5α,6α- AND 5β,6β-DICHLOROMETHYLENE ADDUCTS OF 3β-ACETOXY-5-ANDROSTEN-17-ONE

Bojan Hamlin Jennings, Sharon Martin Boudreau, Beverly Braasch, and Cheryl Garganta

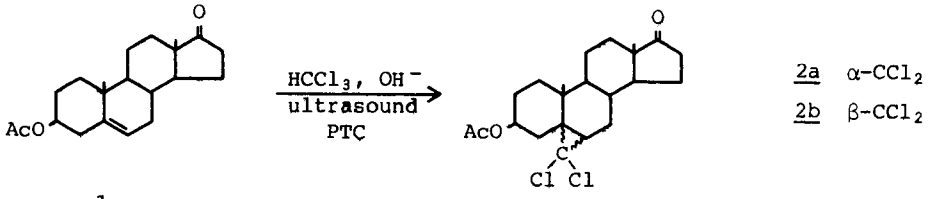
Department of Chemistry, Wheaton College, Norton, Massachusetts 02766

Received 12-16-81

ABSTRACT

Both the 5α,6α- and 5β,6β-dichloromethylene adducts (2a and 2b) of 3β-acetoxy-5-androsten-17-one (1) are produced when the latter is exposed to dichlorocarbene generated from chloroform and base by Phase Transfer Catalysis using ultrasound as a means of agitation. The ^{1}H NMR substituent effects of 5α,6α- and 5β,6β-dichloromethylene on the angular methyl groups (Zürcher values) are given. The ^{13}C NMR spectra for both compounds are presented and discussed.

We used ultrasound instead of mechanical stirring [1] to generate dichlorocarbene from chloroform and base by Phase Transfer Catalysis (PTC). The carbene reacted with 3β-acetoxy-5-androsten-17-one (1) to yield a mixture of 5α,6α- and 5β,6β- adducts (2a and 2b; 1:3).



1

Beta orientation of the dichloromethylene group in the major product (2b) was established by X-ray crystallographic data [3]; isomer 2a must, therefore, have the α-configuration. Thus we have unambiguous structural assignments for the first recorded pair of 5α,6α- and 5β,6β-dichloromethylene adducts from the same Δ^5 steroid.

The ^{1}H NMR data for these compounds was used to calculate the substituent effects of the α- and β- dichloromethylene groups on the

angular methyl groups (Zürcher values [4]). The δ value for the $C_{19}H_3$ signal of the α-isomer (2a), found at 1.20 ppm, compared with that of 3β-acetoxy-5α-androstan-17-one (0.86 ppm, as calculated from recorded Zürcher values [4]), gives a $C_{19}H_3$ Zürcher value of 0.34 ppm for 5α,6α-CCl_2. Similar comparison of the chemical shift for the C_{19}-protons of Compound 2b (at 1.29 ppm) with that of 3β-acetoxy-5β-androstan-17-one (1.00 ppm) leads to a $C_{19}H_3$ Zürcher value of 0.29 ppm for 5β,6β-CCl_2. As expected, the substituent effects on $C_{18}H_3$, calculated in the same way, are small and essentially the same for both 5α,6α- and 5β,6β-CCl_2, namely 0.04 and 0.05 ppm respectively.

Table I displays ^{13}C NMR data for 2a and 2b, along with shielding values calculated for the parents of the two compounds (3β-acetoxy-5α-androstan-17-one (13) and 3β-acetoxy-5β-androstan-17-one (14), and substituent effects (δ_2-δ_{parent}) [5] of 5α,6α-CCl_2 and 5β,6β-CCl_2 on each carbon. The values of these substituent effects are measures of the degree to which the α- or the β-CCl_2 influences the ^{13}C NMR resonance of a given carbon.

The data are arranged according to the multiplicity of the signals in order to facilitate discussion; a sequential listing of the shifts is also given at the bottom of the Table. Models (Dreiding for 2a and to scale from X-ray data [3] for 2b) were used to ascertain the geometric relationships discussed below.

