The Addition of Dihalocarbenes to 3β-Acetoxy-*B*-norandrost-5-en-17-one

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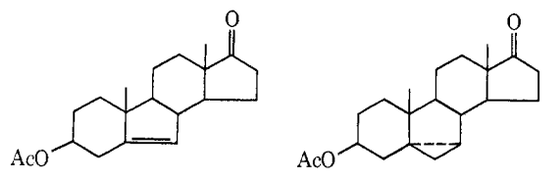
Depending on the nature of the dihalocarbene used and the stereochemistry of its addition to the title olefin, either a stable bicyclo[3.1.0]hexane ring system is formed or rearrangement occurs readily to give a 6,7-dihalo-Δ^5 steroid. Cyclopropane derivatives **8** and **9** are formed, respectively, from difluorocarbene and from chlorofluorocarbene when the latter adds to give an α-endo-F product. Both dichlorocarbene addition and the α-endo-Cl derivative arising from the reaction with chlorofluorocarbene give rise to 6,7-dihalo-Δ^5 steroids **6** and **12** *via* spontaneous ring opening of the initially formed cyclopropyl intermediates. Unlike the β addition of difluorocarbene to "normal" $\Delta^{5(6)}$ steroid olefins, the reaction with Δ^5 *B*-norsteroids occurs from the α face.

Recently[1] the Simmons–Smith reaction has been applied to the unsaturated *B*-norsteroid **1** to form the 5,7α and 5,7β cyclosteroids **2** and **3**, respectively, the latter compound being formed almost exclusively.



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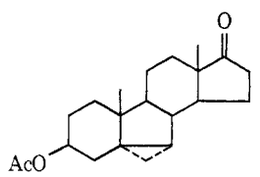

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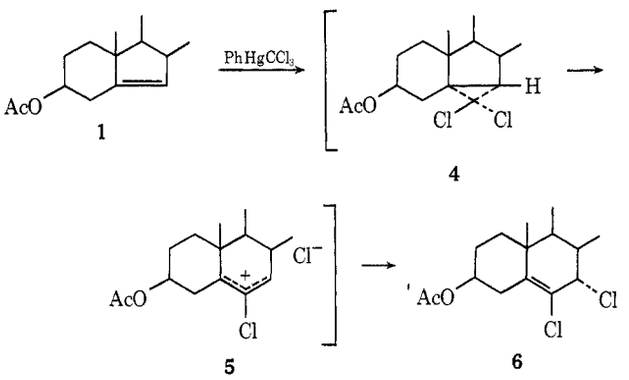
When a dihalogenocarbene is used in place of methylene for the formation of the bicyclo[3.1.0]hexane system, the reaction displays several interesting aspects which are not present in the unsubstituted case. Firstly, depending on ring strain and the halide used, the products formed are found to be either the 5,7 cyclosteroids or compounds derived from a thermal rearrangement of the initially formed adduct. Secondly, the thermal rearrangement observed suggests a concerted heterolytic process,[2] subject to the same stereochemical consequences predicted for the concerted rearrangement of a cyclopropyl cation ion *via* a solvolysis.[3]

Previous studies have indicated that both dichloro- and dibromocarbenes generated either from haloform and *tert*-alkoxide or the thermal decomposition of sodium trihaloacetates fail to add to $\Delta^{5(6)}$ steroids possessing a 10β-methyl group. In contrast, difluorocarbene has been shown to add β to the $\Delta^{5(6)}$ position.[4] Attempts to isolate any addition product from the reaction of **1** and dichlorocarbene generated from the thermal decomposition of the sodium salt of trichloroacetic acid in diglyme[5] proved fruitless. Apparently the steric requirements for addition are such as to allow the side reaction between the carbene and the trichloroacetate anion to predominate.[6,7]

The use of phenyl(trichloromethyl)mercury,[8] which has been shown to react with olefins by a free carbene mechanism,[9] results in the effective addition of dichlorocarbene to the *B*-norsteroid **1**.[10] In contrast to 6,6-dichlorobicyclo[3.1.0]hexane, which is thermally stable to heating at 75° for 2 hr in tetrahydrofuran,[11] the strained 6,6-dichlorobicyclo[3.1.0]hexane system present in compound **4** undergoes a spontaneous rearrangement at 80° *via* the ion pair **5** to form the allylic product **6**.



