[CONTRIBUTION FROM THE RESEARCH LABORATORIES OF SYNTEX, S.A., MEXICO D. F., MEX.]

Steroids. CCXXVII.[1-3] Steroidal Dihalocyclopropanes

BY LAWRENCE H. KNOX, ESPERANZA VELARDE, SARAH BERGER, DOLORES CUADRIELLO, PAUL W. LANDIS[4] AND ALEXANDER D. CROSS

RECEIVED FEBRUARY 7, 1963

The addition of dichloro- and difluorocarbenes to unsaturated steroids is described. Differences in the relative reactivities of dihalocarbenes toward monoölefinic steroids, conjugated and unconjugated steroidal dienes, and the geometry of the adducts are also discussed. Structural assignments are based on infrared spectral data, proton magnetic resonance spectral studies, and on considerations of steric and electronic factors governing the reactions.

Knowledge of the chemistry and biological activity of steroids containing a cyclopropane ring was limited, until recently, to the *i*-steroids,[5] 16,17-methylene-20-keto-steroids[6] and a few photochemically-induced rearrangement products.[7] Accordingly, a general method was sought for the preparation of this class of compounds. This paper describes the addition of dihalocarbenes to several unsaturated steroids with the formation of steroidal dihalocyclopropanes, and the comparative behavior of dichloro- and difluorocarbenes is discussed.

In the interval since initiation of our investigation, numerous new steroidal cyclopropanes have been reported. Addition of diazomethane to an α,β-unsaturated ketone followed by expulsion of nitrogen from the resultant pyrazoline, the method utilized first for preparation of the 16,17-methylene steroids,[6] has since been successfully applied to the synthesis of 1,2-methylene-3-keto-[8] and 16,16-spirocyclopropyl-20-keto-steroids.[9] Internal displacement of an electronegative substituent from the γ-carbon of a keto-steroid by an anion generated at the α-carbon atom has been utilized to synthesize $9\beta,19$-,[10] $12\beta,18$-,[11] $5\alpha,7\alpha$-[12] and $17\beta,18$-cyclo-steroids.[13] Barton and his co-workers have obtained 5,9-cyclo-steroids from the action of chromous chloride on 9α-halo-1,4-diene-3-ketones.[14] Further photochemical rearrangements have been reported leading to 1,5-[15] and $5\beta,19$-cyclo-steroids.[16] Solvolysis of 19-substituted-5-enes leads to $5\beta,19$-cyclo-steroids,[17] as do also the reactions of 19-hydroxy-steroids with 2-chloro-1,1,2-trifluorotriethylamine[18] and of 4β-hydroxy-steroids with lead tetraacetate.[13]

Following Doering and Hoffman's demonstration in 1954 that dihalocarbenes generated from haloforms in the presence of base could be trapped by olefins affording dihalocyclopropane derivatives in excellent yield,[19] several interesting reactions involving dihalocarbene intermediates have been uncovered.[20-26] For our study of the addition of dihalocarbenes to steroids containing sensitive functions in addition to carbon–carbon double bonds, a source of dihalocarbenes generated under neutral conditions was desirable. Thermal decomposition of the sodium salts of trichloroacetic acid[20] and chlorodifluoroacetic acid[24] in a suitable aprotic solvent appeared promising. Decomposition of sodium trichloroacetate in refluxing 1,2-dimethoxymethane has been reported to give a nearly quantitative yield of sodium chloride after 22 hours,[20] while sodium chlorodifluoroacetate in refluxing 2,2′-dimethoxydiethyl ether ("diglyme") afforded a 60–65% yield of the theoretical amount of carbon dioxide.[24] We have found the decomposition of both salts in "diglyme" at 125–150° to be essentially complete within 10 to 15 minutes, based on formation of sodium chloride. Reaction times in the experiments herein described are based on these observations.

Dihalocarbenes generated in "diglyme" from these sodium salts do indeed readily add to unsaturated steroids with few exceptions. That these adducts are, in fact, cyclopropanes follows from the known reactions of dihalocarbenes with carbon–carbon double bonds.[19-26] Assignment of the stereochemistry of the products by purely chemical means, however, poses some major difficulties. Our stereochemical structural assignments rest primarily on electronic factors and classical concepts of steric hindrance to reagent approach, and partly on molecular rotation data and nuclear magnetic resonance (n.m.r.) spectral analyses.

(1) This paper also constitutes Spectra and Stereochemistry, Part V. For Part IV (Steroids. CCXXVI) see A. D. Cross and P. W. Landis, *J. Am. Chem. Soc.*, **84**, 3784 (1962).

(2) A preliminary account of a part of this work was published by L. H. Knox, E. Velarde, S. Berger and D. Cuadriello, *Chem. Ind.* (London), 860 (1962).

(3) Presented in part at the Second International Symposium on Fluorine Chemistry sponsored by the Division of Industrial and Engineering Chemistry, American Chemical Society, in coöperation with Air Force Materials Control and the University of Denver, July 17–20, 1962.

(4) Eli Lilly and Co., Indianapolis 6, Ind.

(5) *Cf.* L. F. Fieser and M. Fieser, "Steroids," Reinhold Publishing Corp., New York, N. Y., 1959, p. 314.

(6) (a) A. Wettstein, *Helv. Chim. Acta*, **27**, 1803 (1944); (b) A. Sandoval, G. Rosenkranz and C. Djerassi, *J. Am. Chem. Soc.*, **73**, 2383 (1951); (c) H. L. Slates and N. L. Wendler, *ibid.*, **81**, 5472 (1959); (d) G. Nominé and D. Bertin, *Bull. soc. chim. France*, 550 (1960); (e) R. Villotti, O. Halpern and A. Bowers, *Gazz. chim. ital.*, in press; (f) R. Wiechert and E. Kaspar, *Chem. Ber.*, **93**, 1710 (1960); (g) K. Kocsis, P. G. Ferrini, D. Arigoni and O. Jeger, *Helv. Chim. Acta*, **43**, 2178 (1960).

(7) (a) D. H. R. Barton and W. C. Taylor, *J. Chem. Soc.*, 2500 (1958); (b) D. H. R. Barton and A. S. Kende, *ibid.*, 688 (1958).

(8) R. Wiechert and E. Kaspar, *Chem. Ber.*, **93**, 1710 (1960).

(9) V. Georgian and N. Kundu, *Chem. Ind.* (London), 1755 (1962).

(10) H. Wehrli, M. S. Heller, K. Schaffner and O. Jeger, *Helv. Chim. Acta*, **44**, 2162 (1961).

(11) V. Georgian, J. F. Kerwin, M. E. Wolff and F. F. Owings, *J. Am. Chem. Soc.*, **84**, 3594 (1962).

(12) Q. R. Peterson, *ibid.*, **82**, 3677 (1960); G. H. R. Summers, *Proc. Chem. Soc.*, 24 (1960).

(13) K. Heusler, J. Kalvoda, P. Wieland, G. Anner and A. Wettstein, *Helv. Chim. Acta*, **45**, 2575 (1962).

(14) O. Gnoj, E. P. Oliveto, C. H. Robinson and D. H. R. Barton, *J. Chem. Soc.*, 207 (1961).

(15) (a) W. W. Kwie, B. A. Shoulders and P. D. Gardner, *J. Am. Chem. Soc.*, **84**, 2268 (1962); (b) K. Weinberg, E. C. Utzinger, D. Arigoni and O. Jeger, *Helv. Chim. Acta*, **43**, 236 (1960); (c) H. Dutler, C. Ganter, H. Ryf, E. C. Utzinger, K. Weinberg, K. Schaffner, D. Arigoni and O. Jeger, *ibid.*, **45**, 2346 (1962); (d) C. Ganter, E. C. Utzinger, K. Schaffner, D. Arigoni and O. Jeger, *ibid.*, **45**, 2403 (1962); (e) R. Wenger, H. Dutler, H. Wehrli, K. Schaffner and O. Jeger, *ibid.*, **45**, 2420 (1962).

(16) D. H. R. Barton and J. M. Beaton, *J. Am. Chem. Soc.*, **83**, 4083 (1961).

(17) J. J. Bonet, H. Wehrli and K. Schaffner, *Helv. Chim. Acta*, **45**, 2615 (1962); O. Halpern, J. A. Edwards and R. Villotti, unpublished observations.

(18) L. H. Knox and A. D. Cross, manuscript in preparation.

(19) W. von E. Doering and H. K. Hoffman, *J. Am. Chem. Soc.*, **76**, 6162 (1954).

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

(21) W. E. Parham and E. E. Schweizer, *J. Org. Chem.*, **24**, 1733 (1959).

(22) (a) P. K. Kadaba and J. O. Edwards, *ibid.*, **25**, 1431 (1960); (b) F. W. Grand and W. B. Cassie, *ibid.*, **25**, 1433 (1960).

(23) W. T. Miller, Jr., and C. S. Kim, *J. Am. Chem. Soc.*, **81**, 5008 (1959).

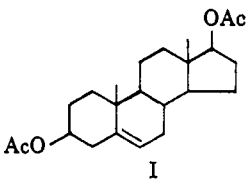
(24) J. M. Birchall, G. W. Cross and R. N. Haszeldine, *Proc. Chem. Soc.*, 81 (1960).

(25) W. I. Bevin, R. N. Haszeldine and J. C. Young, *Chem. Ind.* (London), 789 (1961).