Quartets (-CH_3). The resonance for C_{18} (δ13.6, Table I) in both 2a and 2b is essentially the same as for both parents (13 and 14), just as expected for a carbon far removed from the -CCl_2 [5].

C-19 appears at δ18.6 for 2a, 6.4 ppm downfield from C-19 of its parent (13), whereas C-19 of 2b, at δ21.2, lies upfield from parent 14

Table I. ^{13}C NMR Data for Compounds 2a and 2b[a]

Substituent Effect[d] α-CCl_2	Parent of 2a (13) Calc'd[b] δ	2a observed δ	Carbon	2b observed δ	Parent of 2b (14)[c] δ	Substituent Effect[d] β-CCl_2
			QUARTETS ($-CH_3$)			
-0.2	13.8	13.6	18	13.6	13.9	-0.3
6.4	12.2	18.6	19	21.2[e]	23.8	-2.6
		21.1	$\underline{C}H_3C(=O)$	21.3[e]		
			TRIPLETS ($>CH_2$)			
-0.5	36.8	36.3	1	35.6(34.2)[f]	30.0	5.6(4.2)
-0.7	27.4	26.7	2	25.3(25.8)	~25.3	~0.0(0.5)
-2.5	33.0	30.5	4	25.8(25.3)	~30.8	~-5.0(-5.5)
-7.4	30.8	23.4	7	34.2(35.6)	25.3	8.9(10.3)
0.1	20.5	20.6	11	20.8	20.4	0.4
-0.2	31.6	31.4	12	31.3	31.9	-0.6
-0.1	21.7	21.6	15	21.5	21.8	-0.3
0.4	35.2	35.6	16	36.0(35.6)	35.9	0.1(-0.3)
			DOUBLETS ($\geq CH$)			
-2.1	73.3	71.2	3	68.4	~71.3	-2.9
0.5(2.1)	28.5	29.0(30.6)	6	29.8(31.5)	26.4	3.4(5.1)
-4.4(-6.0)	35.0	30.6(29.0)	8	31.5(29.8)	35.3	-3.8(-5.5)
-12.1	54.4	42.3	9	45.4	40.2	5.2
0.2	51.4	51.6	14	53.0	51.7	1.3

Table I. ^{13}C NMR Data for Compounds 2a and 2b (cont.)

Substituent Effect[d] α-CCl_2	Parent of 2a (13) Calc'd[b] δ	2a observed δ	Carbon	2b observed δ	Parent of 2b (14)[c] δ	Substituent Effect[d] β-CCl_2
			SINGLETS (-$\overset{|}{\underset{|}{C}}$-)			
-8.6	44.6	36.0	5	34.6	36.6	-2.0
1.5	35.6	37.1	10	36.7	35.3	1.4
-0.2	47.7	47.5	13	47.2	47.8	-0.6
		72.9	>CCl_2	72.6		
		170.0	$\underset{\underset{O}{\|\|}}{COCH_3}$	170.4		
		219.6	C_{17}=O	219.9		

Absorption listed in sequence (δ values, ppm):

2a 13.6, 18.6, 20.6, 21.1, 21.6, 23.4, 26.7, 29.0, 30.5, 30.6, 31.4, 35.6, 36.0, 36.3, 37.1, 42.3, 47.5, 51.6, 71.2, 72.9, 170.0, 219.6.

2b 13.6, 20.8, 21.2, 21.3, 21.5, 25.3, 25.8, 29.8, 31.3, 31.5, 34.2, 34.6, 35.6, 36.0, 36.7, 45.4, 47.2, 53.0, 68.4, 72.6, 170.4, 219.9.

