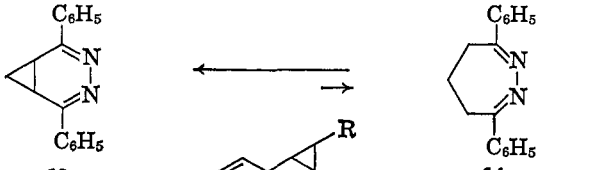
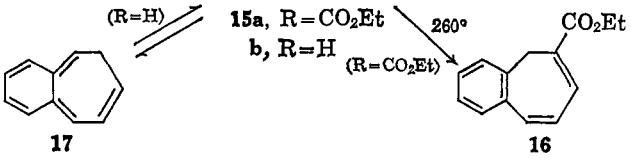


11 **12**

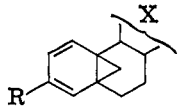


13 **14**

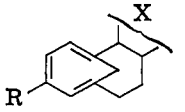


15a, R=CO_2Et
b, R=H

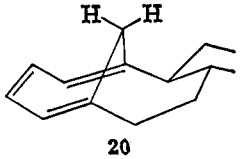
17 **16**



18a, R=OMe; X=A
b, R=OAc; X=A
c, R=N⟨ ⟩; X=A
d, R=Me; X=B



19a, R=OMe; X=A
b, R=OAc; X=A
c, R=N⟨ ⟩; X=A
d, R=OMe; X=B
e, R=OMe; X=C
f, R=OAc; X=C
g, R=Me; X=B
h, R=Me; X=C



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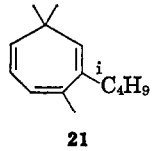
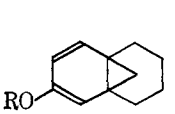


21

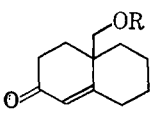
ethanolic hydrofluoric acid there was obtained 5β,19-cycloandrost-1-ene-3,17-dione (**3a**). This transformation is considered to involve regeneration of the same carbonium ion (*e.g.*, **7**), as is formed from the alcohol **2a** with the fluoramine **1**. The carbonium ion then collapses by proton loss from C-1 to afford **3a**.[3] Further evidence for the intervention of a charged species, such as **7**, came from the conversion of *both* **3a** and **4a** by aqueous methanolic hydrochloric acid to 5β-chloromethylestr-1-ene-3,17-dione (**8**).[20] The structure of the latter followed from elemental analysis, the presence of infrared absorptions for saturated cyclopentanone (1740 $cm.^{-1}$) and conjugated cyclohexanone (1670 $cm.^{-1}$) carbonyls, the strong ultraviolet absorption at 233 mμ (log ε 3.93), and characteristic resonances in the n.m.r. for CH_2Cl (AB pattern at 197.5, 208, 210, and 221.5 c.p.s., J = 11.3 c.p.s.), C-4 methylene (AB pattern at 118.5, 136.5, 163, and 181 c.p.s., J = 18 c.p.s.),[12,13] and CH—CH=CH—CO (A and B protons of ABX systems: C-1–H as a 4-line resonance at 417 and 423, 427 and 433 c.p.s., and C-2–H as an apparent two-line resonance at 358 and 368 c.p.s.; $J_{1,2}$ = 10.1 c.p.s., $J_{2,10}$ small, and $J_{1,10}$ = 5.8 c.p.s.).

The availability of the carenone system, as in **3**, allowed exploration of the norcaradiene–cycloheptatriene equilibrium. It was anticipated that the equilibrium should reflect any adverse strains imposed on ring A expansion by the rigidity of the remainder of the molecule. Prior evidence that the integrity of the norcaradiene system could be maintained and expansion to the cycloheptatriene inhibited was already at hand in the experience of Eschenmoser and his collaborators who prepared the norcaradiene **9** during their synthesis of colchicine.[21] Results of other studies of this equilibrium appeared during the course of present researches. Vogel reviewed[22] the isomerism and, with co-workers, showed subsequently that the norcaradiene **10** does not isomerize to the cycloheptatriene form.[23] A related norcaradiene **11**, synthesized by the same school, exists as the stabilized aromatic analog **12**,[24,25] but Maier has prepared a stable norcaradiene analog **13** where a favorable conjugated system would be distorted by ring expansion to **14**.[27] Analogously, the norcaradiene **15a** is stabilized by conjugation and only passes over to the cycloheptatriene **16**, by a proton shift, on heating to 260°.[28] For the parent hydrocarbon **15b**, Vogel has demonstrated a thermally induced equilibrium (**15b** ⇄ **17**).[29] Reports have appeared very recently of norcaradiene and cycloheptatriene structures resulting from the addition

(20) Further chemical transformations of this compound will be the subject of a later communication.
(21) J. Schreiber, W. Leimgruber, M. Pesaro, P. Schudel, T. Threlfall, and A. Eschenmoser, *Helv. Chim. Acta*, **44**, 540 (1961).
(22) E. Vogel, *Angew. Chem.*, **74**, 829 (1962).
(23) E. Vogel, W. Wiedemann, H. Kiefer, and W. F. Harrison, *Tetrahedron Letters*, 673 (1963).
(24) E. Vogel and H. D. Roth, *Angew. Chem.*, **76**, 145 (1964).
(25) Our independent efforts to prepare related tricyclic norcaradienes (*e.g.*, ii) foundered when it was found that the decalenone iii treated with the fluoramine **1** gave as the sole isolable product the chlorofluoroacetate ester iv, the 2,4-dinitrophenylhydrazone of which showed a characteristic doublet at 378 c.p.s., J_{HF} = 49.7 c.p.s., for the CHClF proton.[26]



ii



iii, R=H
iv, R=COCHClF

(26) Unpublished results with Dr. I. T. Harrison.
(27) G. Maier, *Angew. Chem.*, **75**, 920 (1963).
(28) R. Huisgen and G. Juppe, *Ber.*, **94**, 2332 (1961).
(29) E. Vogel, D. Wendisch, and W. R. Roth, *Angew. Chem.*, **76**, 432 (1964).

Table I.[a] Physical Properties of Norcaradienes and Cycloheptatrienes[b]

Norcaradiene	λ_{max}, mμ (log ε)	N.m.r. frequencies of geminal methylene protons (*J*), c.p.s.	Cycloheptatriene	λ_{max}, mμ (log ε)	N.m.r. frequencies of geminal methyiene protons (*J*), c.p.s.
15b[c]		−21 (1 H) and 78 (1 H) c.p.s.	**17**[c]		28 (broad band, 2 H)
9[d]		62 (1 H, d) (*J* = 4.5) and 145 (1 H, d) (*J* = 4.5)	**12**[e]	256 259 298	−30 (2 H, singlet)
10[f]	249 (3.45) 255 (3.45) 278 (3.47)	−24 (1 H, d) (*J* = 4) and 86 (1 H, d) (*J* = 4)	**19a**	257 (3.74)	59.5 and 69.5; 183 and 193 (*J* = 10.0)
			19b	257 (3.78)	*ca.* 65 and 75; 195 and 205 (*J* = 10.0)
13[g]		14 (1 H, m) (J_{gem} = 3.5) and 125 (1 H, m) (J_{gem} = 3.5)	**19c**	222 (4.13) 283 (3.91)	Resonance doublets *ca.* 68 and 185 partly obscured
			Cycloheptatriene (tropilidine)	261[h]	132 (room temp.),[i] 86 and 173 (−170°)[j]