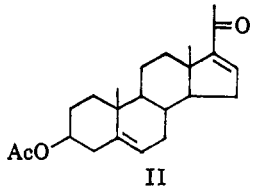
(26) D. Seyferth, J. M. Burlitch and J. K. Heeren, *J. Org. Chem.*, **27**, 1491 (1962).

Attempts to isolate 5,6- or 16,17-dichloromethylene derivatives by the addition of dichlorocarbene to Δ^5-androstene-3β,17β-diol diacetate (I) or $\Delta^{5,16}$-pregnadien-3β-ol-20-one acetate (II) under a variety of conditions were fruitless, affording a quantitative recovery of the starting materials. However, difluorocarbene reacted with both the Δ^5- and $\Delta^{5,16}$-olefins I and II with formation of a single adduct in each case, considered to be the 5β,6β-difluoromethylene derivatives IIIa and IV, respectively. In the ultraviolet spectrum the adduct of the $\Delta^{5,16}$-diene II with difluorocarbene absorbed strongly at 240 mμ, indicative of the Δ^{16}-20-ketone chromophore. The stereochemistry of these adducts and related compounds could be deduced from the following reasoning.

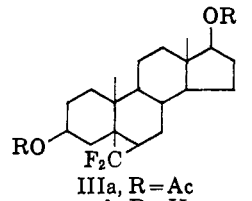
The failure of dichlorocarbene to add to the Δ^5-double bond of Δ^5- or $\Delta^{3,5}$-steroids bearing a 10β-methyl group, but successful addition to the Δ^5-double bond of $\Delta^{3,5}$-19-norsteroids (*vide infra*), suggested very strongly that the steric requirements of the large dichloromethylene carbene preclude approach to, and electrophilic attack upon, the Δ^5-double bond from the β-face of the olefins I and II.[27,28] For addition, the carbene must attain a position astride the double bond such that its



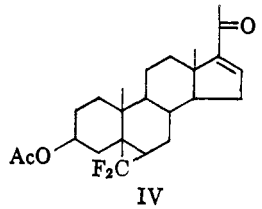
I



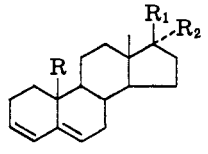
II



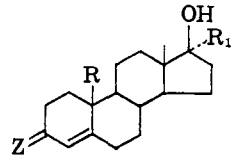
IIIa, R=Ac
b, R=H



IV



Va, R = Me, R_1 = OH, R_2 = H
b, R = R_2 = H, R_1 = OH
c, R = H, R_1 = OH, R_2 = C≡CH
d, R = Me, R_1 = OAc, R_2 = H
e, R = R_2 = H, R_1 = OAc
f, R = H, R_1 = OAc, R_2 = C≡CH
g, R = Me, R_1 = Ac, R_2 = OH
h, R = Me, R_1 = Ac, R_2 = OAc



VIa, R = Me, R_1 = H, Z = O
b, R = R_1 = H, Z = O
c, R = H, R_1 = C≡CH, Z = O
d, R = Me, R_1 = H, Z = H, OH
e, R = R_1 = H, Z = H, OH
f, R = H, R_1 = C≡CH, Z = H, OH

unfilled orbitals overlap with the π-bond orbitals, and in this configuration, one halogen atom projects toward the rotating 10β-methyl group. With the smaller difluorocarbene, the methyl–fluorine interaction is apparently not severe enough to prevent orbital overlap and addition. This concept of steric inhibition to approach of the larger carbene explains precisely the observed results and requires that carbene addition to the Δ^5-double bond be beta. If addition were to proceed from the α-face, there is no apparent reason why addition of dichlorocarbene to a Δ^5-double bond should not occur easily. The readiness with which difluorocarbene *and* dichlorocarbene add to the Δ^3-double bond of $\Delta^{3,5}$-dienes is considered to indicate addition in these cases from the α-face, by an extension of the above reasoning.[29] Furthermore, the resistance of the 3,4-adducts to hydrogenation of the Δ^5-double bond is comprehensible only if the adduct has the bulky dihalomethylene group attached 3α,4α when strong steric hindrance develops to approach of the catalyst plus hydrogen to the α- as well as to the β-face.

Molecular rotation differences further support the 5β,6β-stereochemistry for the difluorocarbene adducts IIIa and IV (see Table I). The molecular rotation changes observed on passing from Δ^5-androstene-3β,17β-diol diacetate (I) to the 5β,6β-difluoromethylene adduct IIIa and to the β-epoxide B are positive and of the same order of magnitude. The molecular rotation change on passing from I to its α-epoxide A, however, is negative. These changes parallel those which occur on conversion of other Δ^5-steroids into their α- and β-epoxides.[32]

TABLE I

MOLECULAR ROTATION DATA FOR Δ^5-ANDROSTENE-3β,17β-DIOL DIACETATE AND SOME DERIVATIVES

Steroid	$[M]_D$	$\Delta[M]_D$	
Δ^5-Androstene-3β,17β-diol diacetate (I)	−202°[a]		
α-Epoxide (A)	−269°[b]	(A-I)	−67°
β-Epoxide (B)	−103°[c]	(B-I)	+99°
β-Difluoromethylene adduct (IIIa)	−127°	(IIIa-I)	+75°

[a] P. Wieland and K. Miescher, *Helv. Chim. Acta*, **32**, 1768 (1949). [b] L. Ruzicka and A. C. Muhr, *ibid.*, **27**, 503 (1944). [c] L. H. Knox, unpublished observation.

Next, the reaction of dihalocarbenes with steroidal conjugated $\Delta^{3,5}$-dienes was investigated. $\Delta^{3,5}$-Androstadien-17β-ol acetate (Vd), $\Delta^{3,5}$-19-norandrostadien-17β-ol acetate (Ve) and 17α-ethynyl-$\Delta^{3,5}$-19-norandrostadien-17β-ol acetate (Vf) were conveniently synthesized by a common route. Reduction of testosterone (VIa), 19-nortestosterone (VIb), and 17α-ethynyl-19-nortestosterone (VIc) with lithium aluminum hydride and treatment of the resulting Δ^4-3ξ,17β-diols VId,e,f with 50% aqueous acetic acid afforded the corresponding $\Delta^{3,5}$-dienes Va,b,c which were acetylated to furnish the desired $\Delta^{3,5}$-diene acetates Vd,e,f. A convenient

(27) Addition of electrophiles to Δ^5-double bonds of $\Delta^{3,5}$-dienes takes place usually from the β-face. The electronic requirements of maximum orbital overlap in the transition state, leading to a 6β-axially bonded substituent, normally outweighs the steric hindrance to the β-face approach due to the 10β-methyl group.

(28) For recent references to electrophilic attack on $\Delta^{3,5}$-dienyl ethers, see A. Bowers, L. I. Ibañez and H. J. Ringold, *J. Am. Chem. Soc.*, **81**, 3707 (1959).

(29) Partly on the basis of the above structural assignments the proposal has been made that for the long-range spin–spin coupling of angular methyl protons with fluorine in fluorosteroids, a *cis* stereochemical relationship of the coupling nuclei is preferred.[30] However, the above arguments do not constitute a rigid proof of stereochemistry. In the event that unrecognized factors are operating during the addition of the dihalocarbenes which overwhelm those factors considered here and lead to a reversal of the stereochemistry depicted above, then the proposals made earlier[30] become untenable. However, subsequent investigations of many other fluorosteroids lead us to believe that our original suggestions are correct.[1] Moreover, Roberts and his co-workers have recently demonstrated in convincing manner that the long-range five-bond H–F coupling between the methyl group and one of the fluorines of 1,1-difluoro-2,3-dichloro-3-phenyl-3-methylcyclobutane is a *cis* interaction, *unless* in this molecule there exists a very unusual reversal of the relative magnitudes of the coupling constants of fluorine with the *cis* and *trans* protons of the adjacent methylene.[31] In the remainder of the discussion the utilization of n.m.r. spectral data for the determination of structure and stereochemistry is made subject to the limitations outlined above.

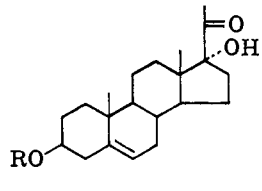
(30) A. D. Cross and P. W. Landis, *J. Am. Chem. Soc.*, **84**, 1736 (1962).

(31) M. Takahashi, D. R. Davis and J. D. Roberts, *ibid.*, **84**, 2935 (1962).

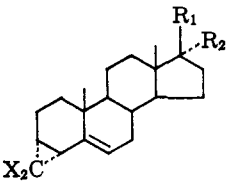
(32) See, for example, A. Bowers, L. C. Ibañez and H. J. Ringold, *Tetrahedron*, **7**, 138 (1959).

synthesis of $\Delta^{3,5}$-pregnadien-17α-ol-20-one acetate (Vh)[33] involved successive tosylation of Δ^5-pregnene-3β,17α-diol-20-one (VIIa), treatment of the tosylate VIIb with hot collidine–xylene, and acetylation of the resulting $\Delta^{3,5}$-pregnadien-17α-ol-20-one (Vg).