[a] Resonances are given in ppm (δ±0.03) using $CDCl_3$ as the internal standard, spectrometer frequency 62.8 MHz. Off-resonance decoupled spectra were used to determination of multiplicity. [b] Calculated for 3β-acetoxy-5α-androstan-17-one (13) by use of Blunt and Stother's tables [5]. [c] Since neither the values for 3β-acetoxy-5β-androstan-17-one nor the requisite substitution effects for β-steroids are available, the values shown are the observed data for 3β-acetoxy-5β-androstan-17-one [5] with adjustments made for replacement of the C_3-hydroxy by acetate: at C-2 (-2.6 ppm), C-3 (4.5 ppm), and C-4 (-2.7 ppm). These corrections were derived from observed values for two pairs of 3β-alcohol--acetate derivatives of 5β,14β-androstanes [11]. The resonances for all other carbons in the 3β-OH--3β-OAc pairs have essentially the same δ values. [d] δ_2-δ_{parent}; see text. [e] Distinguished by selective decoupling. [f] Resonance assignments in parentheses are possible alternatives.

by 2.6 ppm. This difference results from the magnetic anisotropy of the cyclopropyl ring, the influence of which has been described in terms of cones lying above and below the plane of the ring, their axes perpendicular to the plane, their vertices at its center [6]. Atoms lying within the cone should be shielded whereas those outside are deshielded. Although the angle of the cones has been variously estimated [6,7], it would seem that it should be large enough to encompass protons attached to the cyclopropyl ring (~100°) since they are known to be shielded. (See also the discussion of C-9, below.) C-19 of 2a lies in a deshielded region (surface of ~120° cone) whereas C-19 of 2b is well within a shielded zone (74.2° cone). The latter is shielded by no more than -2.6 ppm because it is δ- and almost syn-axial to the endo-Cl and therefore experiences a counter, deshielding influence [5].

The third set of quartets, at δ21.1 (2a) and δ21.3 (2b) is within the normal range for acetate methyl carbon [5].

Triplets ($-\overset{1}{C}H_2$). For both compounds the δ values for C-11, 12, 15, and 16, all distant from the substituent, are essentially the same as those for the corresponding carbons in each parent compound (13 and 14).

For the assignments of the other four methylene carbons (C-1, 2, 4, and 7); first consider 2a. C-1 and C-2 are both quite far from the cyclopropyl ring; although C-1 is δ to the chlorines, it escapes their influence because it is not syn-axial, the C-1--exo-Cl dihedral angle being ~50°; --endo, ~85°. Both carbons, therefore, resonate at essentially the same frequencies as C-1 and C-2 in the parent (13).

C-4 of 2a is in the same position as C-7 relative to the

cyclopropyl ring (~100° cones) and also relative to a chlorine. The ring shields both carbons. C-4 suffers a counter, deshielding anti-γ-effect [5]: both C-5 and C-cyclopropyl, which lie between C-4 and the γ-syn-axial exo-Cl, are fully substituted. This effect is lacking for C-7 and it is therefore further shielded by the γ-syn-axial endo-Cl. Accordingly, δ30.5 is assigned to C-4 (-3.2 ppm) and δ23.4 to C-7 (-7.4 ppm).

In contrast with 2a, none of the resonances for 2b which remain after assignments are made for C-11, 12, 15 and 16 are near the resonance for C-1 of parent 14 (δ30.0). Either δ25.3 or δ25.8 is suitable for C-2 which, being ε to the chlorines and far from the cyclopropyl ring, should resonate at approximately the same frequency as parent 14 (δ~25.3). C-4 in 2b, as in 2a, is shielded by the cyclopropyl ring (100.0° cone). It is γ-gauche to the exo-Cl, with a C-4--Cl dihedral angle of 8.6°. Thus either δ25.8 (-5.0 ppm) or δ25.3 (-5.5 ppm) is appropriate for C-4. C-7 in 2b, unlike 2a, is deshielded by the ring (112.7° cone; see discussion for C-9) and may be less shielded by the γ-endo-Cl than in 2a because it is farther from the chlorine (C-7, C-6, C-cyclopropyl angle is 122.4° in 2b, ~120° in 2a). It lies at δ34.2 or δ35.6 (8.9 or 10.3 ppm). This leaves δ35.6 or δ34.2 for C-1, deshielded (5.6 or 4.2 ppm), in sharp contrast with the situation in 2a.

Doublets (-$\overset{|}{\underset{|}{C}}$H). The signals for C-3, at δ71.2 for 2a and δ68.4 for 2b (confirmed by selective decoupling), are both somewhat upfield from the respective parents.