1 **4** **5** **6**

The axial configuration of the C-7 chlorine of compound **6** was determined by nmr spectroscopy: d of d at δ 4.4 (J_{7-8} = 3.4, J_{7-4} = 1.5 Hz). Because of the stereospecificity shown for the recapture step, *i.e.*,

(1) J. Joska, J. Fajkos, and F. Sorm, *Collect. Czech. Chem. Commun.*, **33**, 2049, 3342 (1968).

(2) M. S. Baird and C. B. Reese, *Tetrahedron Lett.*, 1379 (1967); 2117 (1969); D. C. F. Law and S. T. Tobey, *J. Amer. Chem. Soc.*, **90**, 2376 (1968); M. S. Baird, D. G. Lindsay, and C. B. Reese, *J. Chem. Soc. C*, 1173 (1969); C. W. Jefford and W. Wojnarowski, *Tetrahedron*, **25**, 2089 (1969).

(3) P. v. R. Schleyer, G. W. Van Dine, U. Schöllkopf, and J. Paust, *J. Amer. Chem. Soc.*, **88**, 2868 (1966); C. H. DePuy, L. G. Schnack, and J. W. Hausser, *ibid.*, **88**, 3343 (1966).

(4) L. H. Knox, E. Verlarde, S. Berger, D. Cuadriello, P. W. Landis, and A. Cross, *ibid.*, **85**, 1851 (1959).

(5) W. M. Wagner, *Proc. Chem. Soc.*, 229 (1959).

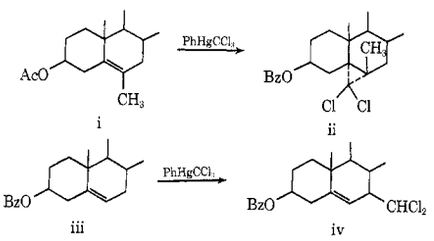
(6) W. M. Wagner, H. Kloosterziel, and S. van der Ven, *Recl. Trav. Chim. Pays-Bas*, **80**, 740 (1961).

(7) W. M. Wagner, H. Kloosterziel, and A. F. Bickel, *ibid.*, **81**, 925, 933 (1962).

(8) D. Seyferth, J. M. Berlitch, R. J. Minasz, J. Y.-P. Mui, H. D. Simmons, Jr., A. J. H. Treiber, and S. R. Dowd, *J. Amer. Chem. Soc.*, **87**, 4259 (1965).

(9) D. Seyferth, J. Y.-P. Mui, and J. M. Burlitch, *ibid.*, **89**, 4953 (1967).

(10) The phenyl(trichloromethyl) mercury reagent has recently been used as starting material for the addition of dichlorocarbene to the hindered Δ^5 position of 6-methylcholesteryl acetate (i) to give ii. Cholesteryl benzoate (iii) failed to give addition and afforded the allylic insertion product iv [F. T. Bond and R. H. Cornelia, *Chem. Commun.*, 1189 (1968)].

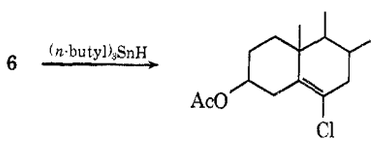


i ii iii iv

(11) E. Bergman, *J. Org. Chem.*, **28**, 2210 (1963).

5 → **6**, in similar dichlorpropane rearrangements,[12] the axial (α) configuration of the C-7 chlorine in compound **6** clearly leads to the 5,7β assignment of configuration for the initially formed cyclopropyl derivative **4**.

The allylic nature of the 7-chloro substituent in compound **6** was demonstrated by its hydrogenolysis with tributyltin hydride[13] to the known monochloro derivative **7**.[14]