[a] Minus sign indicates resonance at higher fields than TMS; d = doublet; m = multiplet. [b] See ref. 11. [c] See ref. 29. [d] See ref. 21. [e] See ref. 24. [f] See ref. 23. [g] See ref. 27. [h] Using data of R. F. Zürcher, *Helv. Chim. Acta*, **46**, 2054 (1963). [i] N. S. Bhacca, L. F. Johnson, and J. N. Shoolery, "NMR Spectra Catalog," Varian Associates, Palo Alto, Calif., 1961. [j] F. R. Jensen and L. A. Smith, *J. Am. Chem. Soc.*, **86**, 956 (1964).

of di(trifluoromethyl)carbene,[30] dicyanocarbene,[31] and cyanotrifluoromethylcarbene[32] to aromatic systems. The adduct from benzene and the last of these carbenes is a rapidly equilibrating mixture of the norcaradiene and cycloheptatriene isomers.[32] Models[33] of steroids with ring A as for the norcaradiene system **18** suggested that in this form the steroid might be less strained than in the cycloheptatriene form **19**. When the norcarenone **3a** was treated with anhydrous methanol and *p*-toluenesulfonic acid there was obtained an enolic methyl ether **19a** (n.m.r. three-proton singlet at 220 c.p.s.) showing an ultraviolet maximum at 256–258 mμ (log ε 3.76) and infrared absorptions for cyclopentanone (1742 cm.$^{-1}$) and a conjugated polyene system (1630, 1605, and 1515 cm.$^{-1}$). Brief exposure to hot, dilute, aqueous acid regenerated the norcarenone **3a**. The n.m.r. spectrum showed striking changes from the norcarenone **3**. In particular the doublets for geminal cyclopropyl protons in **3** (*J* = 4.5 c.p.s.) were absent, and a pair of doublets (*J* = 10.0 c.p.s.) was observed at 64 and 188 c.p.s. The corresponding enol acetate **19b** (n.m.r. three-proton singlet at 132.5 c.p.s.) was also prepared from **3a** by treatment with acetic anhydride, acetic acid, and *p*-toluenesulfonic acid. A third derivative, the enamine, resulted from reaction of the norcarenone **3a** with *p*-toluenesulfonic acid and pyrrolidine. Physical properties for these derivatives and known norcaradienes and cycloheptatrienes are summarized in Table I and indicate that these enol derivatives are the cycloheptatrienes **19a**, **19b**, and **19c**, respectively, and not the norcaradienes **18a–c**, thereby adding strength to our original conclusions.[3] Of particular significance are the coupling constant magnitudes for the geminal methylenes. For all the norcaradienes J_{gem} is in the range 3.5–4.5 c.p.s. This value is in good accord with recently published data for 5β,19-cyclo steroids[16] and other cyclopropanes.[34,35] Conversely, J_{gem} for the cycloheptatriene ring is *ca.* 10 c.p.s., a value consistently held in all the enol derivatives obtained from the norcarenone **3a**. Examination of the n.m.r. spectra of **19b** in pyridine, benzene, and deuteriochloroform solvents showed no change in the magnitude of J_{gem}. Molecular models demonstrated that for the cycloheptatrienes **19** ring A is nonplanar as in **20**, and conjugation of the double-bond system is accordingly reduced. This fact is reflected in both the n.m.r. and ultraviolet spectra. Both methylene protons of cycloheptatriene resonate at 132 c.p.s. for a spectrum recorded at room temperature.[36] Anet has shown that equivalence in this case is due to a rapid inversion between two nonplanar structures.[37] At −150° the rate of inversion is substantially reduced, allowing the chemical shift between the two stereochemically different methylene protons of the nonplanar structure to be measured. A value of 76 c.p.s. was recorded, and Anet estimated the true chemical shift to be about 80 c.p.s. In a parallel study Jensen and Smith studied the n.m.r. spectrum of cycloheptatriene at −170° and found a chemical shift of 86 c.p.s.[38] It was apparent from the rigid structure **20** that one of the methylene bridge protons is held over the Δ^2-double bond and is consequently subject to strong shielding. Structure **20** is therefore analogous to cycloheptatriene at very low temperature, and it is of interest that the chemical shift between the methylene protons is 124 c.p.s. This figure is higher than that recorded by either Anet or Jensen and Smith and undoubtedly reflects extra shieldings and deshieldings of these two protons by other bonds in the steroid molecule, and perhaps an even greater distortion from planarity of the cycloheptatriene in our cases.[39,40]

(30) D. M. Gale, W. J. Middleton, and C. G. Krespan, *J. Am. Chem. Soc.*, 87, 657 (1965).
(31) E. Cigarek, *ibid.*, 87, 652 (1965).
(32) E. Cigarek, *ibid.*, 87, 1149 (1965).
(33) A. S. Dreiding, *Helv. Chim. Acta*, **42**, 1339 (1959).
(34) No signs are given to coupling constants throughout this paper. J_{gem} for cyclopropanes is considered to be negative[35] and it is supposed that this finding holds for steroidal cyclopropanes[15] also.
(35) *Inter alia*, K. B. Wiberg and B. J. Nist, *J. Am. Chem. Soc.*, **85**, 2788 (1963); T. Shono, T. Morikawa, A. Oku, and R. Oda, *Tetrahedron Letters*, 791 (1964); H. M. Hutton and I. Schaefer, *Can. J. Chem.*, **41**, 683 (1963).
(36) See Table I, footnote *i*.
(37) F. A. L. Anet, *J. Am. Chem. Soc.*, 86, 458 (1964).
(38) See Table I, footnote *j*.
(39) That the observed doublets at 64 and 128 c.p.s. were indeed due to mutually coupled methylene protons was proved by a double-

Another n.m.r. spectral change in passing from structure **3a** to **19** concerned the olefinic protons. An enol methyl ether derived from **3a** should maintain for the norcaradiene form **18a** $J_{1,2}$ = 10 c.p.s. for the olefinic protons of the Δ^1-double bond.[41] On the other hand, the adjacent olefinic protons of the cycloheptatriene form **19a** (*cf.* **20**) must reflect both the single bond character of the C-1–C-2 link and the angle subtended by the C-1–H and C-2–H bonds. The observed coupling, $J_{H\text{-}1\text{–}H\text{-}2}$ = 6 c.p.s., is in accord with structure **19a**, therefore. A further spectral change characteristic of the ring A cycloheptatriene system is the downfield shift of the 18-proton resonance by *ca.* 10 c.p.s. from its normal frequency for the particular 17-substituent in the molecule, irrespective of the identity of the C-3 substituent. Calculated $\nu_{H\text{–}18}$ values for androstan-17β-ol, -17β-acetate, and -17-one are 43.5, 46.5, and 51.5 c.p.s.[42] The cycloheptatrienes **19g**, **19f**, and **19c** showed $\nu_{H\text{–}18}$ 53, 57, and 61.0 c.p.s., respectively.

For a number of polyalkylated cycloheptatrienes, Conrow and his co-workers found λ_{max} 265–269 mμ (log ϵ 3.55–3.59).[43] However, for large substituents strong steric compression is generated when the ring is in planar form. Thus, for 2-*t*-butyl-3,7,7-trimethylcycloheptatriene (**21**) the rate of ring inversion is slower and the lower ultraviolet absorption maximum wave length, λ_{max} 255 mμ, reflects the reduced ability to maintain a planar arrangement of conjugated double bonds. This value is in good agreement with the values found for the nonplanar cycloheptatrienes, **19a** and **19b** (see Table I).