C-6 is β to two chlorines (deshielding) [5] and is incorporated

in the cyclopropyl ring (shielding) [9]. Since the only suitable resonances for this carbon are at δ29.0 (or 30.6) for 2a and at δ29.8 (or 31.5) for 2b, we see that the two conflicting influences are more balanced in 2a (substituent effect: 0.5 or 2.1 ppm) than in 2b (substituent effect: 3.4 or 5.1 ppm).

C-8, lying on the surface of an ~90° cone in 2a, 80.0° in 2b, is shielded by the cyclopropyl ring in both compounds. Accordingly their signals at δ30.6 (or δ29.0) and δ31.5 (or δ29.8) appear upfield from those of the parents (13 and 14).

In both 2a and 2b C-9 is δ- but not syn-axial to the chlorines. In 2a it is on the surface of an ~30° cone, strongly shielded, and resonates at δ42.3 (-12.1 ppm). On the other hand, C-9 of 2b, at δ45.4 is deshielded (5.2 ppm). This carbon is on the surface of a 107° cone and the fact that it is deshielded indicates that the angle of the cone which separates the shielding from the deshielding region is less than 107°.

The signal for C-14, in the C/D ring system, is at δ51.6 for 2a, close to that of parent 13; it is downfield more than expected (1.3 ppm) for 2b (δ53.0).

Singlets (-$\overset{|}{\underset{|}{C}}$-). C-5 of 2a, at δ36.0, is shielded by -8.6 ppm; C-5 of 2b, at δ34.6, by -2.0 ppm. Like tertiary C-6, C-5 is β to two chlorines (deshielding) and also part of the cyclopropyl ring (shielding) but, being quaternary, it is, unlike C-6, overall shielded because incorporation in the ring is more important than chlorine proximity [10].

C-10 is mildly deshielded (1.5 ppm) in both 2a and 2b. It lies on a 100° cone emanating from the cyclopropyl ring and is γ-syn-axial

to the endo-Cl with complete substitution of the intervening C-5 and C-cyclopropyl.

C-13, at a C/D juncture, is too far from the substituted site to be affected and, for both 2a and 2b, its resonance is essentially the same as that of the respective parent and also each is about the same as the other (δ47.5 and δ47.2).

The resonances for $-CCl_2$, at δ72.9 for 2a and δ72.6 for 2b, can be compared with absorption at δ56.1 for the α-carbon in 1,1-dichlorocyclopropane [9]. The $\overset{\overset{O}{\|}}{C}OCH_3$ and $\overset{\overset{O}{\|}}{C}$-17 absorptions at δ170 and δ220 respectively are normal for acetate and ketone carbonyl.

EXPERIMENTAL

The following instruments were used: Perkin-Elmer Model 137 Infrared Spectrometer; Perkin-Elmer Model 337 Grating Infrared Spectrometer; Varian Model T-60 NMR Spectrometer for ^1H NMR; Bruker Model WM-250 Spectrometer for both noise and off-resonance decoupled ^{13}C NMR Spectra. Perkin-Elmer 241 Polarimeter; Bronsonic Ultrasonic Cleaner, Model B32, 55 KHz, 150 watts, 10x15x15 (depth) cm^3. 3β-Acetoxy-5-androsten-17-one (dehydroepiandrosterane acetate) was purchased from Sigma Chemical Company; 18-crown-6, dibenzo-18-crown-6 (DBC), benzyltriethylammonium chloride (TEBA), and cetyltrimethylammonium bromide (CTMA) were obtained from Aldrich Chemical Company; alcohol-free $HCCl_3$ was prepared by washing reagent grade $HCCl_3$ three times with water and passing through Whatman phase separating paper. Brinkmann Silica Gel 60 was used for column chromatography; eluant solvents (benzene and ethyl acetate) were reagent grade. Merck thin layer chromatography (TLC) plates coated with 0.2 mm Silica Gel 60, without fluorescent indicator, were used. All IR spectra were taken as KBr discs; NMR spectra were obtained from $DCCl_3$ solutions, tetramethylsilane as internal reference. Melting points were taken in sealed tubes and are uncorrected. The molecular weight determination of Compound 2b and elemental analyses were made at Schwartzkopf Microanalytical Laboratory, Inc., Woodside, N.Y.

