The Preparation of 4,6-Dichloro Steroids

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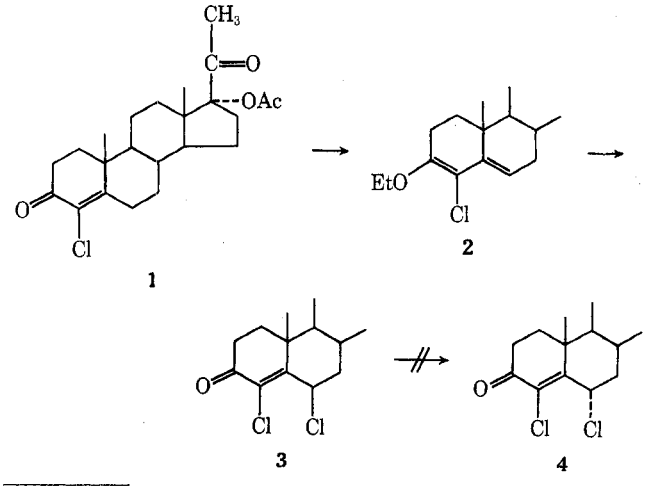
Chlorination of a steroid incorporating the 6-chloro-4,6-dien-3-one system gives a 4,6,7-trichloro intermediate which on dehydrochlorination yields the corresponding 4,6-dichloro-4,6-dien-3-one. The structure and mechanism of formation of the trichloro intermediate is discussed.

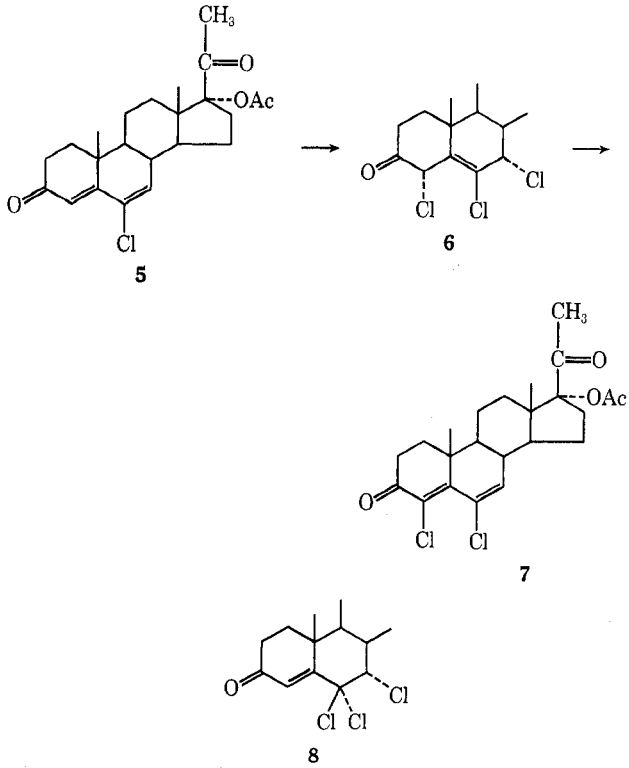
A recent report[1] describes the synthesis of some steroids incorporating a 4,6-dichloro-4,6-dien-3-one system. We should now like to report our related studies in this field which provide new information on the mechanism of formation of these compounds and the structure of their intermediates.

Our initial approach to this system involved reaction of the readily available 4-chloro steroids under a variety of conditions. Thus, reaction of **1**[2] with triethyl orthoformate in the presence of sulfuric acid gave the enol ether **2** which was converted into **3** on treatment with *N*-chlorosuccinimide. Examination of the nmr spectrum of **3** indicated that the chlorine atom at C-6 had the expected β configuration, since the C-6α (equatorial) proton exhibited a narrow doublet of doublets at δ 5.67 (J = 3.8 and 1.8 Hz).[3]