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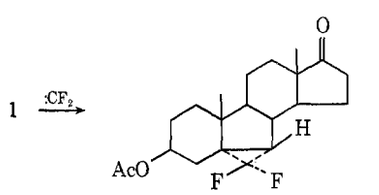
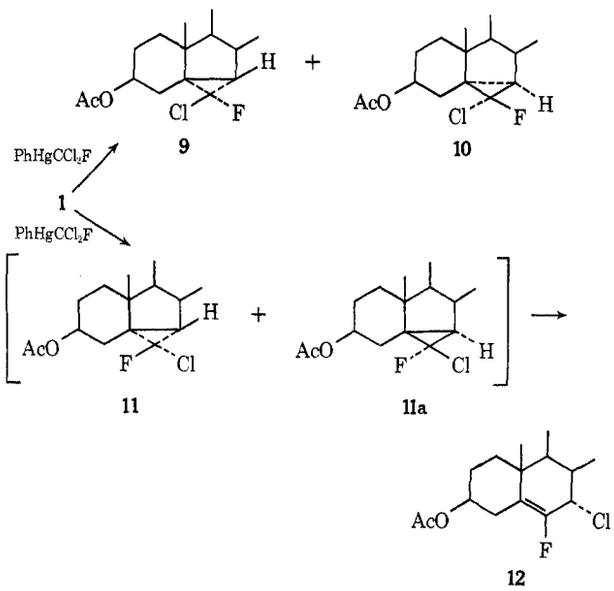
It was anticipated that the difluorocarbene generated by thermal decomposition of sodium difluorochloroacetate would successfully add to the *B*-norsteroid **1**, since $:CF_2$ produced in a like manner has previously been shown to add readily to the double bond of steroidal 5-ene systems.[4] Ring opening of such an adduct, *i.e.*, **4** → **6**, would require ionization of a fluorine atom. Since the rate of thermal rearrangement will depend on the ionizing ability of the leaving groups, *i.e.*, $Br^- > Cl^- > F^-$,[15] it was anticipated that the difluorocarbene adduct would be considerably more stable than the corresponding dichloro derivative; therefore, isolation of the cyclopropyl addition product should be possible. When compound **1** was treated with difluorocarbene generated by the dropwise addition of a solution of the sodium salt of difluorochloroacetate in diglyme[16] to a refluxing solution of **1** in the same solvent, the adduct **8** was formed in 65% yield.



8

Inspection of a Dreiding model of the 5,7α adduct indicates that a splitting of the C-19 H signal by long-range coupling with the β-endo-F atom would be expected since the geometrical requirements of the converging vector rule are fulfilled.[17] The nmr spectra of **8** reveals a sharp singlet, δ 1.07, for the C-19 angular Me proton resonance, suggestive therefore of the 5,7β stereochemistry.

The thermal stability of the difluorocarbene adduct as compared to the spontaneous rearrangement of the dichlorocarbene adduct demonstrates the dependence on the ionizing ability of the leaving group. As a means of clarifying the stereochemical factors involved in the ease of rearrangement, **1** was treated with fluorochlorocarbene generated by the thermolysis of phenyl(fluorodichloromethyl)mercury.[18] As expected, the reaction led to a mixture of products containing the cyclopropyl adducts **9** or **10** as well as the rearranged product **12**.



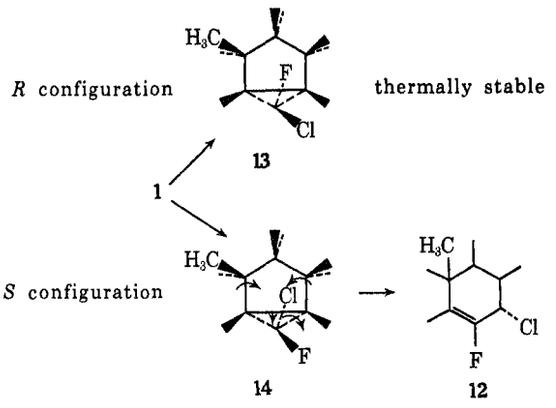
There has recently been much work regarding the ring opening of halocyclopropanes and it is well established that a stereospecific opening of the ring is concerted with the departure of the leaving group.[3,19] The concerted rearrangement of a cyclopropyl to an allylic cation should proceed by a stereospecific disrotatory process such that the groups trans to the leaving group rotate outward and those cis to it rotate inward.[20] In a bicyclo[3.1.0]hexane system such as **11**, however, the outward rotatory process is strongly hindered, since a six-membered ring cannot accommodate the trans,trans allyl cation which would be formed. On the other hand, an inward rotatory process is possible, since the cis,cis allyl cation is permissible in a six-membered ring system.

Application of these concepts to the present case predicts that compound **12** is the result of ring opening of a cyclopropyl derivative **11** or **11a** having the halides disposed in the *S* configuration, *i.e.*, **14**.