Lithium aluminum hydride reduction of the enol ether **19a** gave the corresponding 17β-alcohol **19d**, characterized further as the acetate **19e**. Aqueous methanolic acid hydrolysis of the enol ethers **19d** and **19e** then led to the norcarenone derivatives **3b** and **3c**, respectively, for which spectral properties were as expected (see Experimental section). 17β-Hydroxy-5β,19-cycloandrost-1-en-3-one (**3b**) was also prepared in excellent yield by direct reduction of the enol acetate **19b** with lithium aluminum hydride. Acetylation of this compound **3b** with acetic anhydride and pyridine at room temperature furnished with 17β-acetate **3c**, but using the same reagents and reflux the enol diacetate **19f** resulted.

Sodium borohydride reduction of 17β-hydroxy-5β,-19-cycloandrost-1-en-3-one acetate **3c** in aqueous dioxane gave the 3,17-diol 17-monoacetate **5c** (no olefinic protons by n.m.r. and infrared). Chemical evidence for structure **5c** stemmed from oxidation to the corresponding saturated 3-ketone **5d**, separately prepared by hydrogenation of the norcarenone derivative **3c**. Hence, borohydride reduction proceeds by hydride attack at C-1 followed by 1,2-addition to carbonyl. Smooth 1,4-addition to the norcarenone system **3** was encountered several times (*vide infra*) and is reminiscent of borohydride reduction of other Δ^1-3-ketones.[44] Similar 1,4-additions took place with other anions. Methylmagnesium bromide reacted with 17β-hydroxy-5β,19-cycloandrost-1-en-3-one (**3b**) to give a product considered to be 17β-hydroxy-1α-methyl-5β,19-cycloandrostan-3-one (**5e**) and a cycloheptatriene (λ_{max} 256 mμ (log ϵ 3.75)) (*vide infra*). The former underwent acid-catalyzed isomerization to a 1-methyltestosterone, probably **2d**, although the melting point differed from the patent literature value.[45] Further treatment of the 1α-methyl 3-ketone **5e** with methyl Grignard furnished the 1α,3ξ-dimethyl-3ξ,17β-diol **5f**. The cycloheptatriene product from the original Grignard treatment is considered to be compound **19g** formed by 1,2-addition at C-3 in the norcarenone **3b** followed by elimination of the tertiary 3-hydroxy during work-up. This would yield the norcaradiene **18d** for which isomerization to **19g** should be spontaneous. Apart from the ultraviolet evidence, bands characteristic of the cycloheptatriene ring were visible in the infrared spectrum at 1615, 1600, and 1500 cm.$^{-1}$, while the n.m.r. spectrum showed a three-proton resonance at 126 c.p.s. (vinylic methyl). The latter resonance showed distinct broadening due to long-range coupling. Low-field resonance equivalent to three olefinic protons was visible at 348 and 387 c.p.s. (AB pattern, $J_{1,2}$ = *ca.* 6 c.p.s., with further splitting due to long-range coupling) and at 341.5 c.p.s. (C-4–H, broadened singlet). The derived 17β-acetate ester **19h** showed spectral characteristics which supported these structural assignments (see Experimental section).

Although the norcarenone system **3** was of more intrinsic interest, the facility with which the 5,10-bond was reformed during chemical investigations prompted additional studies of the 10β-fluoro product **4a** (*vide supra*). Reduction with lithium aluminum hydride in tetrahydrofuran furnished the 3,17-diol **4b** as an oil. Dehydrogenation of **4b** by 2,3-dichloro-5,6-dicyano-1,4-benzoquinone gave 10β-fluoro-17β-hydroxy-5,19-cyclo-5,10-secoandrost-4-en-3-one (**4c**)[19] (λ_{max} 242 mμ), the 17β-acetate **4d** of which was also prepared. When the aluminum hydride reduction was prolonged, and a larger excess of reagent was employed, there resulted an oily mixture which was oxidized with an excess of manganese dioxide[46,47] before chromatographic separation was attempted. Three crystalline products were obtained, one of which, the diol **5b**, was already known (*vide supra*) and was further characterized as the derived diacetate **5g**. The two remaining products contained no fluorine by elemental analysis but retained an enone chromophore (λ_{max} 244 mμ (log ϵ 4.16)). Structures **4e** and **4f** were assigned therefore to these compounds, and all available information is in agreement with these formulations. The purity of the starting material **4a** was carefully checked to ensure that no norcarenones **3** were present.

Since the tertiary fluorine was removed from the saturated nonallylic C-10 position in **4a** by lithium aluminum hydride reduction, similar reduction of **6a**, the fluorine-containing hydrogenation product of **4a**

resonance experiment, for which we are indebted to Mr. P. W. Landis, Eli Lilly and Co., Indianapolis 6, Ind.

(40) The possibility that the bridge methylenes in the cycloheptatrienes **19** can be inverted through the plane of the steroid by heating is under study, although the barrier to inversion must be quite high.

(41) *Cf.* J = 10.1 c.p.s. for olefinic protons of **15b**.[26]

(42) See Table I, footnote *h*.

(43) K. Conrow, M. E. H. Howden, and D. Davis, *J. Am. Chem. Soc.*, **85**, 1929 (1963).

(44) For a recent example see R. Hodges, S. G. McGeachin, and R. A. Raphael, *J. Chem. Soc.*, 2515 (1963).

(45) R. Wiechert, German Patent 1,122,944 (1962). The 1α configuration of methyl in our product is preferred since axial introduction of methyl in 1,4-additions of Grignard reagent have been previously recorded by A. J. Birch and M. Smith, *Proc. Chem. Soc.*, 356 (1962).

(46) R. M. Evans, *Quart. Rev.* (London), **13**, 61 (1959).

(47) I. T. Harrison, *Proc. Chem. Soc.*, 110 (1964).

(*vide supra*), was also attempted. The sole isolable crystalline product was free of fluorine and was assigned the diol structure **6b**. Diacetate **6c** and diketone **6d** derivatives were prepared. Hydrogenation of the fluorine-free Δ^4-3-ketone **4e** gave 17β-hydroxy-5ξ,10ξ-5,19-cycloandrostan-3-one (**6e**), oxidation of which gave an isomer **6f** of the dione **6d**. These two diones, which show marked differences in optical rotation, must be stereoisomeric at C-5 and/or C-10. Reduction of the dione **6f** afforded a diol **6g** which is a stereoisomer of **6b** and likewise exhibits significantly different optical properties, as did the derived diacetate **6h** on comparison with the stereoisomeric diester **6c**. If the mechanism of reductive fluorine removal involves inversion at C-10 and is the same for reduction of **4a** and **6a** (*i.e.*, no double bond participation when a group such as $^-AlH_3F$ departs from C-10), then the stereochemical differences can probably be attributed to hydrogenation from different faces of the 10β-fluoro-Δ^4-3-ketone and the 10α-H-Δ^4-3-ketone. However, in the absence of further information this supposition must remain purely speculative.