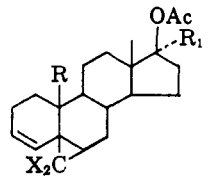
While dichlorocarbene adds exclusively to the Δ^3-double bond of $\Delta^{3,5}$-steroids when a 10β-methyl group is present, with the 19-nor compounds addition occurs exclusively at the Δ^5-double bond. Thus, $\Delta^{3,5}$-androstadien-17β-ol acetate (Vd) and $\Delta^{3,5}$-pregnadien-17α-ol-20-one acetate (Vh) reacted with dichlorocarbene with formation of the adducts VIIIa and VIIIb, respectively, as the only isolable products. These adducts on low-pressure hydrogenation in ethanol over a platinum oxide catalyst were recovered unchanged. In contrast, $\Delta^{3,5}$-19-norandrostadien-17β-ol acetate (Ve) and its 17α-ethynyl derivative Vf, on reaction with dichlorocarbene, yielded exclusively the 5,6-dichloromethylene derivatives IXa and IXb. The presence of a Δ^3-double bond in these latter adducts could be inferred from the presence of a weak band in their infrared spectra at 6.05 μ, which appeared consistently in all Δ^3-5,6-dihalomethylene adducts prepared in this study, as well as from the n.m.r. spectra. In addition, the adduct IXa could be hydrogenated readily in ethanol over a platinum oxide catalyst at atmospheric pressure to the corresponding saturated 5,6-dichloromethlyene derivative Xa. The 5β,6β-geometry in these adducts follows from the stereochemical and electronic arguments presented above, and is consistent with the n.m.r. spectral data (*vide infra*).[29]



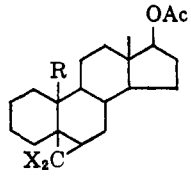
VIIa, R = H
b, R = Tos



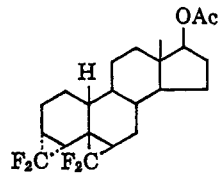
VIIIa, R_1 = OAc, R_2 = H, X = Cl
b, R_1 = Ac, R_2 = OAc, X = Cl
c, R_1 = OAc, R_2 = H, X = F
d, R_1 = Ac, R_2 = OAc, X = F
e, R_1 = OH, R_2 = X = H
f, R_1 = OH, R_2 = H, X = Cl
g, R_1 = OH, R_2 = H, X = F



IXa, R = R_1 = H, X = Cl
b, R = H, R_1 = C≡CH, X = Cl
c, R = Me, R_1 = H, X = F
d, R = R_1 = H, X = F



Xa, R = H, X = Cl
b, R = Me, X = F
c, R = H, X = F



XI

With one exception, difluorocarbene, in contrast to dichlorocarbene, reacted with $\Delta^{3,5}$-steroids possessing a 19-methyl group with formation of two isomeric difluoromethylene derivatives. These result from attack at the Δ^3- and the Δ^5-double bonds, respectively. Reaction of the $\Delta^{3,5}$-steroid Vd with difluorocarbene afforded the two isomeric adducts VIIIc and IXc. The adduct IXc, whose infrared spectrum showed a weak band at 6.05 μ, readily absorbed 1 mole of hydrogen in 95% ethanol over a platinum oxide catalyst at atmospheric pressure with formation of Xb. Under the same conditions, VIIIc was recovered quantitatively. From the reaction of $\Delta^{3,5}$-pregnadien-17α-ol-20-one acetate (Vh) with difluorocarbene, a single adduct (VIIId) was isolated, which resulted from attack at the Δ^3-double bond. On attempted hydrogenation in ethanol over platinum oxide catalyst the adduct VIIId was recovered unchanged.

3α,4α-(Dichloromethylene)-Δ^5-androsten-17β-ol acetate (VIIIa) and the corresponding 3α,4α-difluoromethylene derivative VIIIc were interrelated by conversion to the halogen-free compound VIIIe. This was accomplished by saponification of the acetates VIIIa and VIIIc, followed by dehalogenation of the resultant alcohols VIIIf and VIIIg, respectively, with sodium in liquid ammonia, when the same cyclopropane VIIIe was obtained in each case.

The reaction of $\Delta^{3,5}$-19-norandrostadien-17β-ol acetate (Ve) with difluorocarbene afforded the Δ^3-5β,6β-difluoromethylene derivative IXd which was readily hydrogenated to give Xc, and which showed a weak absorption band in the infrared spectrum at 6.05 μ. The 5,6-addition was supported by n.m.r. analysis. Whereas there was not found any mono-adduct resulting from attack at the Δ^3-double bond, there was isolated, in fair yield, the bis-difluoromethylene derivative XI. The structure of the latter is assigned from its elementary analysis, n.m.r. spectrum, and from the general considerations outlined above concerning reagent approach.

From the collected n.m.r. data (Table II) it is immediately apparent that the vinyl proton signal which disappears on difluorocarbene addition to $\Delta^{5,16}$-pregnadien-3β-ol-20-one acetate (II) is that due to the proton at C_6 in the diene. Moreover, the conjugated Δ^{16}-20-one system is associated with a marked shift ($\Delta\delta$) to higher frequencies of the 18-methyl ($\Delta\delta$, *ca.* 18 c.p.s.) and 21-methyl ($\Delta\delta$, *ca.* 6 c.p.s.) resonance singlets, as compared with the corresponding signals in the n.m.r. spectra of the unconjugated 17β-acetyl steroids XIIa and XIIb. Both of these shifts also appear in the spectrum of the adduct IV. Using Zürcher's value[34] for the shift of the 19-methyl resonance frequency of 5α-androstane caused by a Δ^5-double bond ($\Delta\delta$ 11.5 c.p.s.) it is calculated that the 5β,6β-difluoromethylene substituent shifts the 19-methyl frequency *ca.* 13.5 c.p.s. to higher frequencies relative to 5α-androstane. A feature of the spectrum of the adduct IV is that the 19-methyl proton resonance is split into a doublet (J = 2.3 c.p.s.). Similarly, the n.m.r. spectrum of the 5β,6β-difluorocarbene adduct IIIa manifests a doublet (J = 2.2 c.p.s.) for the 19-methyl resonance, due to long-range spin–spin coupling of the angular methyl protons with *one* of the fluorine atoms. Such long-range coupling through more than 4 σ-bonds is considered to be possible only when a vector directed along the C–F bond, and originating at the carbon atom, converges upon and intersects a vector drawn along an angular methyl C–H bond in the direction of the proton and originating at the methyl carbon.[1] In the current work a 19-methyl resonance doublet was observed in the n.m.r. spectra of all adducts formed by difluorocarbene addition to the Δ^5-double bond of a steroid containing a 10β-methyl substituent.

(33) This $\Delta^{3,5}$-diene was originally prepared by an alternative route in these laboratories: O. Halpern and J. A. Zderic, *Chem. Ind.* (London), 1540 (1962).

(34) R. F. Zürcher, *Helv. Chim. Acta*, **44**, 1380 (1961).

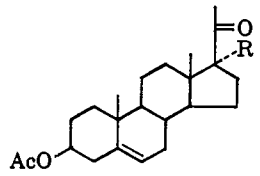
TABLE II

N.M.R. FREQUENCIES[35] FOR Δ^5-PREGNENES, THEIR DIFLUOROCARBENE ADDUCTS AND RELATED COMPOUNDS[a]

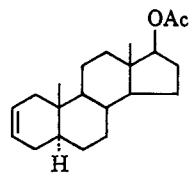
Steroid	18-Me	19-Me	21-OAc	21-Me	C_6–H	C_{16}–H	Ref.
II	56.1	64.3	121.8	135.5	325 (m)	402 (m)	b
	55.5	63					36
XIIa	37.5	61.5					36
	39.4	62.2	122.8	128.8	312 (m)		c
XIIb	38.8	62.0	122.5 (2 OAc)	126.4	315 (m)		b
IV	53.7	65.8[d]	121.7	134.1		400 (m)	b
I (5,6-satd.)	46.4	49.6	119.6 (2 OAc)				b
I	48.1	61.6	120.5 (2 OAc)		319 (m)		b
		61.9					34
IIIa	46.8	64.0[e]	119.9 (2 OAc)				b

[a] m = multiplet; all other resonances are singlets, or doublets with J-values as indicated. [b] This work. [c] P. Buchschacher, M. Cereghetti, H. Wehrli, K. Schaffner and O. Jeger, *Helv. Chim. Acta*, **42**, 2122 (1959). Their values have been converted to those given in Table II by taking $\Delta\delta$, TMS–benzene = 384 c.p.s. [d] J = 2.3 c.p.s. [e] J = 2.2 c.p.s.