The nmr spectrum of compound **12**, d of d at δ 4.44 (J_{7-8} = 3.5, J_{7-4} = 1.5 Hz), is almost identical with that found for compound **6** and strongly suggests that the chlorine at C-7 is axial (α). The necessity for sterospecific[12] recapture of the halide in the ion pair produced by ring opening leads to the conclusion that **11** and not **11a** represents the initially formed cyclopropyl precursor of **12**.

The thermally stable chlorofluoro adduct, on the other hand, must possess the *R* configuration, *i.e.*, **13**, since in this form only ionization of the fluorine atom is permissible for ring opening. As discussed previously for the difluoro adduct **8**, compound **10** would be expected to show splitting of the C-19 H signal by long-range coupling with the fluorine atom.[17] This was not found to be the case, implying again an α addition leading to compound **9**.

(12) I. Fleming and E. J. Thomas, *Tetrahedron Lett.*, 2485 (1971).
(13) G. I. M. Van Der Kerk, J. G. Naltes, and J. G. H. Suijten, *J. Appl. Chem.*, **7**, 366 (1937).
(14) J. S. Mihina, *J. Org. Chem.*, **27**, 2807 (1962).
(15) J. Hine, "Physical Organic Chemistry," 2nd ed, McGraw-Hill, New York, N. Y., 1962,p184.
(16) J. M. Birchall, G. W. Cross, and R. N. Haszeldine, *Proc. Chem. Soc.*, **81** (1960).
(17) A. Cross and P. W. Landis, *J. Amer. Chem. Soc.*, **86**, 4005 (1964).
(18) D. Seyferth and K. V. Darragh, *J. Organometal Chem.*, **11**, 9 (1968).
(19) C. S. Foote, *J. Amer. Chem. Soc.*, **86**, 1853 (1964); P. v. R. Schleyer, *ibid.*, **86**, 1854 (1966).
(20) R. B. Woodward and R. Hoffmann, *ibid.*, **87**, 395 (1965).



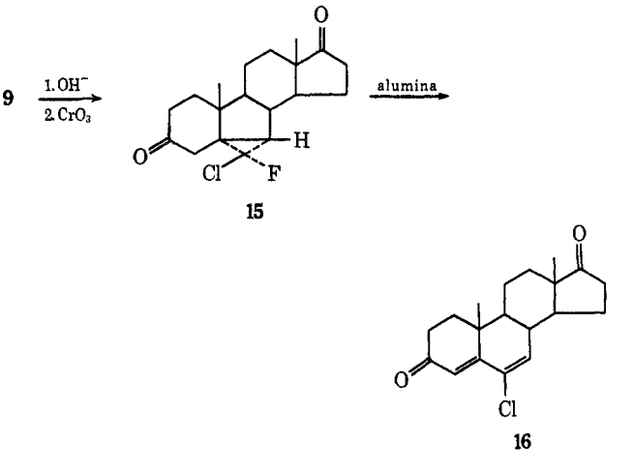
Molecular rotation differences calculated for 3β-acetoxy-*B*-norandrost-5-en-17-one (1) and appropriate derivatives (Table I) further support the 5,7β configuration of the difluoro adduct **8** as well as the chlorofluoro derivative **9**. The molecular rotation changes observed on passing from 3β-acetoxy-*B*-norandrost-5-en-17-one (1) to the difluoro adduct **8** and the chlorofluoro compound **9** are positive. These changes parallel more closely the molecular rotation change observed on passing from **1** to the α-epoxide B as compared to the β-epoxide A.

TABLE I
MOLECULAR ROTATION DATA FOR 3β-ACETOXY-*B*-NORANDROST-5-EN-17-ONE AND SOME DERIVATIVES

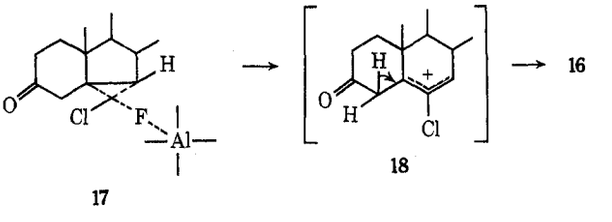
	[M]D		Δ[M]D
3β-Acetoxy-*B*-norandrost-5-en-17-one (1)[a]	−165°		
3β-Acetoxy-5β,6β-oxido-*B*-norandrostan-17-one (A)[b]	+200.8°	A–1	+365°
3β-Acetoxy-5α,6α-oxido-*B*-norandrostan-17-one (B)[c]	+63°	B–1	+228°
6,6-Difluoro-3β-acetoxy-5,7-cyclo-5β-androstan-17-one (**8**)	+109°	8–1	+274°
6-Chloro-6-fluoro-(*R*)-3β-acetoxy-5,7-cyclo-5β-androstan-17-one (**9**)	+88°	9–1	+253°