Experimental[48]

5β,19-Cycloandrost-1-ene-3,17-dione (**3a**) *and 10β-Fluoro-5,10-seco-5,19-cycloandrost-4-ene-3,17-dione* (**4a**). A mixture of 19-hydroxyandrost-4-ene-3,17-dione (**2a**, 20.0 g., 0.066 mole), 2-chloro-1,1,2-trifluorotriethylamine (**1**, 17.1 g., 0.090 mole), and acetonitrile (260 ml., distilled from phosphorus pentoxide) was heated under reflux for 45 min. The residual oil obtained after distillation of solvent *in vacuo* was adsorbed from hexane onto Florisil (1 kg.). Crystalline fractions eluted with hexane–ether (3:2) were combined (8.8 g., 46.8%) and recrystallized from acetone, affording 6.0 g. of **3a**, m.p. 180–182°. A further crystallization from acetone gave the analytical sample: m.p. 185–187°; $[\alpha]D$ +253°; λ_{max} 272 mμ (log ϵ 3.80); ν_{max} 3020 (w), 1742, 1665, and 1010 cm.$^{-1}$; n.m.r. 22 and 70.5 (doublets, J = 4.2 c.p.s., cyclopropyl protons), 55 (18-H), 340 and 350 (H-2, J = 10.0 c.p.s.), 432 and 442 (1-H, J = 10 c.p.s.), 136.5, and 155, 165, and 183.5 c.p.s. (C-4 methylene, J = 18.5 c.p.s.).

Anal. Calcd. for $C_{19}H_{24}O_2$: C, 80.24; H, 8.51. Found: C, 80.40; H, 8.61.

Further elution with the same solvent system yielded a mixture of **3a** and the 10β-fluoro derivative **4a** (1.35 g.), followed by **4a** (7.62 g., 38%), m.p. 179–182° after recrystallization from acetone: $[\alpha]D$ −68°; λ_{max} 241 mμ (log ϵ 4.09); ν_{max} 1740 and 1650 cm.$^{-1}$; n.m.r. 54.5 (18-H) and 346 (4-H, singlet showing small allylic coupling).

Anal. Calcd. for $C_{19}H_{25}FO_2$: C, 74.99; H, 8.28; F, 6.24. Found: C, 75.18; H, 8.28; F, 5.97.

When the mixture of **3a** and **4a** (1.35 g.) was rechromatographed on Florisil, there was obtained an additional 0.43 g. of **3a** and 0.10 g. of **4a**.

5β,19-Cycloandrostane-3,17-dione (**5a**). Hydrogenation of **3a** (100 mg.) in 95% ethanol (20 ml.) over a 5% palladium-on-charcoal catalyst (100 mg.) resulted in the absorption of 1 molar equiv. of hydrogen in 30 min. The product was isolated in the usual manner and recrystallized twice from acetone to give a pure specimen of **5a**: m.p. 136–137°; $[\alpha]D$ +112°; ν_{max} 1738 and 1708 cm.$^{-1}$; n.m.r. as published elsewhere.[16]

Anal. Calcd. for $C_{19}H_{26}O_2$: C, 79.68; H, 9.15; O, 11.17. Found: C, 79.81; H, 9.25; O, 11.32.

A solution of the saturated diketone **5a** (18 mg.) in dry ether (10 ml.) was added dropwise with stirring to a suspension of lithium aluminum hydride (20 mg.) in dry ether (10 ml.). After stirring for 30 min., the product was isolated in the usual manner. Recrystallization from methanol afforded the diol **5b**: m.p. 154–155°; $[\alpha]D$ 56°; ν_{max} 3300 cm.$^{-1}$ and no carbonyl absorption (*vide infra*).

Reduction of 19-Hydroxyandrost-4-ene-3,17-dione Tosylate (**2b**) *with Lithium–Liquid Ammonia.* A solution of the tosylate ester **2b**[16] (2.9 g.) in dry tetrahydrofuran (50 ml.) was added to liquid ammonia (500 ml.), followed by lithium metal (1.4 g.) in small portions over a period of 30 min. The mixture was stirred for an additional 3 hr. when solid ammonium chloride was added in small portions until the blue color was discharged. Ammonia was allowed to evaporate and the residue was extracted several times with ether. Evaporation of the ether extracts afforded an oily product which was adsorbed from benzene onto Florisil (150 g.). The crystalline fractions eluted with benzene–ether (4:1) consisted of the diol **5b** (260 mg., 13.7%), m.p. 145–147°. Recrystallization from methanol afforded the analytical sample, m.p. 155–157°, $[\alpha]D$ +56°. The latter was identical by melting point, mixture melting point, and infrared spectral comparison with a sample of **5b** obtained by lithium aluminum hydride reduction of the dione **5a**, as described above.

Anal. Calcd. for $C_{19}H_{30}O_2$: C, 78.57; H, 10.02. Found: C, 78.63; H, 10.33.

Further elution with benzene–ether (1:1) yielded unchanged tosylate **2b** (370 mg.).

Oxidation of the above diol **5b** with 8 *N* chromic acid[49] in purified acetone yielded the dione **5a**, whose melting point was undepressed on admixture with a sample prepared from hydrogenation of the rearrangement product **3a**.

Androst-4-ene-3,17-dione (**2c**) *from* **5a**. A mixture of the 5β,19-cyclo steroid **5a** (220 mg.), ethanol (15 ml. of 95%), and concentrated hydrochloric acid (5 ml.) was heated under reflux for 1 hr. The cooled mixture was diluted with ether, washed successively with water, saturated aqueous sodium bicarbonate, and water to neutrality, dried (sodium sulfate), and evaporated. The crystalline residue (190 mg.) furnished, by two crystallizations from methanol, analytically pure androst-4-ene-3,17-dione (**2c**), m.p. 168–170°, $[\alpha]D$ +197°, λ_{max} 240 mμ (log ϵ 4.21), identical by mixture melting point and infrared comparison with an authentic sample.

5,10-Seco-5,19-cyclo-10β-fluoroandrostane-3,17-dione (**6a**). When the product **4a** (1.0 g.) was hydrogenated over 5% palladium on charcoal, 1 molar equiv. of hydrogen was absorbed in 10 min. Recrystallization of the crude product from hexane afforded the dione **6a**: m.p. 100–102°; $[\alpha]D$ +67°; ν_{max} 1743, 1700,

(48) Melting points are uncorrected. Optical rotations were determined in chloroform solutions and ultraviolet spectra were measured in 95% ethanol. Infrared spectra, determined with potassium bromide disks on a Perkin-Elmer Model 21 spectrometer equipped with sodium chloride optics, are by Sr. Erlín Avila and his staff.

(49) K. Bowden, I. M. Heilbron, E. R. H. Jones, and B. C. L. Weedon, *J. Chem. Soc.*, 39 (1946); A. Bowers, T. J. Halsall, E. R. H. Jones, and A. J. Lenin, *ibid.*, 2548 (1953).

and multiple medium intensity absorptions in the region 770–1100 cm.$^{-1}$; n.m.r. 54 c.p.s. (18-H).

Anal. Calcd. for $C_{19}H_{27}FO_2$: C, 74.47; H, 8.88; F, 6.28. Found: C, 74.97; H, 9.14; F, 6.06.

5β,19-Cycloandrost-1-ene-3,17-dione (**3a**) *from 10β-Fluoro-5,10-seco-5,19-cycloandrost-1-ene-3,17-dione* (**4a**). A mixture of the fluoro steroid **4a** (1.0 g.), 95% ethanol (30 ml.), and 48% hydrofluoric acid (10 ml.) was heated under reflux for 1 hr. Dilution of the reaction mixture with water and extraction with ether, followed by saturated aqueous sodium bicarbonate and water washes of the ethereal solution, then solvent removal by evaporation, led to the norcarenone **3a** (0.90 g.), showing a single maximum in the ultraviolet absorption spectrum at 272 mμ. Recrystallization from acetone afforded a pure specimen, m.p. 180–182°, identical by infrared spectral comparison with authentic **3a**.