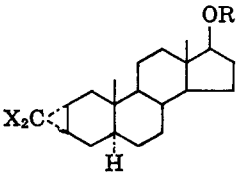
From the number of vinyl proton signals, one can easily determine the sites of addition of dihalocarbenes to $\Delta^{3,5}$-dienes (Table III). Dichlorocarbene adds to $\Delta^{3,5}$-androstadien-17β-ol acetate (Vd) to give a single



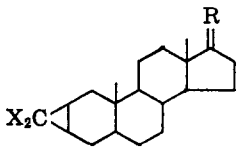
XIIa, R = H
b, R = OAc



XIII



XIVa, R = Ac, X = Cl
b, R = H, X = Cl
c, R = X = H
d, R = Ac, X = F
e, R = H, X = F



XVa, R = β-OAc, X = Cl
b, R = β-OAc, X = F
c, R = β-OH, X = F
d, R = O, X = F

product, the n.m.r. spectrum of which shows only one vinyl proton signal. This defines the structure as the 3,4-adduct VIIIa, the stereochemistry being assigned from the theoretical considerations outlined earlier. Table III also contains spectral data for two isomeric adducts VIIIc and IXc which result from the reaction of the diene Vd with difluorocarbene. One isomer, IXc, showed two vinyl proton signals in the n.m.r. spectrum with a doublet for the 19-methyl proton resonance, in agreement with β-face addition.[1,29] Had the difluorocarbene added to the Δ^5-double bond from the α-face no splitting of the 19-methyl resonance would be expected. The n.m.r. spectrum of the isomeric 3,4-difluoromethylene derivative VIIIc shows only a singlet for the 19-methyl resonance. This experimental finding is compatible with the conclusion made earlier (*vide supra*) that addition of dihalocarbenes to the Δ^3-double bond proceeds from the α-face. Molecular models[37] of a 3β,4β-difluoromethylene-Δ^5-steroid reveal that one fluorine is suitably oriented with respect to the 19-methyl protons such that long-range H–F coupling would be expected,[1,29] resulting in a split 19-methyl resonance.

Similarly, the products of addition of dichloro- and difluorocarbenes to the diene Vh were identified as the 3,4-dihalomethylene adducts VIIIb and VIIId, respectively, by inspection of the vinyl proton resonances. The n.m.r. spectrum of the difluoromethylene derivative VIIId shows an unsplit 19-methyl resonance (Table III).

From the vinyl proton resonances of the dihalocarbene adducts IXa and IXd it was apparent that addition to the $\Delta^{3,5}$-19-norsteroid Ve proceeds at the Δ^5-double bond (Table III). The second product from the reaction of Ve with difluorocarbene showed no vinyl proton signals in the n.m.r. spectrum and is therefore the bis-adduct XI, though the n.m.r. spectrum provides no information concerning the stereochemistry.

A comparison of the C_3- and C_4-proton resonances in the n.m.r. spectra of the 5β,6β-dihalomethylene compounds IXa and IXd revealed long-range coupling of the C_4-olefinic proton with at least one of the fluorine atoms in the product IXd since extensive secondary splitting of this proton resonance signal was apparent. This is in contrast to the spectrum of the dichlorocarbene adduct IXa where the C_4-proton signal is a pair of quartets with apparent J-values *ca.* 10 c.p.s., *ca.* 1.5 c.p.s. and <1 c.p.s., the smaller splittings presumably arising from long-range coupling with allylic protons. A similar situation exists in the n.m.r. spectrum of the adduct IXb where a pair of multiplets is observed for the C_4-proton resonance with J_{3H-4H} *ca.* 10 c.p.s.

When Δ^2-androsten-17β-ol-acetate (XIII)[38] was heated under reflux in "diglyme" with 6 molar equivalents of sodium trichloroacetate, there was isolated a single adduct, the elemental composition of which corresponded to XIVa, or the stereoisomer XVa. That the adduct is probably the 2α,3α-derivative XIVa follows from the arguments presented in the sequel. Saponification, followed by reduction of the alcohol XIVb with sodium in liquid ammonia, afforded the 2,3-methylene derivative XIVc.

With difluorocarbene the olefin XIII gave two isomeric addition products, inseparable by chromatography on Florisil. Fractional crystallization from methanol, however, readily separated the two isomers, m.p. 165–167° and m.p. 130–132°, compositional analyses for which were compatible with the 2,3-(difluoromethylene)-androstan-17β-ol acetates XIVd and XVb. The n.m.r. spectra of both isomers were devoid of vinyl proton resonances and, for each compound, the 18- and 19-methyl resonances were almost coalesced (Table IV). This caused difficulty in inspection of the 19-methyl resonance for splitting due to long-range coupling with fluorine. However, even in these spec-

(35) Nuclear magnetic resonance spectra were obtained with 5–10% (w./v.) solutions of the steroid in deuteriochloroform containing tetramethylsilane (TMS) as an internal reference. Varian A-60 and HR-60 spectrometers were employed, all spectra run on the former instrument being calibrated, *via* arbitrary reference samples, against the spectra obtained on the higher resolution HR-60 machine. The latter was equipped for calibration by the standard side band technique. Accuracies are of the order of ±1 c.p.s. for the chemical shift, δ, which is quoted as c.p.s. downfield from the TMS reference, and ±0.3 c.p.s. for coupling constants, J, expressed as c.p.s. A variation of less than ±0.5 c.p.s. for δ-values was found for the same sample run at regular intervals over the 8-month period during which the work was carried out. There was negligible change in δ or J when one sample was examined several times in a 6-hour period. Angular methyl proton resonance splittings were examined by scale expansion with both instruments. A. D. C. thanks the Universidad Nacional Autónoma de Mexico for the use of the A-60 spectrometer.

(36) J. N. Shoolery and M. T. Rogers, *J. Am. Chem. Soc.*, **80**, 5121 (1958).

(37) A. S. Dreiding, *Helv. Chim. Acta*, **42**, 1339 (1959).

(38) R. E. Marker, O. Kamm, D. M. Jones and L. W. Mixon, *J. Am. Chem. Soc.*, **59**, 1363 (1937); J. A. Edwards and A. Bowers, *Chem. Ind.* (London), 1962 (1961).

TABLE III

N.M.R. FREQUENCIES[35] FOR THE ADDUCTS OF $\Delta^{3,5}$-STEROID DIENES AND DIHALOCARBENES[a,b,c]

Steroid	18-Me	19-Me	C_7-H	C_4-H	C_6-H	17-OAc	Misc. protons
Vd	49.7	57.5	*ca.* 338 (m)	355 (m)	321 (m)	121.1	
VIIIa	49.1	56.4			343 (m)	121.5	
VIIIc	49.1	57.2			330 (m)	120.8	
IXc	48.6	62.5[e]	*ca.* 355 (m)	306 (m)*		121.3	
Xb[d]	45.4	61.6[f]				117.0	
VIIIb	38.8	54.7			345 (m)	121.4	125.0 (21-Me)
VIIId	38.9	56.6			333 (m)	121.2	124.8 (21-Me)
IXd	47.2		*ca.* 357 (m)	315 (m)*		121.0	
IXa	45.9		*ca.* 364 (m)	320 (m)		121.0	
XI	46.1					121.0	
IXb[d]	47.8		*ca.* 360 (m)	315 (m)		117.3	144.2 (C≡CH)

[a] All resonances are singlets, except where indicated otherwise. [b] m = multiplet, * = further split by long-range coupling with fluorine. [c] Multiplets generally covered 10–20 c.p.s. [d] 6% (w./v.) solution in carbon tetrachloride. [e] J = 2.4 c.p.s. [f] J = 2.0 c.p.s.

tra distinct shoulders on the side of the angular 19-methyl signal of the lower-melting isomer suggested a split methyl resonance with J = 1–2 c.p.s. By saponification the 17β-acetates XIVd and XVb were converted to the 17β-alcohols XIVe and XVc, respectively, for which the 18-methyl signals of the n.m.r. spectra are moved separately to lower frequencies by 3–4 c.p.s., thus exposing the 19-methyl resonances. The n.m.r. spectrum of the alcohol which was obtained by hydrolysis of the lower-melting acetate displayed a distinct splitting of the 19-methyl signal (J = 1.6 c.p.s.). From molecular models[37] it can be seen that in the 2β,3β-adduct the stereochemical requirements for long-range H–F coupling of the angular methyl protons through more than four σ-bonds are met.[1,29,30] Accordingly, the lower-melting acetate and the derived alcohol are tentatively assigned the structures XVb and XVc, respectively. However, the isomeric alcohol, which should possess structure XIVe, gives an n.m.r. spectrum in which the 19-methyl resonance appears as an ill-resolved doublet, J = *ca.* 1 c.p.s.[39] Therefore, the stereochemistry of the two isomers could not be conclusively determined by the n.m.r. method. Oxidation of the alcohol XVc afforded the 17-ketone XVd, but the n.m.r. spectrum revealed that the 18-methyl resonance had been restored to a position virtually coincident with the 19-methyl resonance. No information concerning the stereochemical identity of the dichlorocarbene adduct XIVa is obtainable from the n.m.r. spectrum of this compound.

TABLE IV

N.M.R. FREQUENCIES FOR Δ^2-ANDROSTEN-17β-OL ACETATE, DIFLUOROCARBENE ADDUCTS AND DERIVATIVES[35]

Steroid	18-Me	19-Me
XIII[a]	45.5	45.5
XIVd	47.2	47.2
XVb	48.2	*ca.* 49.0 and 47.5 (shoulders)
XIVe	42.9	44.9 and *ca.* 46 (shoulder)
XVc	43.9	45.9 and 47.5 (J = 1.6 c.p.s.)
XVd[c]	48.2	*ca.* 48 and 46.7 (shoulder)

[a] 8% (w./v.) solution in carbon tetrachloride.

Molecular rotation differences, $\Delta[M]\delta$ (Table V), appear in agreement with the provisonal structural assignments to the stereoisomeric difluoromethylene adducts. The molecular rotation change which occurs on passing from Δ^2-androsten-17β-ol acetate XIII to the α-difluoromethylene adduct XIVd is significantly more negative than that observed in formation of the β-difluoromethylene adduct XVb. These changes parallel the $[M]_D$ changes coincident upon conversion of Δ^2-cholestene into its α- and β-epoxides.