We then attempted to prepare the enol ethyl ether of **3**, since it is known that the dehydrogenation of such compounds with 2,3-dichloro-5,6-dicyanobenzoquinone (DDQ) leads to the corresponding 4,6-dien-3-one system.[4] However, all attempts to form the enol ether under standard conditions were unsuccessful. As a consequence, it was not unexpected to find that attempted dehydrogenation of the ketone **3** with DDQ or chloranil gave only recovered starting material. It is interesting to note that **3** was recovered unchanged after attempted isomerization with hydrogen chloride in acetic acid to the corresponding 6α isomer **4**. These reaction conditions[5] readily convert 4-unsubstituted 6β-chloro steroids into the 6α (equatorial) isomers. The stability of **3** under equilibrating conditions is probably associated with the steric hindrance in **4** (or the corresponding transition state) due to eclipsing of the chlorine atoms. Other workers have observed similar results in the 4-methyl-6β-acetoxymethyl, 4-methyl-6β-bromo,[6] and the 4,6β-dimethyl[7] series.

However, the desired 4,6-disubstituted 4,6-dienes were readily obtained utilizing C-6 substituted 4,6-dienes as starting materials. Thus, reaction of **5**[5,8] in chloroform with 1 molar equiv of chlorine gave the trichloro intermediate **6** which was dehydrohalogenated with pyridine to give the desired 4,6-dichloro-4,6-diene **7**.[9] Similar reactions with 6-chloro-6-dehydrocortisone acetate gave **17** and **18**. The earlier workers[1] reported that reaction of **5** with lithium chloride and *N*-chlorosuccinimide in the presence of hydrogen chloride gave a trichloro intermediate which on treatment with pyridine afforded **7**. These workers suggested **8** as the structure of the trichloro intermediate.





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(1) R. Wiechert, *Experientia*, **24**, 767 (1968).

(2) F. Mukawa, *Bull. Chem. Soc. Jap.*, **33**, 25 (1960).

(3) N. S. Bhacca and D. H. Williams, "Applications of NMR Spectroscopy in Organic Chemistry," Holden-Day, San Francisco, Calif., 1964, p 51.

(4) S. K. Pradhan and H. J. Ringold, *J. Org. Chem.*, **29**, 601 (1964); A. B. Turner and H. J. Ringold, *J. Chem. Soc.*, 1720 (1967); D. Walker and J. D. Hiebert, *Chem. Rev.*, **67**, 153 (1967).

(5) H. J. Ringold, E. Batres, J. Edwards, and J. Zderic, *J. Amer. Chem. Soc.*, **81**, 3485 (1959).

(6) C. W. Shoppee, F. P. Johnson, R. E. Lack, R. J. Rawson, and S. Sternhell, *J. Chem. Soc.*, 2476 (1965).

(7) D. Burn, G. Cooley, B. Ellis, A. R. Heal, and V. Petrow, *Tetrahedron*, **19**, 1757 (1963).

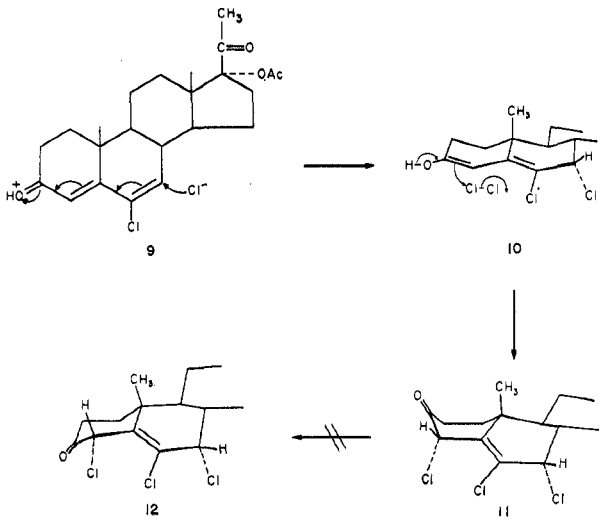
(8) K. Brückner, B. Hampel, and U. Johnsen, *Chem. Ber.*, **94**, 1225 (1961).

(9) Compound **7** could also be readily prepared directly by reaction of **5** with chlorine in propionic acid, by the method of D. N. Kirk, D. K. Patel, and V. Petrow, *J. Chem. Soc.*, 1184 (1954).

In two cases (**6** and **17**) we have isolated and characterized the intermediates prepared by both chlorination procedures (chlorine in chloroform or lithium chloride and *N*-chlorosuccinimide[1]). In each case both methods of preparation gave the same trichloro intermediate, as shown by ir, uv, nmr, and tlc.