5β-Chloromethyl-19-norandrost-1-ene-3,17-dione (**8**). *A. From 10β-Fluoro-5,10-seco-5,19-cycloandrost-4-ene-3,17-dione* (**4a**). A mixture of **4a** (1.0 g.), 95% ethanol (30 ml.), and 12 *N* hydrochloric acid (10 ml.) was heated under reflux for 1 hr. Water was added and the mixture was extracted with ether. After washing with saturated aqueous sodium bicarbonate, followed by water to neutrality, the dried (sodium sulfate) ether solution was evaporated. The residual oil (980 mg.) was adsorbed from hexane onto Florisil (50 g.). The crystalline fractions eluted with hexane–ether (1:1) were combined (470 mg.) and recrystallized from methanol affording **8**: m.p. 180–182°; $[\alpha]_D$ +154°; λ_{max} 233 mμ (log ε 3.93); ν_{max} 1740, 1670, 1615, 770, and 733 cm.$^{-1}$ (C–Cl monochloro compound)[50]; n.m.r. 56 (18-H), and see discussion section.

Anal. Calcd. for $C_{19}H_{25}ClO_2$: C, 71.15; H, 7.85; Cl, 11.06. Found: C, 71.03; H, 7.82; Cl, 11.01.

B. From 5,19-Cycloandrost-1-ene-3,17-dione (**3a**). A mixture of **3a** (1.18 g.), 95% ethanol (30 ml.), and 12 *N* hydrochloric acid (10 ml.) was heated under reflux for 1 hr. The product was isolated as described above and recrystallized twice from methanol affording the new dione **8** (0.55 g.), m.p. 182–184°. The mother liquors were chromatographed on Florisil. Crystalline fractions eluted with hexane–ether (1:1) were combined (130 mg.) and recrystallized from methanol to give an additional 50 mg. of the dione **8**, m.p. 182–184°.

5,10-Seco-5,19-cyclo-3-methoxyandrosta-1(10),2,4-trien-17-one (**19a**). A mixture of **3a** (2.0 g.), methanol (50 ml.), and *p*-toluenesulfonic acid (30 mg.) was heated under reflux for 30 min. The reaction mixture was diluted with ether (250 ml.), washed successively with 5% aqueous sodium bicarbonate solution and water, dried (sodium sulfate), and evaporated to dryness. Recrystallization of the residue from methanol–pyridine afforded the methyl ether **19a**: m.p. 135–136°; $[\alpha]_D$ +246°; λ_{max} 256–258 mμ (log ε 3.76); ν_{max} 1742, 1630, 1605, 1515, 1163, 852, 802, and 738 cm.$^{-1}$; n.m.r. 60.5 (18-H), 220 (OMe), 341.5 (4-H), 346.5 and 352.5, 356 and 362 (1- and 2-protons, J = 6 c.p.s.), *ca.* 58 and 68 and 183 and 193 (pair of doublets, C-19 methylene bridge protons, J = 10.0 c.p.s.).

(50) A. D. Cross, "Introduction to Practical Infrared Spectroscopy," 2nd Ed., Butterworth and Co. (Publishers) Ltd., London, 1964, p. 79.

Anal. Calcd. for $C_{20}H_{26}O_2$: C, 80.49; H, 8.78. Found: C, 80.81; H, 9.08.

Hydrolysis of **19a** (182 mg.) by refluxing for 20 min. in aqueous methanol (4:1, 50 ml.) containing oxalic acid (100 mg.) afforded **3a** (180 mg.), 180–182°, λ_{max} 272 mμ (log ε 3.75), identical with **3a** from mixture melting point and infrared spectral comparisons.

5,10-Seco-5,19-cyclo-3-acetoxyandrosta-1(10),2,4-trien-17-one (**19b**). A solution of **3a** (360 mg.), acetic acid (5 ml.), acetic anhydride (1 ml.), and *p*-toluenesulfonic acid (300 mg.) was stirred at room temperature for 16 hr. The product was isolated by dilution with water and filtration. Crystallization from methanol–pyridine afforded **19b** (180 mg.), m.p. 158–160, raised to 165–166° by a second crystallization from methanol–pyridine: $[\alpha]_D$ +202°; λ_{max} 257 mμ (log ε 3.78); ν_{max} 1750, 1733, 1600, 1505, 1205, 1118, 915, and 803 cm.$^{-1}$; n.m.r. 61.8 (18-H), 132.5 (enol OAc), 351 (4-H), *ca.* 357 and 362, *ca.* 383 and 388 (1- and 2-protons, AB pattern, J = *ca.* 5 c.p.s.), 66.5 and 77.5 (shoulder), and 195 and 205 (pair of doublets, 19-methylene bridge protons, J = 10 c.p.s.). Coupling of methylene bridge protons remains constant on transference to benzene or pyridine solvent.

Anal. Calcd. for $C_{21}H_{26}O_3$: C, 77.27; H, 8.03. Found: C, 77.20; H, 7.97.

3-(N-Pyrrolidyl)-5,10-seco-5,19-cycloandrosta-1(10),-2,4-trien-17-one (**19c**). A mixture of **3a** (284 mg.), dry benzene (50 ml.), pyrrolidine (284 mg.), and *p*-toluenesulfonic acid (30 mg.) was concentrated to 25 ml. by distillation. Additional pyrrolidine (284 mg.) was added and the mixture was refluxed for 1 hr. Evaporation under reduced pressure and crystallization of the residue from methanol yielded the enamine **19c** (180 mg.), m.p. 170–172°, raised to 203–204° by further recrystallization from methanol: $[\alpha]_D$ +242°; λ_{max} 222 mμ (log ε 4.13) and 283 mμ (log ε 3.91); ν_{max} 1735, 1615, 1595, and 1500 cm.$^{-1}$; n.m.r. 61 (18-H), 333 (4-H), 326 and *ca.* 332 (buried), and 351 and 357 (1- and 2-protons, AB pattern, J = 10 c.p.s.), resonance for bridge methylene protons obscured.

Anal. Calcd. for $C_{23}H_{31}NO$: C, 81.85; H, 9.26; N, 4.15. Found: C, 82.04; H, 9.52; N, 4.11.

5,10-Seco-5,19-cyclo-3-methoxyandrosta-1(10),-2,4-trien-17β-ol (**19d**). A solution of the enol ether **19a** (1.3 g.) in dry ether (5.0 ml.) was added dropwise with stirring to a suspension of lithium aluminum hydride (1.0 g.) in ether (150 ml.). After 30 min., the excess hydride was destroyed by cautious addition of ethyl acetate. The mixture was then treated with saturated aqueous sodium sulfate followed by solid sodium sulfate, filtered, and evaporated. The oily residue was adsorbed from benzene onto washed alumina (125 g.) and eluted with benzene. The crystalline eluates were combined (1.0 g.) and recrystallized from methanol–pyridine to give the 17β-alcohol **19d**, m.p. 117–120°, unchanged after further crystallization from methanol–pyridine: $[\alpha]_D$ +133°; λ_{max} 257 mμ (log ε 3.74); ν_{max} 3520, 3330, 1620, 1605, 1518, 1057, 810, 802, and 736 cm.$^{-1}$.

Anal. Calcd. for $C_{20}H_{28}O_2$: C, 79.95; H, 9.39. Found: C, 78.82; H, 9.56.