Procedure for PTC Reactions Using Ultrasound for Agitation. 3β-Acetoxy-5-androsten-17-one (0.6 mmole: 200 mg), catalyst (0.2 mmole: 53 mg 18-crown-6, 72 mg DBC, 46 mg TEBA, 73 mg CTMA), $HCCl_3$ (23 ml), and saturated base (KOH or NaOH, 10 ml) were placed in a 1 liter Erlenmeyer flask, fitted with a reflux condensor, positioned as close as possible to the bottom of the ultrasound tank which was filled with water kept sufficiently hot (by replacement when necessary) to sustain reflux. After exposure to ultrasound for one hour, the mixture was transferred to a separatory funnel along with approximately

200 ml CH_2Cl_2 and water. After separation of layers, the organic phase was washed with 6N HCl and water, then passed through phase separating paper (Whatman 1PS), and evaporated. Before analysis, the last traces of volatile material were removed by a vacuum pump.

The molar ratios of combined products (2a plus 2b) to starting material (1) were determined by ^{1}H NMR as described below. With 18-crown-6 and NaOH, the ratio was 2:1; with KOH, 1:1. DBC, with both bases, gave a 2:1 yield. A 5:1 ratio was achieved with both TEBA and CTMA when NaOH was used; with KOH, only 1:1. Reproducibility (at least four runs) was occasionally poor but all reactions gave at least 50% yield. The yield of 2b was consistently three times that of 2a, determined by ^{1}H NMR.

Analysis of Crude Product Mixtures

TLC. Ethyl acetate-benzene solution (10% ethyl acetate) was used to develop the chromatogram on Silica Gel 60 plates; visualization was accomplished by exposure to iodine vapor. Only two spots appeared, the one with lower R_F value corresponding to 2b, the other to a mixture of 1 and 2a.

^{1}H NMR. The yield data reported above was obtained by comparing the height of the sharp $C_{19}H_3$ peak of 1 (δ1.05) with the height of the superimposed $C_{18}H_3$ peaks of the products, both of which appear at δ0.83. To test the accuracy of this method, we prepared quantitative mixtures of the purified products and starting material, in approximately the mole ratios we perceived in the crude products, and compared the ratios obtained from the methyl peaks in the ^{1}H NMR spectra, as described above, with the known compositions. There was complete agreement.

The relative heights of the $C_{19}H_3$ peaks at δ1.29 (2b) and δ1.20 (2a) were 3:1 (2b:2a).

Isolation and Purification of Products

Crude product mixtures from several PTC reactions were combined and chromatographed on a Silica Gel 60 column, using a 10% ethyl acetate-benzene solvent system. After elution of an orange oil, fractions containing 1 and 2a (^{1}H NMR analysis) were obtained (~14% of material put in column), followed by mixtures of 2a, 2b and 1 (~30%). The final fractions held 2b only (~26%). Dark brown material remained on the column. Compound 2a was separated from 1 by washing early fractions with small amounts of ether or acetone, which removed most of the starting material (1), followed by several recrystallizations from either solvent. (In this latter process, care was taken not to force into solution small amounts (<1 mg from 82 mg) of highly insoluble unidentified material which did not have the correct IR spectrum for 2a). Thus were obtained white crystals of 2a (58 mg, for example, from 657 mg chromatographed fractions): mp 232-233°; Molecular rotation, [M] (.03374 g/ml) 589 nm, +67.0; 578, +71.9; 546, +92.6; 436, +291.2; 365, +1005. UV λ_{max} 295.9 nm. IR 1736(s), 1244(s), 1031(m), 839(m), and 819(m) cm^{-1}. ^{1}H NMR δ0.83 (s, 3H, $C_{18}H_3$), 1.20(s, 3H, $C_{19}H_3$), 2.00(s, 3H, acetate CH_3), 5.02 (heptet, J=1.2 Hz, 1H, C_3H). ^{13}C NMR, see Table I.