(39) A referee suggested that examination of the fluorine resonance spectrum of these compounds should clarify this unsatisfactory situation. Our attempts to obtain well resolved fluorine spectra were, however, unsuccessful.

TABLE V

MOLECULAR ROTATION DATA FOR Δ^2-STEROIDS AND THEIR DERIVED 2α,3α- AND 2β,3β-EPOXIDES AND DIFLUOROMETHYLENE DERIVATIVES

Steroid	$[M]_D$	$\Delta[M]_D$	
Δ^2-Cholestene (i)[a]	+239°		
α-Epoxide (ii)[a]	+139°	ii − i	−100°
β-Epoxide (iii)[a]	+195°	iii − i	−44°
Δ^2-Androsten-17β-ol acetate (XIII)	+128°		
α-Difluoromethylene adduct (XIVd)	+40°	XVIId − XVI	−88°
β-Difluoromethylene adduct (XVb)	+73°	XVIIIb − XVI	−55°

[a] A. Furst and Pl. A. Plattner, *Helv. Chim. Acta*, **32**, 275 (1949).

Having determined the probable stereochemistry of the two isomeric 2,3-difluoromethylene derivatives, it was then possible to correlate the stereochemistry at carbon atoms 2 and 3 in the single dichlorocarbene adduct obtained from olefin XIII. Saponification of the two difluoromethylene derivatives XIVd and XVb afforded the alcohols XIVe and XVc, respectively. The alcohol XIVe was dehalogenated by sodium and liquid ammonia, although the reduction proceeded more slowly than the reduction of the analogous 2,3-dichloromethylene adduct. The 2α,3α-methylene-androstan-17β-ol (XIVc) thus obtained was shown by melting point, mixture melting point and comparison of infrared spectra to be identical with the 2,3-methylene derivative similarly obtained from the dichlorocarbene adduct. The latter substance, therefore, probably possesses structure XIVa.

Experimental[40]

General Procedure for Reactions of Unsaturated Steroids with Dihalocarbenes. (a) **Dichlorocarbene.**—The steroid in "diglyme" was treated with sodium trichloroacetate (4–6 molar equivalents), added in 10 equal portions at 10-minute intervals in the following manner. A mixture of the steroid (0.003 mole) and one portion of the salt in "diglyme" (50–100 ml.) was held at 125–130° for 10 minutes. The mixture was then cooled to below 100°, a second portion of the salt added, and the mixture again maintained at 125–130° for 10 minutes. After the final addition, the mixture was cooled, precipitated sodium chloride removed by filtration, solvent evaporated *in vacuo*, and the product isolated by chromatography on Florisil (100/200 mesh).

(b) **Difluorocarbene.**—A mixture of the steroid (0.003 mole) and sodium chlorodifluoroacetate (4 molar equivalents) in "diglyme" (50–100 ml.) was heated under reflux for 15 minutes and then cooled to below 100°. An additional 4 molar equivalents of the salt was added, and the mixture was again refluxed

(40) Melting points are uncorrected. Optical rotations were determined in chloroform solutions and ultraviolet spectra were measured in 95% ethanol. Infrared spectra, determined in potassium bromide disks on a Perkin–Elmer model 21 spectrometer equipped with sodium chloride optics, are by Dr. Matthews and his staff. Unless otherwise stated, yields of dihalocarbene adducts are based on unrecovered starting material.

for 15 minutes. The mixture was then worked as described above and the products isolated by chromatography on Florisil.

5β,6β-(Difluoromethylene)-androstane-3β,17β-diol Diacetate (IIIa).—A solution of 2.25 g. (0.006 mole) of Δ⁵-androstene-3β,17β-diol diacetate (I), m.p. 164–166°, in "diglyme" (100 ml.) was treated with 7.2 g. (0.048 mole) of sodium chlorodifluoroacetate as previously described. The crude product, m.p. 123–130°, was crystallized from hexane affording unchanged olefin I (1.64 g.), m.p. 163–165°. The mother liquor was adsorbed from hexane on Florisil (100 g.). Elution with hexane–ether (4:1) furnished an additional 300 mg. of the less polar product I, followed by adduct IIIa (300 mg.), m.p. 140–145°. Recrystallization from hexane gave 210 mg. (58%) of the pure difluoro derivative IIIa, m.p. 155–157°, $[\alpha]_D$ −30°.

Anal. Calcd. for $C_{24}H_{34}O_4F_2$: C, 67.89; H, 8.07; F, 8.95. Found: C, 68.07; H, 7.89; F, 8.94.

Reaction of Δ⁵,¹⁶-Pregnadien-3β-ol-20-one Acetate (II) with Difluorocarbene.—A solution of 4.28 g. (0.012 mole) of the diene II, m.p. 174–176°, in "diglyme" (100 ml.) was treated with 28.8 g. (0.096 mole) of sodium chlorotrifluoroacetate as described above and the crude product (4.5 g.) adsorbed on Florisil (200 g.). The crystalline fractions eluted with hexane–ether (7:1) consisted of unreacted diene II (2.21 g.), m.p. 165–167°. Further elution with ether yielded 1.02 g. (43%) of the 5β,6β-difluoromethylene derivative IV, m.p. 103–105°. Recrystallization from methanol afforded the analytical sample, m.p. 109–110°, $[\alpha]_D$ +15°, λ_{max} 238–240 mμ (log ε 3.98).

Anal. Calcd. for $C_{24}H_{32}O_3F_2$: C, 70.91; H, 7.93; F, 9.35. Found: C, 70.77; H, 8.17; F, 9.70.

Δ⁴-Androstene-3ξ,17β-diol (VId).—A solution of 15.0 g. of testosterone (VIa) in tetrahydrofuran (100 ml.) was added dropwise with stirring in 30 minutes to a suspension of lithium aluminum hydride (15.0 g.) in ether (500 ml.). After stirring at room temperature for an additional 2 hours, 400 ml. of ether was added and the excess of hydride destroyed by cautious addition of ethyl acetate. A saturated solution of sodium sulfate was then added, followed by sufficient solid sodium sulfate to form a clear supernatant ether–tetrahydrofuran solution. Filtration, followed by evaporation and crystallization of the crude product from methanol, afforded 14.5 g. (95%) of the allylic alcohol VId, m.p. 167–169°. Three crystallizations from methanol furnished the analytical sample, m.p. 210–215°, $[\alpha]_D$ +53°.

Anal. Calcd. for $C_{19}H_{30}O_2$: C, 78.57; H, 10.62. Found: C, 78.36; H, 10.41.

Δ³,⁵-Androstadien-17β-ol (Va).—The crude alcohol VId, obtained by lithium aluminum hydride reduction of testosterone (30.0 g.) as described above, was dissolved in acetic acid (600 ml.). Water (600 ml.) was slowly added and the mixture heated at steam-bath temperature for 30 minutes. The product which separated in crystalline form after 10–15 minutes was collected on a filter, washed to neutrality with water, and dried. The yield of the diene Va amounted to 27.5 g. (96%), m.p. 148–150°, unchanged on recrystallization from acetone, $[\alpha]_D$ −112° [lit. m.p. 157–159°, $[\alpha]_D$ −120° (ethanol)[41]; m.p. 156°, $[\alpha]_D$ −139°[42]] λ_{max} 228 mμ (log ε 4.16), 234–236 mμ (log ε 4.18) and 243 mμ (log ε 3.98).

Δ³,⁵-Androstadien-17β-ol Acetate (Vd).—Acetylation of the 17β-alcohol Va (27.5 g.) by pyridine–acetic anhydride and recrystallization of the crude product from methanol afforded the 17β-acetate Vd (21.0 g., 62% from testosterone), m.p. 126–127°, $[\alpha]_D$ −173° [lit. m.p. 125.5–130.2°, $[\alpha]_D$ −132° (ethanol)[41]; m.p. 128°, $[\alpha]_D$ −147° (ethanol)[42]].

Anal. Calcd. for $C_{21}H_{30}O_2$: C, 80.21; H, 9.62; O, 10.18. Found: C, 79.92; H, 9.64; O, 10.40.

Δ⁴-19-Norandrostene-3ξ,17β-diol (VIe).—To a suspension of lithium aluminum hydride (18.5 g.) in ether (1.2 l.) was added a solution of 18.5 g. of 19-nortestosterone (VIb) in tetrahydrofuran (200 ml.) during 30 minutes at room temperature. After stirring for an additional 2 hours, ether (400 ml.) was added and the product isolated as described above for the alcohol VId. Recrystallization from methanol yielded the alcohol VIe (15.3 g., 82.5%), m.p. 155–156°. Further recrystallization from methanol furnished the analytical sample, m.p. 156–158°, $[\alpha]_D$ +41°.

Anal. Calcd. $C_{18}H_{28}O_2$: C, 78.21; H, 10.21; O, 11.58. Found: C, 78.23; H, 10.21; O, 11.36.