It is of some interest to discuss the structure and mechanism of formation of the trichloro intermediates. Structure **8** could be ruled out since the trichloro intermediates were shown by nmr to exhibit no vinyl protons in the region of 5–7 ppm.[10]

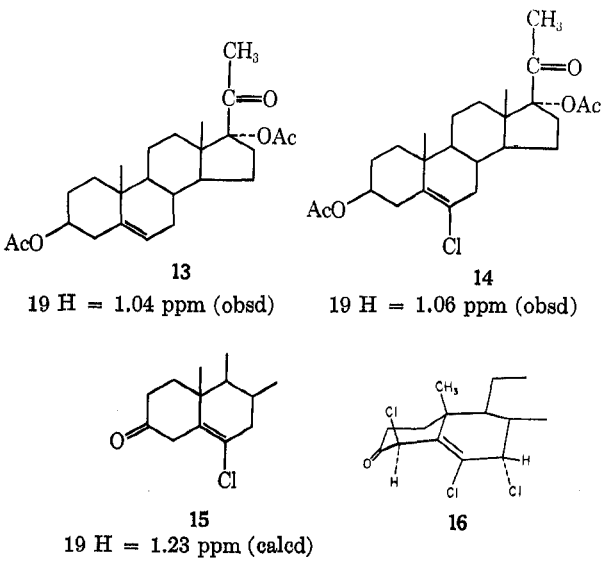
The structure of **6** (and **17**) could be assigned based on the accepted mechanism for the addition of halogens to α,β-unsaturated ketones.[11] In such acid-catalyzed chlorinations,[12] protonation of the C-3 carbonyl of **5** to give **9** could be postulated, followed by axial attack of chloride ion at C-7 to give the enol **10**.



In the halogenation of unhindered enols, it is well known[13] that the halogen attacks in the direction best suited for maximum overlap with the π orbitals of the double bond (perpendicular to the plane of the double bond). In the present case, it is seen that axial attack of the halogen from the top side of **10** is seriously hindered by the presence of the axial C-10β angular methyl group. Consequently, axial attack from the bottom of **10** would be expected to supervene to give **11** in which ring A exists in a "boat" conformation. Flexible forms such as **11** generally undergo a conformational flip to give the thermodynamically more stable chair conformation **12**. In the present example, however, the latter conformation could be discounted due to the unfavorable eclipsing of the C-4 and C-6 chlorine atoms and the repulsive interaction of the C-3 carbonyl and the C-4 carbon–chlorine dipoles. The thermodynamic stability of **11** and **3** can thus be rationalized in terms of the similar steric environments in **12** and **4**, respectively.

These assignments were substantiated by means of the following observations. In the nmr, the C-7 proton of **6** gave a well-resolved doublet at δ 4.44 (J = 3.0 Hz) thus substantiating its equatorial configuration. The absorption of the C-4 proton, which occurred as a sharp signal at δ 4.82, did not permit assignment of configuration. However, the predicted conformation of ring A and the stereochemistry at C-4 could be supported on the basis of the chemical shift of the C-19 protons, as outlined in the following scheme (Chart I).

CHART I



The observed value (1.04 ppm) for the C-19 protons in **13**[14] did not differ significantly from the observed value (1.06 ppm) for the C-19 protons in **14**.[15] Thus, the addition of a chlorine atom at C-6 had little effect on the chemical shift of the C-19 protons in **14** and a chemical shift of 1.23 ppm could be calculated[16] for compound **15**. Structure **16** represents the hypothetical product arising from β chlorination of the enol **10**. In this case the axial C-4 chlorine atom would be expected to deshield the C-19 protons and to give rise to a downfield shift (>1.25 ppm).[17] However, the observed value (0.90 ppm) indicated that an upfield shift had occurred, which is best explained on the basis of structure **11**. In a related case it has been noted that the C-3 carbonyl (in a ring A boat conformation) exerts a shielding effect on the C-19 protons,[18] resulting in a diamagnetic shift of the latter.