[a] See J. Joska and F. Sorm, *Collect. Czech. Chem. Commun.*, **23**, 1377 (1958). [b] J. Joska and J. Fajkos, *ibid.*, **28**, 621 (1963). [c] J. Joska, J. Fajkos, and F. Sorm, *ibid.*, **28**, 82 (1963).

The thermally stable α-F endo derivative **15** derived from the acetate **9** would be expected to ring open as predicted by the Woodward–Hoffmann–DePuy rule if ionization of the fluorine atom could be realized. However, the lack of reactivity of alkyl fluorides toward normal solvolysis reactions would tend to preclude such a reaction leading to rearranged product. On the other hand, the greater reactivity shown by alkyl fluorides as compared to other alkyl halides in the Friedel–Crafts reaction[21] suggested the use of a Lewis acid as a catalyst for the ring-opening reaction. The cyclopropyl derivative **9** was hydrolyzed and then oxidized with Jones reagent to the dione **15** which, when treated with neutral alumina (grade I), quantitatively rearranged to the diene **16**.



The alumina in the role of a Lewis acid can be pictured to bring about the loss of fluoride ion with simultaneous ring opening leading to the ion pair **18**. Loss of a proton at C-4 then affords the observed product **16**.[22]

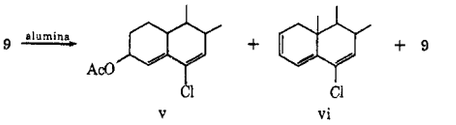


Evidence for structure **16** was provided by the observed *m/e* 318 molecular ion peak and by comparison with the known absorption maxima and melting point.[23]

The necessary condition of maximum overlap which is postulated for the transition state of the addition of a dihalocarbene to a $\Delta^{5(6)}$ steroid olefin requires a β-axial attack of the carbene at the C-6 position with the development of a partial positive charge at tertiary C-5.[4,10] The inability of dichlorocarbene to give any β-addition product[10] is rationalized as being due to the steric hindrance of the 10β-methyl group. The fact that no α-addition product is observed may be rationalized as being due to a transition state which would require an axial attack at C-5 with the development of a partial positive charge at the secondary C-6. In the case of 6-methyl cholesteryl acetate, however, where axial attack at C-5 would lead to a positive charge at tertiary C-6, an α-addition product has been realized under forcing conditions.[10] With the smaller difluorocarbene the electronic requirement of maximum overlap outweighs the steric hindrance to the β-face ap-

(21) G. A. Olah, "Friedel-Crafts and Related Reactions," Interscience, New York, N. Y., 1964, p 428. For the acid-catalyzed solvolysis of alkyl fluorides, see A. Streitwieser, "Solvolytic Displacement Reactions," McGraw-Hill, New York, N. Y., 1962, p 50.

(22) When compound **9** was treated with alumina, ring opening also occurred. In this case, however the major product v was contaminated with starting material **9** as well as triene vi.



(23) K. Brückner, B. Hampel, and V. Johnsen, *Chem. Ber.*, **94**, 1225 (1961).

proach.[24] In the case of the *B*-norandrost-5-ene steroid, inspection of a Dreiding model leads to the conclusion that a carbene addition to the double bond from the β face will encounter a greater steric repulsion from the 10β-methyl group than is found in the normal $\Delta^{5(6)}$ steroid. Since the necessity for maximum overlap in the transition state at the C-6 position in the *B*-norsteroid may be accommodated at the α face, the α-side addition of a dihalocarbene to a *B*-norsteroid can be considered to be the most favored process in light of the steric and electronic considerations.

Experimental Section

General.—All melting points were taken in glass capillaries and are corrected. The nuclear magnetic resonance spectra were determined using a Varian A-60 spectrometer with tetramethylsilane as the internal standard. A Cary 14 spectrophotometer was used to obtain the ultraviolet spectra. The high-resolution mass spectra were obtained with a Consolidated Electrodynamics Corp. 21-110 mass spectrometer.