Δ³,⁵-19-Norandrostadien-17β-ol (Vb).—A solution of the diol VIe (15.3 g.) in acetic acid (300 ml.) at steam-bath temperature was slowly diluted with water (300 ml.). After 30 minutes, the product was isolated by dilution with water and ether extraction. The crude product (13.7 g.) was adsorbed on neutral alumina (600 g.). The crystalline fractions eluted with hexane–ether (9:1) were pooled (11.0 g.) and crystallized from methanol affording 7.8 g. (55%) of the diene Vb, m.p. 112–114°. Recrystallization from methanol gave the analytical sample, m.p. 114–116°, $[\alpha]_D$ −155°, λ_{max} 230 mμ (log ε 4.28) and 236 mμ (log ε 4.31).

Anal. Calcd. for $C_{18}H_{26}O \cdot {}^1/_2H_2O$: C, 80.85; H, 10.18; O, 8.98. Found: C, 80.92; H, 10.27; O, 8.66.

Δ³,⁵-19-Norandrostadien-17β-ol Acetate (Ve).—Acetylation of the alcohol Vb (7.8 g.) in acetic anhydride–pyridine in the usual manner gave the acetate Ve (6.9 g., 75.8%), m.p. 116–117°, raised to 121–122° by crystallization from methanol; $[\alpha]_D$ −168°, λ_{max} 230 mμ (log ε 4.28) and 236 mμ (log ε 4.31).

Anal. Calcd. for $C_{20}H_{28}O_2$: C, 79.95; H, 9.39. Found: C, 80.14; H, 9.52.

17α-Ethynyl-Δ⁴-19-norandrostene-3ξ,17β-diol (VIf).—A solution of 15.0 g. (0.051 mole) of 17α-ethynyl-Δ³-norandrosten-17β-ol-3-one (VIc) in tetrahydrofuran (300 ml.) was added in 30 minutes to a suspension of lithium aluminum hydride (15.0 g.) in ether (500 ml.). After stirring for an additional 30 minutes at room temperature, the mixture was worked as described above. The crude product (14.5 g.) was adsorbed on Florisil (500 g.). The crystalline fractions eluted with benzene–ether (4:1) were combined (9.3 g.) and crystallized from methanol affording 4.52 g. (30%) of the diol VIf, m.p. 128–131°. Recrystallization from methanol afforded the analytical sample, m.p. 136–138°, $[\alpha]_D$ −31°.

Anal. Calcd. for $C_{20}H_{28}O_2 \cdot H_2O$· C, 75.43; H, 9.50. Found: C, 75.32; H, 9.66.

17α-Ethynyl-Δ³,⁵-19-norandrostadien-17β-ol (Vc).—Treatment of the diol VIf (14.0 g.) in 50% aqueous acetic acid as described above afforded a crude product (11.4 g.) which was adsorbed onto neutral alumina (550 g.). The crystalline fractions eluted with benzene–ether (1:1) were combined (8.3 g.) and crystallized from methanol to yield 6.0 g. (46.5%) of the diene Vc, m.p. 108–110°. The analytical sample was obtained by recrystallization from hexane and had m.p. 118–119°, $[\alpha]_D$ −264°, λ_{max} 230 mμ (log ε 4.25) and 236 mμ (log ε 4.28).

Anal. Calcd. for $C_{20}H_{26}O$: C, 85.05; H, 9.28. Found: C, 84.87; H, 9.03.

17α-Ethynyl-Δ³,⁵-norandrostadien-17β-ol Acetate (Vf).—A mixture of the alcohol Vc (12 g.), acetic anhydride (36 ml.) and *p*-toluenesulfonic acid (144 mg.) was held at 75° with stirring for 2.5 hours. The cooled mixture was then cautiously diluted with water (100 ml.) and the precipitated product collected on a filter, washed with water to neutrality, and dried. The crude acetate (10.0 g.) was adsorbed onto neutral alumina (500 g.). Elution with hexane afforded the acetate Vf, m.p. 170–172°, unchanged on recrystallization from acetone; $[\alpha]_D$ −234°, λ_{max} 230 mμ (log ε 4.31) and 236 mμ (log ε 4.34).

Anal. Calcd. for $C_{22}H_{28}O_2$: C, 81.44; H, 8.70. Found: C, 81.69; H, 9.00.

Δ⁵-Pregnene-3β,17α-diol-20-one 3β-Tosylate (VIIb).—A mixture of Δ⁵-pregnene-3β,17α-diol-20-one (VIIa, 25.0 g.), *p*-toluenesulfonyl chloride (25.0 g.) and pyridine (100 ml.) was stirred at room temperature for 17 hours. Chloroform (1 l.) was added and the mixture washed successively with 5% aqueous sulfuric acid, saturated aqueous sodium bicarbonate, and water. The organic layer was dried (sodium sulfate) and evaporated, and the residue crystallized from hexane affording 36.0 g. of the tosylate ester VIIb, m.p. 138–140°. A sample recrystallized from hexane had m.p. 141–143°, $[\alpha]_D$ −50°.

Anal. Calcd. for $C_{28}H_{38}O_5S$: S, 6.58. Found: S, 6.37.

17α-Hydroxy-Δ³,⁵-pregnadien-20-one (Va).—A mixture of 36.0 g. of the tosylate VIIb, collidine (126 ml.) and xylene (126 ml.) was heated under reflux for 2 hours, diluted with ether (750 ml.), washed with 5% aqueous sulfuric acid followed by water, dried (sodium sulfate) and evaporated. Crystallization of the crude product from acetone afforded 12.2 g. (52.5% from VIIb) of the diene Vg, m.p. 173–175°. Recrystallization from acetone gave the analytical sample, m.p. 178–180°, $[\alpha]_D$ −158°; λ_{max} 228 mμ (log ε 4.19), 234–236 mμ (log ε 4.21) and 243 mμ (log ε 4.02).

Anal. Calcd. for $C_{21}H_{30}O_2$: C, 80.21; H, 9.62; O, 10.18. Found: C, 79.78; H, 9.44; O, 10.40.

17α-Acetoxy-Δ³,⁵-pregnadien-20-one (Vh).—A solution of the alcohol Vg (11.0 g.) in acetic acid (450 ml.) containing acetic anhydride (90 ml.) and *p*-toluenesulfonic acid (11.0 g.) was stirred at room temperature for 2.5 hours. Water (400 ml.) was added, the product collected by filtration, washed to neutrality, and dried. Crystallization of the crude product from acetone–hexane gave 3.0 g. of the acetate Vh, m.p. 165–168°. Adsorption of the mother liquor onto neutral alumina (400 g.) and elution with benzene afforded an additional 2.45 g. of the acetate Vh, m.p. 165–167°, raising the yield to 5.45 g. (43%). Recrystallization from acetone–hexane afforded the analytical sample, m.p. 180–181°, $[\alpha]_D$ −152°; λ_{max} 228 mμ (log ε 4.22), 235 mμ (log ε 4.25) and 243 mμ (log ε 4.05).

Anal. Calcd. for $C_{23}H_{32}O_3$: C, 77.49; H, 9.05; O, 13.46. Found: C, 77.22; H, 8.80; O, 13.65.

(41) R. T. Blickenstaff and E. L. Foster, *J. Org. Chem.*, **26**, 5029 (1961).

(42) G. Rosenkranz, S. Kaufmann and J. Romo, *J. Am. Chem. Soc.*, **71**, 3689 (1949).

Reaction of $\Delta^{3,5}$-Androstadien-17β-ol Acetate (Vd) with Dichlorocarbene.—To a solution of 10.8 g. (0.036 mole) of the diene Vd in "diglyme" (300 ml.) at 120–130°, 26.4 g. (0.144 mole) of sodium trichloroacetate was added in 10 equal portions at 10-minute intervals. The crude product, isolated as described above, was crystallized twice from methanol yielding the 3α,4α-dichloromethylene derivative VIIIa (3.85 g.), m.p. 153–157°. A further crystallization from methanol gave the analytical sample, m.p. 157–159°, $[\alpha]_D$ −62°.

Anal. Calcd. for $C_{22}H_{30}O_2Cl_2$: C, 66.49; H, 7.65; O, 8.05; Cl, 18.27. Found: C, 66.23; H, 7.74; O, 8.29; Cl, 17.95.

The mother liquors were adsorbed on Florisil (600 g.). Elution with hexane–ether (9:1) (9 fractions of 200 ml.) gave first unchanged starting material Vd (1.1 g.) (fractions 1–3). From fractions 5–9 (1.6 g.) there was obtained, after several crystallizations from methanol, an additional 900 mg. of the adduct VIIa, m.p. 148–151°. The yield of the latter thus amounted to 4.75 g. (54%).

Reaction of $\Delta^{4,5}$-Androstadien-17β-ol Acetate (Vd) with Difluorocarbene.—A solution of 10.8 g. (0.034 mole) of the diene Vd and 21.6 g. (0.142 mole) of sodium chlorodifluoroacetate in "diglyme" (600 ml.) was heated under reflux for 10 minutes. After cooling to below 100° an additional 21.6 g. of the salt was added, and the mixture again maintained at reflux for 10 minutes. The crude product was recrystallized twice from hexane affording 3α,4α-(difluoromethylene)-Δ^5-androsten-17β-ol acetate (VIIIc), 3.0 g. (28.9%), m.p. 178–179°, $[\alpha]_D$ −62°.

Anal. Calcd. for $C_{22}H_{30}O_2F_2$: C, 72.49; H, 8.29; F, 10.40. Found: C, 72.76; H, 8.52; F, 10.24.