5,10-Seco-5,19-cyclo-3-methoxyandrosta-1(10),2,4-trien-17β-ol Acetate. (**19e**). Acetylation of the above

alcohol **19d** (480 mg.) in pyridine and acetic anhydride afforded the 17β-acetate **19e** (530 mg.), m.p. 102–103° after recrystallizations from methanol–pyridine: [α]D +121°; λ_{max} 256–258 mμ (log ε 3.78); ν_{max} 1740, 1625, 1605, 1515, 1235, 1162, 1047, 808, and 740 cm.$^{-1}$.

Anal. Calcd. for $C_{22}H_{30}O_3$: C, 77.15; H, 8.83. Found: C, 76.88; H, 8.83.

17β-Hydroxy-5β,19-cycloandrost-1-en-3-one (**3b**). *A. By Hydrolysis of the Enol Ether* **19d**. A solution of **19d** (0.51 g.) in 20% aqueous methanol (25 ml.) containing *p*-toluenesulfonic acid (0.40 g.) was heated under reflux for 3 hr. The mixture was cooled, diluted with ether (250 ml.), washed with 5% sodium bicarbonate solution followed by water to neutrality, dried (sodium sulfate), and evaporated to dryness. The crystalline residue (0.50 g.) was recrystallized from acetone affording the norcarenone **3b**: m.p. 175–177°; [α]D +173°; λ_{max} 272 mμ (log ε 3.76); ν_{max} 3320, 1655, 1610 (shoulder), 1082, 1060, 1028, 938, 803, and 759 cm.$^{-1}$.

Anal. Calcd. for $C_{19}H_{26}O_2$: C, 79.68; H, 9.15. Found: C, 79.66; H, 9.20.

B. By Reduction of the Enol Acetate **19b** *with Lithium Aluminum Hydride.* To a suspension of lithium aluminum hydride (3.0 g.) in dry ether (100 ml.) there was added dropwise with stirring over 15 min. a solution of the enol acetate **19b** (8.0 g.) in ether (150 ml.). After stirring for 1 additional hr., the excess of metal hydride was destroyed by cautious addition of ethyl acetate. Saturated aqueous sodium acetate was added, followed by solid sodium sulfate. Filtration and evaporation yielded a crystalline residue (3.5 g.), m.p. 153–155°, raised to 172–174° by recrystallization from acetone. The product proved to be identical (mixture melting point and infrared spectral comparison) with the enone **3b** prepared above by hydrolysis of the enol ether **19d**.

17β-Hydroxy-5β,19-cycloandrost-1-en-3-one Acetate (**3c**). *A. By Direct Acetylation of* **3b**. A mixture of the 17β-alcohol **3b** (100 mg.), pyridine (0.2 ml.), and acetic anhydride (0.3 ml.) was kept at room temperature for 4 hr. The product was isolated and recrystallized from methanol to furnish the corresponding acetate **3c**: m.p. 133–135°; [α]D +145°; λ_{max} 272 mμ (log ε 3.76); ν_{max} 1730, 1667, 1240, and 1020 cm.$^{-1}$.

Anal. Calcd. for $C_{21}H_{28}O_3$: C, 76.79; H, 8.59. Found: C, 76.57; H, 8.73.

B. By Hydrolysis of the 3-Methyl Ether 17β-Acetate **19e**. A mixture of **19e** (300 mg.), 20% aqueous methanol (50 ml.), and oxalic acid (300 mg.) was heated under reflux for 10 min. The cooled mixture was diluted with ether (300 ml.), washed successively with 5% aqueous sodium carbonate and water, dried (sodium sulfate), and evaporated. Recrystallization of residue from acetone afforded the norcarenone **3c** (270 mg.), identical by melting point, mixture melting point, and infrared spectrum with the sample of **3c** prepared as described above.

5,10-Seco-5,19-cycloandrost-1(10),2,4-triene-3,17β-diol Acetate (**19f**). A mixture of the norcarenone **3b** (0.47 g.), pyridine (0.5 ml.), and acetic anhydride (1.5 ml.) was heated at steam-bath temperature for 2 hr. Isolation of the product in the usual manner gave the diacetate **19f** (0.52 g.), m.p. 138–145°; m.p. 155–158° after recrystallization from methanol: [α]D +108°; λ_{max} 285 mμ (log ε 3.72); ν_{max} 1755, 1738, 1620, 1603, 1512, 1248, 1215, 1122, 1020, 917, 821, and 765 cm.$^{-1}$; n.m.r. 57 (H-18), 122 (17β-OAc), 131 (3-OAc), 348 (4-H), 355 and *ca.* 361, 374 and *ca.* 388 (1- and 2-protons, doublets, J = *ca.* 6 c.p.s.), *ca.* 194.5 and 204.5, and a buried doublet (methylene bridge protons, J = *ca.* 10 c.p.s.).

Anal. Calcd. for $C_{23}H_{30}O_4$: C, 74.56; H, 8.16. Found: C, 74.38; H, 8.44.

5β,19-Cycloandrostan-3ξ,17β-diol 17-Acetate (**5c**). A solution of sodium borohydride (1.5 g.) in a mixture of dioxane (30 ml.) and water (15 ml.) was added dropwise with stirring to a solution of the norcarenone 17-acetate **3c** (3.26 g.) in dioxane (75 ml.). After 1 hr. the mixture was acidified with acetic acid, diluted with benzene, washed with 5% aqueous sodium bicarbonate followed by water to neutrality, and dried (sodium sulfate), and the solvent was evaporated. The solid residue (3.1 g.) was recrystallized from methanol to yield the saturated alcohol **5c** (2.1 g.), m.p. 145–148°, raised to 153–155° after two further crystallizations from methanol: [α]D +45°; ν_{max} 3460, 1740, 1260, and 1045 cm.$^{-1}$.

Anal. Calcd. for $C_{21}H_{32}O_3$: C, 75.86; H, 9.70. Found: C, 76.05; H, 9.44.

Oxidation of the above alcohol **5c** in acetone with 8 *N* chromic acid led to the corresponding saturated 3-ketone **5d**, identical by melting point, mixture melting point, and infrared spectrum with a sample prepared by hydrogenation of the corresponding Δ^1-3-ketone (*vide infra*).

17β-Hydroxy-5β,19-cycloandrostan-3-one Acetate (**5d**). Hydrogenation of an ethyl acetate solution of the norcarenone **3c** (700 mg.) over palladium on charcoal and recrystallization of the crude product from methanol afforded the saturated 3-ketone **5d** (400 mg.): m.p. 148–149°; [α]D +15°; ν_{max} 1740, 1705, 1255, 1240, 1040, and 1025 cm.$^{-1}$.

Anal. Calcd. for $C_{21}H_{30}O_3$: C, 76.32; H, 9.15. Found: C, 76.65; H, 9.20.

Reaction of Methyl Grignard with 17β-Hydroxy-5β,-19-cycloandrost-1-en-3-one (**3b**). To a 1 *N* ethereal methyl Grignard solution there was added a solution of the enone **3b** (2.19 g., 7 mmoles) in a mixture of benzene (75 ml.) and ether (35 ml.) during 15 min. The mixture was then stirred at room temperature for an additional 7 hr. and the product was isolated in the usual manner. The oil obtained thereby was adsorbed from hexane onto Florisil (100 g.) and eluted with hexane–ether (4:1). The first crystalline fractions consisted of the 3-methylcycloheptatriene derivative **19g** (676 mg.), m.p. 82–84° after three recrystallizations from methanol: [α]D +97°; λ_{max} 216 mμ (log ε 4.32) and 256 mμ (log ε 3.75); ν_{max} 3300, 1615, 1600, 1500, 1060, 1027, 822, and 735 cm.$^{-1}$; n.m.r. 53 (18-H), 126 (vinylic 3-Me), 210 (17α-H), 341.5 (4-H), 346 and 352, and 384 and 390 (1- and 2-protons, doublets, J = 6 c.p.s.), 185 and 195 (1-proton, J = 10 c.p.s., of a pair of doublets for the methylene bridge protons).