3β-Acetoxy-*B*-norandrost-5-en-17-one (1).—A solution of 50 g (0.15 mol) of 3β-acetoxyandrost-5-en-17-one in 500 ml of methylene chloride was ozonized at −70° with an ozone flow of approximately 0.04 mol/hr. At the end of 3 hr the solution turned blue, the ozone was stopped, and the solution was flushed with a stream of nitrogen. The colorless solution was then added dropwise at 0° to a mixture of 100 g of zinc powder in 500 ml of acetic acid and stirred at that temperature for 6 hr. At the end of this time the methylene chloride was removed under reduced pressure and the residue was dissolved in 1.2 l. of 90% acetic acid. To the solution at 0° was added dropwise a solution of 20 g of chromium trioxide dissolved in 400 ml of 90% acetic acid. The mixture was stirred at room temperature for 5 hr, after which time 100 ml of ethanol was added and the mixture was stirred for an additional 15 min. The solvent was then removed at 35° under high vacuum and the residue was treated with 2 l. of water. The mixture was then extracted with ether and the ether solution was repeatedly washed with water. The ether solution was then dried ($MgSO_4$) and the solvent was removed under reduced pressure. The crude keto acid was dissolved in 100 ml of pyridine followed by the addition at 0° of 50 ml of benzoyl chloride. The mixture was then stirred at room temperature for 48 hr, cooled to 0°, and 50 ml of methanol was added. After the solution was stirred for 30 min, 2.5 l. of water was added and the mixture was extracted with ether–methylene chloride (9:1). The organic layer was washed with water and dilute hydrochloric acid (until pyridine is completely removed) and dried ($MgSO_4$). The solvent was then removed under reduced pressure and the residue was triturated with ether to give 18 g of yellow, crystalline β-lactone, mp 168–172°. The solvent was removed from the mother liquor under reduced pressure and the residue was pyrolyzed at 200° (0.1 mm) for 10 min. The crude product was dissolved in a small amount of benzene and washed through 200 g of neutral alumina (grade I) with 1 l. of benzene to give 11 g of 1, mp 129–133°. Pyrolysis of the crystalline β-lactone (18 g) afforded an additional 15 g of 1, mp 133–135°, total yield 26 g (55%) (lit.[25] mp 135–136°).

6,7α-Dichloro-3β-acetoxyandrost-5-en-17-one (6).—A solution of 0.5 g (1.5 mmol) of 1 and 1.18 g (3.0 mmol) of phenyltrichloromethylmercury in 5 ml of dry benzene was refluxed under nitrogen for 48 hr. The mixture was filtered and the solvent was removed under reduced pressure. The residue was chromatographed on 15 g of silica gel. From a 3% ethyl acetate–benzene eluent was obtained 0.35 g of crude product. Crystallization from ether gave 0.2 g of 6, mp 180° dec, $[\alpha]^{25}D$ −79.9° (*c* 0.99, $CHCl_3$).

Anal. Calcd for $C_{21}H_{28}Cl_2O_3$: C, 63.16; H, 7.07; Cl, 17.76. Found: C, 62.86; H, 7.11; Cl, 17.92.

6,6-Difluoro-3β-acetoxy-5,7-cyclo-5β-androstan-17-one (8).—To a refluxing solution of 1 g (3.0 mmol) of 1 in 10 ml of dry diglyme was added over a 45-min period a solution of 7.1 g of the sodium salt of chlorodifluoroacetic acid dissolved in 50 ml of diglyme. After the addition was completed the mixture was refluxed for another 15 min and the solvent was removed under high vacuum. The residue was suspended in a small amount of benzene and washed through 15 g of neutral alumina (grade I) to give 0.71 g of crude product. Crystallization from methylene chloride–ether afforded 0.5 g of 8, mp 187.5–189.5°, $[\alpha]^{25}D$ +29.76° (*c* 1.58, $CHCl_3$).

Anal. Calcd for $C_{21}H_{28}F_2O_3$: C, 68.83; H, 7.70. Found: C, 69.03; H, 7.84.