The mother liquors were adsorbed on Florisil (600 g.). The first fractions (200 ml.) eluted with hexane (19:1) proved to be starting material (Vd), 1.54 g. The remaining fractions were combined (5.25 g.) and crystallized several times from methanol yielding 3.18 g. (29.5%) of 5β,6β-(difluoromethylene)-Δ^3-androsten-17β-ol acetate (IXc), m.p. 117–119°, $[\alpha]_D$ −13°.

Anal. Found: C, 72.80; H, 8.51; F, 10.51.

Hydrogenation of the Δ^3-Androstene Derivative IXc.—A solution of IXc (500 mg.) in ethanol (50 ml.) was hydrogenated over platinum oxide at room temperature and atmospheric pressure. One molar equivalent of hydrogen was absorbed in 4 hours. Crystallization of the product from hexane gave the saturated adduct Xb, m.p. 107–109°, $[\alpha]_D$ −44°.

Anal. Calcd. for $C_{22}H_{32}O_2F_2$: C, 72.09; H, 8.80; F, 10.37. Found: C, 71.75; H, 9.00; F, 10.31.

3α,4α-(**Dichloromethylene**)-Δ^5-androsten-17β-ol (**VIIIf**) was obtained by refluxing the acetate VIIIa (1.0 g.) in 1% methanolic potassium hydroxide solution (100 ml.) for 1 hour. Crystallization of the crude product (750 mg.) from methanol afforded the alcohol VIIIf, m.p. 195–197°, $[\alpha]_D$ −38°.

Anal. Calcd. for $C_{20}H_{28}OCl_2$: C, 67.69; H, 7.94; Cl, 19.96. Found: C, 67.42; H, 7.84; Cl, 19.87.

3α,4α-(**Difluoromethylene**)-Δ^5-androsten-17β-ol (**VIIIg**) was obtained by saponification of the acetate VIIIc as described above. The analytical sample from methanol showed m.p. 194–195°, $[\alpha]_D$ −37°.

Anal. Calcd. for $C_{20}H_{28}OF_2$: C, 74.49; H, 8.75; F, 11.76. Found: C, 74.80; H, 9.07; F, 12.34.

3α,4α-**Methylene-Δ^5-androsten-17β-ol (VIIIe). (a) From the Dichloromethylene Derivative VIIIf.**—A solution of the 3α,4α-dichloromethylene derivative VIIIf (750 mg.) in ether (50 ml.) was added to a solution of sodium (175 mg.) in anhydrous liquid ammonia (150 ml.) with vigorous stirring. After 2 hours, ammonium chloride was added until the blue color was discharged and the ammonia allowed to evaporate. The product was isolated by extraction with ether and recrystallized from methanol affording the cyclopropane VIIIe, m.p. 169–171°, $[\alpha]_D$ −40°.

Anal. Calcd. for $C_{20}H_{30}O$: C, 83.83; H, 10.56. Found: C, 83.31; H, 10.72.

(b) From the Adduct VIIIg.—Reduction of the 3α,4α-difluoromethylene derivative VIIIg with sodium in liquid ammonia was carried out as described above. Several crystallizations of the product from methanol furnished the cyclopropane VIIIe, m.p. 169–171°, which was identical by infrared spectral comparison with the sample of VIIIe obtained from the adduct VIIIf.

Reaction of $\Delta^{3,5}$-Pregnadien-17α-ol-20-one Acetate (Vh) with Dichlorocarbene.—A solution of 2.01 g. (0.006 mole) of the diene Vh was treated with 4.4 g. (0.024 mole) of sodium trichloroacetate in "diglyme" (100 ml.) at reflux temperature as described under the general procedure. The crude product was adsorbed on Florisil (100 g.). Elution with hexane–ether (4:1) furnished first the unchanged diene Vh (0.39 g.). Further elution with the same solvent gave a product (1.1 g.) which was crystallized from methanol to afford 3α,4α-(dichloromethylene)-Δ^5-pregnen-17α-ol-20-one acetate (VIIIb) (370 mg., 19.5%, m.p. 214–215°, $[\alpha]_D$ −60°).

Anal. Calcd. for $C_{24}H_{32}O_3Cl_2$: C, 65.68; H, 7.34; Cl, 16.14. Found: C, 65.23; H, 7.19; Cl, 16.17.

Reaction of the Diene Vh with Difluorocarbene.—The diene Vh (2.01 g., 0.006 mole) was treated with sodium chlorodifluoroacetate (7.32 g., 0.048 mole) in refluxing "diglyme" (50 ml.) as previously described. The product was adsorbed on Florisil (200 g.). The crystalline fractions eluted with hexane–ether (9:1) were combined (1.3 g.) and crystallized from methanol yielding 0.420 g. (19%) of 5β,6β-(dichloromethylene)-Δ^3-19-norandrosten-17β-ol acetate (IXa). A further crystallization from methanol furnished the analytical sample, m.p. 144–145°, $[\alpha]_D$ −34°.

Anal. Calcd. for $C_{21}H_{28}O_2Cl_2$: C, 65.80; H, 7.36; Cl, 18.50. Found: C, 66.13; H, 7.55; Cl, 18.71.

5β,6β-(**Dichloromethylene**)-19-norandrostan-17β-ol **Acetate (Xa).**—A solution of the adduct IXa (0.150 g.) in 95% ethanol (20 ml.) was reduced over platinum oxide at atmospheric pressure. One molar equivalent of hydrogen was taken up in 25 minutes. The product was recrystallized twice from methanol, affording the saturated analog Xa, m.p. 125–126°, $[\alpha]_D$ −11°.

Anal. Calcd. for $C_{21}H_{30}O_2Cl_2$: C, 65.45; H, 7.84; Cl, 18.41. Found: C, 65.51; H, 8.05; Cl, 18.30.

Reaction of the Diene Ve with Difluorocarbene.—A solution of 1.8 g. (0.006 mole) of the diene Ve in "diglyme" (100 ml.) was treated with 7.32 g. (0.048 mole) of sodium chlorodifluoroacetate in the prescribed manner. The crude product was adsorbed on Florisil (100 g.) and eluted with hexane–ether (9:1), collecting 75-ml. fractions. The early crystalline fractions were combined and recrystallized from methanol to yield 0.390 g. (18.6%) of the 5β,6β-difluoromethylene derivative IXd, m.p. 90–91°, $[\alpha]_D$ +26°.

Anal. Calcd. for $C_{21}H_{28}O_2F_2$: C, 71.86; H, 8.05; F, 10.84. Found: C, 72.00; H, 8.33; F, 11.03.

The latter fractions were combined and crystallized from methanol, affording 0.115 g. (5.0%) of 3α,4α:5β,6β-bisdifluoromethylene adduct XI, m.p. 165–168°. Recrystallization from methanol gave the analytical sample, m.p. 172–174°, $[\alpha]_D$ +54°.

Anal. Calcd. for $C_{22}H_{28}O_2F_4$: C, 65.98; H, 7.04; F, 18.98. Found: C, 66.24; H, 7.25; F, 19.41.

5β,6β-(**Difluoromethylene**)-19-norandrostan-17β-ol **Acetate (Xc).**—Hydrogenation of the adduct IXd in 95% ethanol over platinum oxide and crystallization of the product from methanol afforded the dihydro derivative Xc, m.p. 79–80°, $[\alpha]_D$ ±0°.

Anal. Calcd. for $C_{21}H_{30}O_2F_2$: C, 71.57; H, 8.58; F, 10.48. Found: C, 71.37; H, 8.28; F, 10.42.

5β,6β-(**Dichloromethylene**)-17α-ethinyl-Δ^3-19-norandrosten-17β-ol **Acetate (IXb).**—A solution of 1.0 g. (0.003 mole) of the diene Vf in "diglyme" (25 ml.) under reflux was treated with 2.2 g. (4 molar equivalents) of sodium trichloroacetate as previously described. The reaction product was adsorbed on Florisil (50 g.). The crystalline fractions eluted with hexane–ether (9:1) consisted of the adduct IXb, 0.52 g. (41.5%), m.p. 147–154°. Several crystallizations from methanol afforded the analytical sample, m.p. 169–172°, $[\alpha]_D$ −23°.

Anal. Calcd. for $C_{23}H_{28}O_2Cl_2$: C, 67.81; H, 6.93; F, 17.41. Found: C, 67.57; H, 7.06; F, 17.51.

2α,3α-(**Dichloromethylene**)-androstan-17β-ol **Acetate (XIVa).**—A solution of 3.8 g. (0.012 mole) of Δ^2-androsten-17β-ol acetate (XIII),[38] m.p. 101–102°, in "diglyme" (100 ml.) at 125–130° was treated with 13.6 g. (6 molar equivalents) of sodium trichloroacetate as described in the general procedure. The crude product was adsorbed from hexane on Florisil (200 g.). The crystalline fractions eluted with hexane–ether (9:1) were combined and repeatedly crystallized from methanol, affording 680 mg. (22%) of the adduct XIVa, m.p. 163–165°, $[\alpha]_D$ −32°.

Anal. Calcd. for $C_{22}H_{32}OCl_2$: C, 66.15; H, 8.07; Cl, 17.78. Found: C, 66.17; H, 7.94; Cl, 17.40.