Anal. Calcd. for $C_{20}H_{28}O \cdot H_2O$: C, 79.42; H, 10.0. Found: C, 79.70; H, 9.92.

Acetylation of this alcohol **19g** (125 mg.) in a pyridine–acetic anhydride mixture and recrystallization of the crude product from methanol afforded the de-

rived *acetate ester* **19h**: m.p. 127–129°; $[\alpha]_D$ +48°; λ_{max} 216 mμ (log ε 4.35) and 257 mμ (log ε 3.79); ν_{max} 1730, 1610, 1597, 1253, 1240, 1225, 1045, 1025, 812, and 740 cm.$^{-1}$; n.m.r. 57.5 (18-H), 123 (OAc), 126.5 (3-Me), 278 (17α-H), *ca.* 348 and 354, *ca.* 386 and 392 (1- and 2-protons, J = *ca.* 6 c.p.s.), 343.5 (4-H), 43 and 53, and 184.5 and 194.5 (pair of doublets, J = 10 c.p.s., methylene bridge protons).

Anal. Calcd. for $C_{22}H_{30}O_2$: C, 80.93; H, 9.26; O, 9.80. Found: C, 80.59; H, 9.41; O, 9.60.

Further elution of the column with hexane–ether (1:1) afforded 17β-hydroxy-1α-methyl-5β,19-cycloandrost-3-one (**5e**, 500 mg.), m.p. 164–165° after recrystallization from acetone: $[\alpha]_D$ −74°; no absorption in the ultraviolet between 220 and 290 mμ; ν_{max} 3380, 1699, 1055, 1047, and 1028 cm.$^{-1}$; n.m.r. 45.5 (18-H), 66 (1α-Me, doublet, J = 6.7 c.p.s.), 153.5 (C-4-methylene), 209 (OH),220 (17α-), and 32 (cyclopropyl geminal protons, pair of doublets, J = 6 c.p.s., $\Delta\nu$ = 10 c.p.s.).

Anal. Calcd. for $C_{20}H_{30}O_2$: C, 79.42; H, 10.00. Found: C, 79.55; H, 10.27.

Finally, elution of the column with the same solvent system yielded unchanged starting material **3b** (510 mg.).

17β-Hydroxy-1α-methylandrost-4-en-3-one (**2d**).[45] A mixture of the 5β,19-cyclo-3-ketone **5e** (370 mg.), 95% ethanol (30 ml.), and 12 *N* hydrochloric (10 ml.) was heated under reflux for 3 hr. The cooled mixture was diluted with ether and washed with saturated aqueous sodium carbonate followed by water to neutrality. The oily residue obtained after removal of solvent was then adsorbed from hexane onto Florisil (25 g.). The first crystalline fractions eluted with hexane–ether (7:3) showed no absorption in the ultraviolet and consisted of unchanged starting material **5e** (65 mg.). There followed fractions consisting of mixtures of starting material and 1α-methyltestosterone (**2d**, 115 mg.), as shown by infrared spectral analysis and thin layer chromatography. The final fractions eluted with the same solvent system consisted of crystalline 1α-methyltestosterone (**2d**, 90 mg.), m.p. 200–207° after recrystallization from methanol: $[\alpha]_D$ +148°; λ_{max} 243 mμ (log ε 4.18) (lit.[45] m.p. 190–191°; λ_{max} 243 mμ (log ε 4.22); ν_{max} 3460, 1670, 1620, and 1075 cm.$^{-1}$).

Anal. Calcd. for $C_{20}H_{30}O_2$: C, 79.42; H, 10.00. Found: C, 79.12; H, 9.94.

1α,3ξ-Dimethyl-5,19-cycloandrostane-3ξ,17β-diol (**5f**). To an approximately 0.6 *M* ethereal solution of methyl magnesium bromide (60 ml.) there was added in 15 min. a solution of the 1α-methyl-3-ketone **5e** (800 mg.) in a mixture of benzene (10 ml.) and ether (30 ml.). The mixture was stirred for 1 additional hr. at room temperature; the product then was isolated in the usual manner and chromatographed on Florisil (50 g.). The crystalline fraction eluted with hexane–ether (4:1) consisted of the 1α,3ξ-dimethyl-3ξ,17β-diol (**5f**, 150 mg.), m.p. 180–182° after recrystallization from acetone: $[\alpha]_D$ +52°; ν_{max} 3380, 1060, 1025, 883, and 850 cm.$^{-1}$.

Anal. Calcd. for $C_{21}H_{34}O_2$: C, 79.19; H, 10.76. Found: C, 79.32; H, 10.83.

The crystalline fractions further eluted with hexane–ether (1:1) consisted of starting material **5e** (160 mg.).

10β-Fluoro-17β-hydroxy-5,10-seco-5,19-cycloandrost-4-en-3-one (**31**). A solution of the dione **4a** (2.4 g.) in dry tetrahydrofuran (15 ml.) was added dropwise with stirring in 15 min. to a suspension of lithium aluminum hydride (2.0 g.) in tetrahydrofuran (100 ml.). The mixture was stirred at room temperature for 2 hr. Isolation of the product in the usual manner afforded an oily mixture of the corresponding diol **4b**. The latter was taken up in dry dioxane (10 ml.), a solution of dichlorodicyanobenzoquinone (4.0 g.) in dry dioxane (15 ml.) was added, and the mixture was set aside at room temperature for 15 hr. The total reaction mixture was passed through a column of neutral alumina. Elution with methylene chloride afforded discolored crystalline fractions (1.9 g.) which were again chromatographed over a column of alumina eluting with methylene chloride to yield a colorless, crystalline product. Two crystallizations from acetone afforded the conjugated ketone **4c**, m.p. 155–157°; $[\alpha]_D$ −126°; λ_{max} 242 mμ (log ε 4.14); ν_{max} 3360, 1645, and 1035 cm.$^{-1}$.

Anal. Calcd. for $C_{19}H_{27}FO_2$: C, 74.47; H, 8.88; F, 6.20. Found: C, 73.93; H, 9.13; F, 6.13.

Acetylation of **4c** in an acetic anhydride–pyridine mixture afforded the 17β-acetate **4d** which was purified by recrystallization from methanol: m.p. 128–130°; $[\alpha]_D$ −112°; λ_{max} 242 mμ (log ε 4.13); ν_{max} 1730, 1655, 1258, 1050, 1035, 980, and 905 cm.$^{-1}$.

Anal. Calcd. for $C_{21}H_{24}FO_3$: C, 72.38; H, 8.38; F, 5.45. Found: C, 72.34; H, 8.38; F, 5.59.