Anal. Calc'd for $C_{22}H_{30}O_3Cl_2$: C, 63.92; H, 7.32, Cl, 17.15 Found: C, 63.99; H, 7.51; Cl, 17.40.

Chromatographic fractions containing only Compound 2b (^{1}H NMR) were recrystallized from ether to give white orthorhombic crystals (e.g. 299 mg from 363 mg): mp 154.5-155°.MW (Osmometry) Calc'd 413.4 g/m Found 412±5% g/m. [M] (0.01567 g/ml) 589 nm, -7.0; 578, -5.0; 546, -5.8; 436, +158; 365, +863.6. UV λ_{max} 295.3 nm. IR 1733(s), 1245(s), 1042(s), 1025(m), 1013(s), 1007(s), 837(s), 802(m) cm^{-1}. ^{1}H NMR δ0.83(s, 3H, $C_{18}\underline{H}_3$), 1.29(s, 3H, $C_{19}\underline{H}_3$), 2.06(s, 3H, acetate $C\underline{H}_3$), 4.98(m, 1H, $C_3\underline{H}$). ^{13}C NMR, see Table I. X-ray crystallography, see Reference 3.

Anal. Calc'd for $C_{22}H_{30}O_3Cl_2$:C, 63.92; H, 7.32; Cl, 17.15. Found: C, 63.94; H, 7.54: Cl, 17.43.

Multiple recrystallizations from ether (in which 2a is less soluble than 2b) were needed to separate the two products in the intermediate fractions which contained both compounds.

For comparison with ^{1}H NMR data for 2a and 2b, we found the following resonances for 1: δ0.87(s, 3H, $C_{18}\underline{H}_3$), 1.05(s, 3H, $C_{19}\underline{H}_3$), 2.00(s, 3H, acetate $C\underline{H}_3$), 4.51(m, 1H, $C_3\underline{H}$), 5.33(d, 1H, $C_6\underline{H}$).

ACKNOWLEDGMENT

Acknowledgment is made to the donors of the Petroleum Research Fund, administered by the American Chemical Society for support of this work. We also thank Dr. Charles Lerman of Stuart Pharmaceuticals, Division of ICI Americas, for his generosity and expertise in obtaining the ^{13}C NMR spectra. We are indebted to Dr. Styliani Pastra-Landis (Wheaton College/ Brandeis University) for taking the polarimetric data; to Harry Pastra-Landis for suggesting the use of ultrasound; and to Dr. Donna Stevenson Amenta for help with the manuscript.

REFERENCES

1. Cavitation, which is responsible for chemical changes in some other systems [2] is not involved in the reactions reported here: the transmission of ultrasonic energy through the relatively thick glass vessels which were used does not produce cavitation in contained liquids.
2. e.g. Jennings, B. H., and Townsend, S. N., J. PHYS. CHEM. 65, 1574 (1961).
3. Boudreau, S. M., and Jennings, B. H., STEROIDS, subsequent paper in this issue.
4. Bhacca, N. S., and Williams, D. H., "Applications of NMR Spectroscopy in Organic Chemistry: Illustrations from the steroid field," Holden-Day, Inc., San Francisco, Chapter 2 (1966).
5. Blunt, J. W., and Stothers, J. B., ORG. MAG. RES. 9, 439 (1977).
6. Hahn, R. C., and Howard, P. H., J. AM. CHEM. SOC. 94, 3143 (1972).
7. Kohout, L. and Kajkoš, J., COLLECTION CZECHOSLOV. CHEM. COMMUN. 37, 3490 (1972).
8. Stothers, J. B., Tan, C. T., and Teo, K. C., J. MAG. RES. 20, 570 (1975).
9. Stothers, J. B., "Carbon-13 NMR Spectroscopy," Academic Press, New York, p. 60 et seq. (1972).
10. Grutzner, J. B., Jautelat, M., Dence, J. B., Smith, R. A., and Roberts, J. D., J. AM. CHEM. SOC. 92, 7107 (1970).
11. Reference 5, Table 1, Compounds 131, 132, 135, and 136.