Recrystallization of the mother liquors from methanol furnished 1.4 g. of the olefin XIII.

2α,3α-(**Dichloromethylene**)-androstan-17β-ol (**XIVb**).—A solution of the acetate XIVa (1.0 g.) in 2% methanolic potassium hydroxide (100 ml.) was set aside overnight at room temperature. The crude product (0.860 g.), m.p. 171–175°, was isolated by dilution with water and filtration. Recrystallization from methanol gave the pure alcohol XIVb, m.p. 179–180°, $[\alpha]_D$ +39°.

Anal. Calcd. for $C_{20}H_{30}OCl_2$: C, 67.20; H, 8.46; Cl, 19.85. Found: C, 67.25; H, 8.11; Cl, 19.72.

2α,3α-**Methylene-androstan-17β-ol (XIVc).**—To a solution of sodium (300 mg.) in liquid ammonia (150 ml.), there was added with stirring in 15 minutes a solution of the alcohol XIVb (600 mg.) in dry ether (45 ml.). Stirring was continued for 30 minutes when solid ammonium chloride was added until the blue color was discharged. The residue remaining after evaporation of ammonia was thoroughly extracted with ether and the ether extract evaporated. Crystallization of the crude product (530 mg.) from methanol afforded the pure 2α,3α-methylene derivative XIVc, m.p. 127–128°, $[\alpha]_D$ +26°.

Anal. Calcd. for $C_{20}H_{32}O$: C, 83.27; H, 11.18. Found: C, 83.33; H, 11.29.

2α,3α- and 2β,3β-(Difluoromethylene)-androstan-17β-ol Acetate (XIVd and XVb).—A solution of 15.0 g. (0.047 mole) of the olefin XIII in "diglyme" (500 ml.) was treated with 57.3 g. (0.376 mole) of sodium chlorodifluoroacetate as described under the above general procedure. The crude product was adsorbed from hexane on Florisil (900 g.). Elution with hexane–ether (9:1) afforded unchanged olefin XIII (3.5 g.), followed by a mixture of the adducts XIVd and XVb (10.0 g.). Fractional crystallization from methanol yielded the isomer XIVd (3.5 g.), m.p. 165–167°, $[\alpha]_D$ +11°.

Anal. Calcd. for $C_{22}H_{32}O_2F_2$: C, 72.09; H, 8.80; F, 10.37. Found: C, 72.05; H, 8.61; F, 10.62.

From the mother liquors there was isolated the isomeric adduct XVb (1.5 g.), m.p. 130–132°, $[\alpha]_D$ +20°.

Anal. Found: C, 72.21; H, 9.10; F, 10.54.

When the final mother liquors were rechromatographed on Florisil, there was isolated an additional quantity of unchanged olefin XIII (250 mg.) and adduct XVb (540 mg.), m.p. 130–132°. The yields of the isomeric adducts XIVd and XVd amounted to 27.5% and 16.6%, respectively.

2α,3α-(Difluoromethylene)-androstan-17β-ol (XIVe).—Saponification of the acetate XIVd (1.0 g.) was effected by leaving it overnight in 1% methanolic potassium hydroxide solution (50 ml.). The product was isolated in the usual manner and crystallized from methanol to give the alcohol XIVe, m.p. 159–160°, $[\alpha]_D$ +19°.

Anal. Calcd. for $C_{20}H_{30}OF_2$: C, 74.06; H, 9.32; F, 11.71. Found: C, 74.07; H, 9.38; F, 11.47.

2β,3β-(Difluoromethylene)-androstan-17β-ol (XVc).—Saponification of the acetate XVb (1.5 g.) by refluxing 1 hour in 1% methanolic potassium hydroxide solution (100 ml.) furnished the alcohol XVc (1.2 g.), m.p. 146–147° after recrystallization from methanol, $[\alpha]_D$ +15°.

Anal. Found: C, 74.42; H, 9.47; F, 12.09.

2β,3β-(Difluoromethylene)-androstan-17-one (XVd).—Oxidation of the alcohol XVc (250 mg.) in purified acetone (5 ml.) at 0° with 8 *N* chromic acid solution (0.25 ml.)[43] and isolation of the product in the usual manner afforded the ketone XVd, m.p. 100–102° after recrystallization from methanol, $[\alpha]_D$ +97°.

Anal. Calcd. for $C_{20}H_{28}OF_2$: F, 11.79. Found: F, 11.57.

2α,3α-Methylene-androstan-17β-ol (XIVc) from 2α,3α-(Difluoromethylene)-androstan-17β-ol (XIVe).—A solution of the difluoro steroid XIVe (500 mg.) in ether (50 ml.) was added to a solution of sodium (600 mg.) in liquid ammonia (200 ml.) with efficient stirring. After 2 hours, ammonium chloride was added until the blue color was discharged. The product was isolated as previously described and adsorbed on Florisil (25 g.). The first two crystalline fractions obtained by elution with hexane–ether (9:1) (25 ml.) were combined (40 mg.) and crystallized from methanol to afford the cyclopropane XIVc, m.p. 128–129°, undepressed on admixture with a sample of the same derivative XIVc, similarly obtained from the 2α,3α-dichloromethylene analog XIVb, and identical with the latter by comparative infrared spectroscopy.

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

[CONTRIBUTION FROM THE CONVERSE MEMORIAL LABORATORY OF HARVARD UNIVERSITY, CAMBRIDGE 38, MASS.]

Peresters. X. *tert*-Butylperoxy Chloroformate

BY PAUL D. BARTLETT AND HIROSHI MINATO

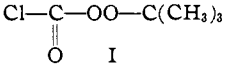
RECEIVED DECEMBER 14, 1962

tert-Butylperoxy chloroformate (I) decomposes in cumene by a concerted radical mechanism and with a half-life of 104 minutes at 60°. Its $\Delta H^{\ddagger}$ is 29.1 kcal., $\Delta S^{\ddagger}$ 10.5 cal./deg. It is an example of a perester which can decompose by the concerted mechanism with a minimum of restricted rotations. Decomposition in cyclohexene and diethyl ether is also by a radical mechanism with much chain involvement of the solvent in the latter case. The addition of lithium perchlorate to the ether medium accelerates the decomposition and converts it to an ionic mechanism of the Criegee rearrangement type. In formic acid, 60% aqueous dioxane and methanol, the decomposition of the perester appears to be entirely ionic but, whereas Criegee rearrangement predominates in formic acid, simple methanolysis occurs in methanol with very little loss of peroxidic oxygen. The aqueous dioxane medium occupies a middle position. Thus, by the choice of conditions, this one perester can be made to undergo concerted homolytic decomposition, chain decomposition involving solvent, Criegee rearrangement or simple solvolysis.

Introduction

It has been observed previously that *tert*-alkylperoxy esters of strong acids readily undergo ionic rearrangement showing strong susceptibility to acid catalysis and to media which favor ionization.[1-5] It has also been observed that when the perester can undergo homolytic fragmentation with the formation of a reasonably stable radical from the acid portion of the ester, carbon dioxide is produced quantitatively by the concerted fission of a C–C and an O–O bond.[6] This concerted decomposition, while it responds to polar substituents in the ester,[7] is not markedly dependent upon solvent.[8]

These two observations establish special interest for the perester *tert*-butylperoxy chloroformate (I) since it can be regarded as the perester of a rather strong acid and is also in a position to yield a chlorine atom by concerted decomposition. It might accordingly show enhanced tendencies toward both the ionic and the concerted radical forming types of reaction.



I

Preparation and Properties.—We have accordingly investigated this perester, which was first made by Davies and Hunter in 1953,[9] in some detail with respect to the rate, mechanism and products of its decomposition. When the perester is prepared by the addition of *tert*-butyl hydroperoxide to liquid phosgene at 0°, the pure material can be obtained by two distillations at 20–21° under 5 mm. pressure. The liquid perester does not explode when scratched, struck with a hammer, or heated on a spatula over a flame. Distillation at 50–60° under 120 mm. pressure occurs without violent decomposition, but the infrared spectrum of the distillate reveals some decomposition products (carbonyl bands at 5.62, 5.74 and 5.82 μ). When ten grams of the perester was allowed to stand at room temperature for an hour, it warmed spontaneously, exploded, and burned. Another specimen was successfully kept for ten hours at room temperature surrounded by a water-bath. A slightly wet sample kept at −25° for 47 days underwent slow hydrolysis developing the infrared bands of carbon dioxide and of acetone. No reaction occurred in the anhydrous perester in this period of time.

(1) R. Criegee, *Ann.*, **560**, 127 (1948).
(2) P. D. Bartlett and J. L. Kice, *J. Am. Chem. Soc.*, **75**, 5591 (1953).
(3) H. L. Goering and A. C. Olson, *ibid.*, **75**, 5853 (1953).
(4) P. D. Bartlett and R. R. Hiatt, *ibid.*, **80**, 1398 (1958).
(5) P. D. Bartlett and T. G. Traylor, *ibid.*, **83**, 856 (1961).
(6) P. D. Bartlett and R. R. Hiatt, *ibid.*, **80**, 1398 (1958).
(7) P. D. Bartlett and C. Rüchardt, *ibid.*, **82**, 1756 (1960).
(8) K. H. Lee, unpublished work in this Laboratory.
(9) A. G. Davies and K. J. Hunter, *J. Chem. Soc.*, 1808 (1953).