The substantial ultraviolet absorption [λ_{max} 240 mμ (ϵ ~5500)] associated with the trichloro derivatives **6** and **17** may be explained by the nonplanarity of the β,γ-unsaturated ketone system which causes some over-

(10) It should be noted that many of the reported compounds (ref 1) incorporate a methylene bridge at C-1 and C-2. We do not exclude partial structure **8** in such cases.

(11) E. S. Gould, "Mechanism and Structure in Organic Chemistry," Henry Holt and Co., New York, N. Y., 1959, p 527.

(12) When the chloroform utilized as a solvent was first treated with alumina, the chlorination of 6-chloro-6-dehydrocortisone acetate had to be initiated by the addition of a catalytic amount of hydrogen chloride.

(13) E. J. Corey, *Experientia*, **9**, 329 (1953).

(14) Purchased from Searle Chemicals, Inc., Chicago, Ill.

(15) J. S. Mihina, *J. Org. Chem.*, **27**, 2807 (1962).

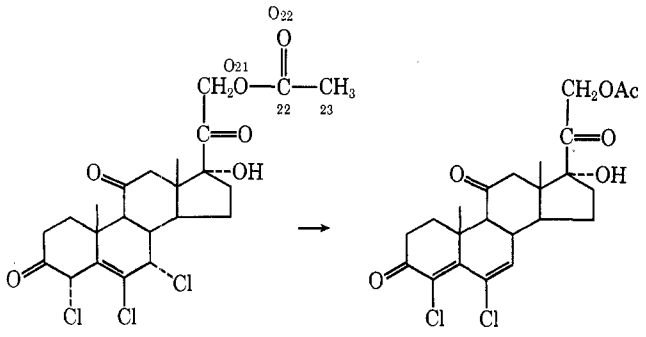
(16) Reference 3, p 19.

(17) Any minor contributions due to the C-7α chlorine atom have been ignored in this calculation.

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

lap of the nonbonding p orbital of the oxygen atom and the π orbital of the double bond.[19,20]

The conformation of ring A and stereochemistry of the substituents assigned to the trichloro intermediates have been fully confirmed by the single crystal X-ray analysis of **17**.



17 18

The bond lengths and bond angles involving the nonhydrogen atoms are given in Tables I and II. The

Table I

Bond Lengths (Å)[a] in 17 Averaged over Thermal Motion[b]

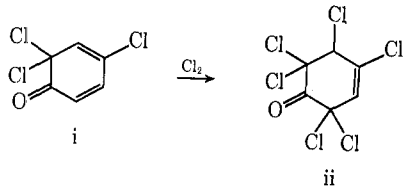
C(4)-Cl(4)	1.804 (5)	C(6)-C(7)	1.491 (6)
C(6)-Cl(6)	1.730 (5)	C(7)-C(8)	1.514 (7)
C(7)-Cl(7)	1.820 (5)	C(8)-C(9)	1.557 (6)
		C(8)-C(14)	1.522 (6)
C(3)-O(3)	1.192 (6)	C(9)-C(10)	1.558 (6)
C(11)-O(11)	1.182 (6)	C(9)-C(11)	1.535 (7)
C(17)-O(17)	1.419 (6)	C(10)-C(19)	1.558 (6)
C(20)-O(20)	1.171 (7)	C(11)-C(12)	1.525 (6)
C(21)-O(21)	1.438 (7)	C(12)-C(13)	1.521 (7)
C(22)-O(21)	1.314 (7)	C(13)-C(14)	1.533 (7)
C(22)-O(22)	1.134 (8)	C(13)-C(17)	1.556 (6)
		C(13)-C(18)	1.533 (6)
C(1)-C(10)	1.546 (6)	C(14)-C(15)	1.550 (7)
C(1)-C(2)	1.551 (6)	C(15)-C(16)	1.547 (7)
C(2)-C(3)	1.483 (8)	C(16)-C(17)	1.539 (8)
C(3)-C(4)	1.522 (8)	C(17)-C(20)	1.552 (7)
C(4)-C(5)	1.513 (6)	C(20)-C(21)	1.523 (9)
C(5)-C(6)	1.329 (7)	C(22)-C(23)	1.520 (8)
C(5)-C(10)	1.520 (7)		

[a] Estimated standard deviation of last significant figures appears in parentheses. [b] Second atom is assumed to ride on first: W. R. Busing and H. A. Levy, *Acta Crystallogr.*, **17**, 142 (1964).

average C–H distance is 0.97 Å. There are two intermolecular O–O distances indicative of weak hydrogen bonding: O(3)–O(17) is 2.95 Å and O(17)–O(20) is 3.13 Å. A stereoscopic view of the molecule is shown in

(19) L. Vollbracht, W. G. B. Huysmans, W. J. Mijs, and H. J. Hageman, *Tetrahedron*, **24**, 6265 (1968).