Reduction of the Dione **4a** *with an Excess of Lithium Aluminum Hydride and Oxidation of the Resulting Diols.* A solution of the fluorodione **4a** (2.0 g., purity 98%) in dry tetrahydrofuran (30 ml.) was added in 15 min. to a stirred suspension of lithium aluminum hydride (4.0 g.) in dry ether (200 ml.). The mixture was stirred at room temperature for 16 hr. The oily product (2.0 g.), isolated in the usual manner, was stirred at room temperature with a suspension of manganese dioxide (40 g.) in chloroform (200 ml.) for 20 hr. Filtration and evaporation afforded an oil (1.68 g.) which was chromatographed on Florisil (100 g.). The first crystalline fractions eluted with hexane–ether (3:2) were homogeneous by thin layer plate chromatography and consisted of 5,19-cycloandrostan-3ξ,17β-ol (**5b**, 120 mg.), m.p. 150–153° after a single recrystallization from acetone. This product was identical by mixture melting point and infrared spectral comparison with a sample of **5b** prepared by two independent routes already described above.

Oxidation of the diol **5b** in acetone with 8 *N* chromic acid gave the known dione **5a** which was identified by mixture melting point and infrared spectral comparison with dione **5a** obtained by catalytic hydrogenation of the 1-en-3-one **3a**.

The corresponding *diacetate* **5g** was prepared by exposure of the diol **5b** to pyridine–acetic anhydride mixture at room temperature and work-up in the normal manner. The diester **5g** showed m.p. 120–122° after two crystallizations from methanol: $[\alpha]_D$ +62°; ν_{max} 1740, 1250, 1220, 1110, 1040, and 915 cm.$^{-1}$.

Anal. Calcd. for $C_{23}H_{34}O_4$: C, 73.76; H, 9.15. Found: C, 74.07; H, 9.01.

Continued elution of the column with hexane–ether (3:2) yielded additional crystalline fractions (130 mg.), m.p. 130–135°, consisting of the diol **5b** of 80% purity as

estimated by paper chromatography. The yield of this diol thus amounted to 224 mg. (13.3% from **4a**).

The crystalline fractions obtained by further elution with the same solvent system consisted of 17β-hydroxy-5,10-seco-5,19-cycloandrost-4-en-3-one (**4e**, 480 mg., 29.2% from **4a**), m.p. 155–156° after recrystallization from methanol: $[\alpha]_D$ −169°; λ_{max} 246 mμ (log ε 4.16); ν_{max} 3440, 1660, 1060, 867, 832, and 670 cm.$^{-1}$; n.m.r. 47.5 (18-H) and 344 c.p.s. (4-H).

Anal. Calcd. for $C_{19}H_{28}O_2$: C, 79.12; H, 9.79. Found: C, 78.94; H, 9.52.

Finally, elution with the same solvent system afforded crystalline 5,10-seco-5,19-cycloandrost-4-ene-3,17-dione (**4f**, 130 mg., 18% from **4a**), m.p. 166–168° after recrystallization from methanol: $[\alpha]_D$ −164°; λ_{max} 246 mμ (log ε 4.16); ν_{max} 1738, 1663, 1640 (shoulder), 1060, 828, 818, and 670 cm.$^{-1}$; n.m.r. 55 (18-H) and 346 c.p.s. (4-H).

Anal. Calcd. for $C_{19}H_{26}O_2$: C, 79.68; H, 9.15. Found: C, 79.70; H, 9.21.

Lithium Aluminum Hydride Reduction of the Saturated 10-Fluoro-3,17-dione **6a**. A solution of the dione **6a** (1.0 g.) in anhydrous ether (50 ml.) was added dropwise with stirring to a suspension of lithium aluminum hydride (1.0 g.) in ether (100 ml.). Stirring was continued for 1 hr. at room temperature and the product was isolated in the usual manner. The crude product (990 mg.) was recrystallized from acetone to give the corresponding saturated diol **6b**, m.p. 137–139°, $[\alpha]_D$ +71°; ν_{max} 3140–3530 and 1025 cm.$^{-1}$.

Anal. Calcd. for $C_{19}H_{32}O_2$: C, 78.03; H, 11.03. Found: C, 78.35; H, 10.97.

Acetylation of the saturated diol **6b** (100 mg.) in a mixture of pyridine (1 ml.) and acetic anhydride (3 ml.) afforded the derived *diacetate* **6c** which was purified by recrystallization from methanol. The analytical sample had m.p. 108–109°; $[\alpha]_D$ +58°; ν_{max} 1740, 1245, 1033, and 960 cm.$^{-1}$.

Anal. Calcd. for $C_{23}H_{36}O_4$: C, 73.36; H, 9.64. Found: C, 73.35; H, 9.40.

The saturated *dione* **6d** corresponding to the above saturated diol **6b** was prepared when the latter (350 mg.) was oxidized in acetone (20 ml.) at 0–5° with 8 *N* chromic acid in the usual manner. The product was isolated by dilution with water and filtration. Recrystallization from acetone afforded **6d**, m.p. 161–162°, $[\alpha]_D$ +148°; ν_{max} 1735, 1698, 1255, 1125, 1115, 1050, 1005, 920, and 850 cm.$^{-1}$.

Anal. Calcd. for $C_{19}H_{28}O_2$: C, 79.12; H, 9.79. Found: C, 79.32; H, 9.41.

Catalytic Hydrogenation of 17β-Hydroxy-5,10-seco-5,19-cyclo-10ξ-androst-4-en-3-one (**4e**). Hydrogenation of the enone **4e** (200 mg.) in absolute ethanol (40 ml.) over a 5% palladium-on-charcoal catalyst (200 mg.) resulted in an uptake of 1 molar equiv. of hydrogen in 20 min. Recrystallization of the crude product from hexane gave the saturated ketone **6e**: m.p. 90–92°; $[\alpha]_D$ −21°; ν_{max} 3280, 1705, and 1050 cm.$^{-1}$.

Anal. Calcd. for $C_{19}H_{30}O_2$: C, 78.57; H, 10.41. Found: C, 78.29; H, 10.54.

Oxidation of the 17β-hydroxy-β-ketone **6e** (70 mg.) was accomplished in acetone with 8 *N* chromic acid as described above. Recrystallization of the product from methanol afforded the corresponding *dione* **6f**, a stereoisomer of the dione **6d**, and showing m.p. 154–155°; $[\alpha]_D$ +66°; ν_{max} 1733, 1690, 1250, 1208, 1120, 1055, 1010, and 920 cm.$^{-1}$.

Anal. Calcd. for $C_{19}H_{28}O_2$: C, 79.12; H, 9.79. Found: C, 79.39; H, 10.05.

Lithium Aluminum Hydride Reduction of the Saturated Dione **6f**. A solution of the dione **6f** (135 mg.) in dry tetrahydrofuran (5 ml.) was added to a suspension of lithium aluminum hydride (130 mg.) in tetrahydrofuran (15 ml.). The mixture was stirred at room temperature for 30 min. and the product was isolated in the normal manner. Recrystallization from acetone gave a saturated *diol* **6g**, stereoisomeric with **6b**, with m.p. 140–143°, $[\alpha]_D$ −24°, ν_{max} 3100–3520 and 1025 cm.$^{-1}$.

Anal. Calcd. for $C_{19}H_{32}O_2$: C, 78.03; H, 11.03. Found: C, 77.99; H, 11.03.

Acetylation of this diol **6g** in a pyridine–acetic anhydride mixture afforded the corresponding *diacetate* **6h**, a stereoisomer of **6c**, and showing m.p. 116–118°; $[\alpha]_D$ −27°; ν_{max} 1730, 1245, 1045, 1028, 938, and 830 cm.$^{-1}$.

Anal. Calcd. for $C_{23}H_{34}O_4$: C, 78.03; H, 11.03. Found: C, 77.99; H, 11.03.