6-Chloro-6-fluoro-(*R*)-3β-acetoxy-5,7-cyclo-5β-androstan-17-one (9) and 6-Fluoro-7α-chloro-3β-acetoxyandrost-5-en-17-one (12).—A solution of 3 g (9.0 mmol) of 1 and 6 g (15.8 mmol) of phenyl(fluorodichloromethyl)mercury in 50 ml of dry benzene was refluxed for 48 hr. The precipitated phenylmercuric chloride was filtered and the filtrate was concentrated under reduced pressure. The resultant semisolid was chromatographed on 75 g of silica gel. Elution with 1% ethyl acetate–benzene gave several fractions consisting mostly of 9 (by tlc analysis). These fractions were combined and crystallized from methylene chloride–ether to give 0.45 g of 9, mp 194–196° dec, $[\alpha]^{25}D$ +23.1° (*c* 0.69, $CHCl_3$).

Anal. Calcd for $C_{21}H_{28}ClFO_3$: C, 65.87; H, 7.37; F, 4.96. Found: C, 65.92; H, 7.38; F, 5.08.

Continuation of the chromatography with 1% ethyl acetate–benzene afforded 0.65 g of crude 12. Crystallization from ether gave 0.5 g of 12: mp 178° dec; $[\alpha]^{25}D$ −133.1° (*c* 0.42, $CHCl_3$); nmr ($CDCl_3$) δ 4.44 (d of d, $J_{7-8} = 3.5$, $J_{7-4} = 1.5$ Hz).

Anal. Calcd for $C_{21}H_{28}ClFO_3$: C, 65.87; H, 7.37; Cl, 9.26; F, 4.96. Found: C, 65.50; H, 7.43; Cl, 9.24; F, 4.62.

6-Chloro-6-fluoro-(*R*)-5,7-cyclo-5β-androstane-3,17-dione (15).—To a solution of 0.325 g (0.85 mmol) of 9 dissolved in 10 ml of glyme was added 3.5 ml of a 0.244 *M* solution of sodium hydroxide in ethanol. After the solution was stirred for 20 min at room temperature the solvent was removed under reduced pressure and water was added to the residue. The mixture was extracted with ether and the ether solution was dried ($MgSO_4$). The solvent was removed to give 0.298 g of crude 3β-alcohol. The alcohol (0.29 g) was dissolved in acetone (10 ml) and 0.23 ml of Jones reagent was added at 0°. The mixture was stirred at this temperature for 25 min, after which time 1 ml of isopropyl alcohol was added. The solvent was removed under reduced pressure and the residue was extracted with ether. The ether solution was dried ($MgSO_4$) and the solvent was removed. Crystallization of the residue from ether–methylene chloride gave 0.205 g of 15, mp 182° dec, $[\alpha]^{26}D$ +118.2° (*c* 0.80, $CHCl_3$).

Anal. Calcd for $C_{19}H_{24}ClFO_2$: C, 67.35; H, 7.14; Cl, 10.46; F, 5.60. Found: C, 67.55; H, 7.37; Cl, 10,67; F, 5.71.

6-Chloro-4,6-androstadiene-3,17-dione (16).—A mixture of 2 g of neutral alumina (grade I) and a solution of 53.1 mg of 15 dissolved in 15 ml of dry benzene was stirred overnight. The mixture was filtered and the alumina was extracted with ethyl acetate. The benzene and ethyl acetate solutions were combined and the solvents were removed under reduced pressure to give 48.6 mg of crude 16. Trituration with ether afforded 40 mg of 16, mp 194–197° (lit.[24] mp 193–194°), λ_{max}^{EtOH} 284 mμ (ϵ 20,200).

Registry No.—1, 5323-23-9; 6, 37108-24-0; 8, 37108-25-1; 9, 37108-26-2; 12, 37108-27-3; 15, 37108-28-4.

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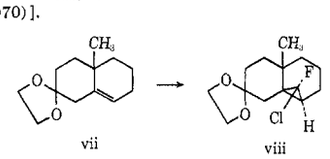
(24) In support of these arguments, the addition of chlorofluorocarbene to 10-methyl-Δ^8-2-octalone 2-ethylene acetal (vii) has recently been shown to take place with almost exclusive β-endo-F stereoselectivity leading to compound viii [R. A. Moss, R. W. Kleinman, and K. L. Williamson, *Chem. Commun.*, 927 (1970)].



vii viii

(25) J. Joska and F. Sorm, *Collect. Czech. Chem. Commun.*, **23**, 1377 (1958).