(20) A similar ultraviolet absorption of a β,γ-unsaturated ketone system (ii) formed by a 1,4 addition of chlorine to a ketodiene system (i) has been noted by H. Labhart and G. Wagniere, *Helv. Chim. Acta*, **42**, 2219 (1959).



i ii

The ultraviolet spectrum of ii [λ_{max} 235 mμ (ϵ 9000)] is an example of a strong nonclassical E. T. band of a β,γ-unsaturated ketone.

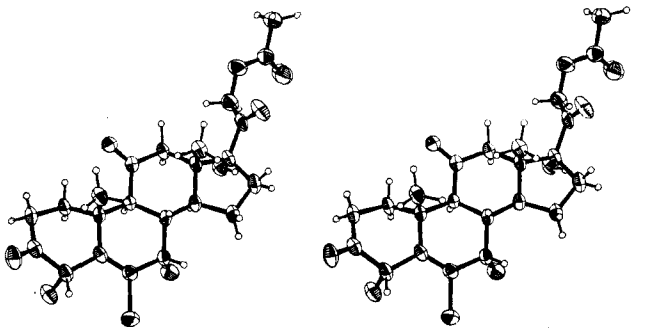


Figure 1.—Stereoscopic illustration of **17**.

Table II

Bond Angles (Degrees)[a] in 17

C(10)-C(1)-C(2)	111.5 (4)	C(9)-C(11)-C(12)	117.3 (4)
C(1)-C(2)-C(3)	113.1 (4)	C(9)-C(11)-O(11)	122.9 (4)
C(2)-C(3)-C(4)	117.1 (4)	C(12)-C(11)-O(11)	119.7 (4)
C(2)-C(3)-O(3)	123.4 (5)	C(11)-C(12)-C(13)	108.9 (4)
C(4)-C(3)-O(3)	119.4 (5)	C(12)-C(13)-C(14)	108.9 (4)
C(3)-C(4)-C(5)	114.4 (4)	C(12)-C(13)-C(17)	116.0 (4)
C(3)-C(4)-Cl(4)	103.2 (3)	C(12)-C(13)-C(18)	110.0 (4)
C(5)-C(4)-Cl(4)	110.4 (3)	C(14)-C(13)-C(17)	99.6 (4)
C(4)-C(5)-C(10)	116.8 (4)	C(14)-C(13)-C(18)	111.0 (4)
C(4)-C(5)-C(6)	120.0 (4)	C(17)-C(13)-C(18)	110.9 (3)
C(10)-C(5)-C(6)	123.2 (4)	C(13)-C(14)-C(8)	113.0 (4)
C(5)-C(6)-C(7)	125.3 (4)	C(8)-C(14)-C(15)	117.9 (4)
C(5)-C(6)-Cl(6)	120.6 (3)	C(13)-C(14)-C(15)	104.3 (4)
C(7)-C(6)-Cl(6)	114.1 (4)	C(14)-C(15)-C(16)	104.3 (4)
C(6)-C(7)-C(8)	112.8 (4)	C(15)-C(16)-C(17)	106.2 (4)
C(6)-C(7)-Cl(7)	106.9 (3)	C(16)-C(17)-C(13)	102.5 (4)
C(8)-C(7)-Cl(7)	112.8 (3)	C(16)-C(17)-C(20)	113.6 (4)
C(7)-C(8)-C(9)	110.6 (3)	C(16)-C(17)-O(17)	112.1 (4)
C(7)-C(8)-C(14)	113.5 (4)	C(13)-C(17)-C(20)	113.4 (4)
C(14)-C(8)-C(9)	111.8 (4)	C(13)-C(17)-O(17)	106.3 (3)
C(8)-C(9)-C(10)	111.1 (3)	C(20)-C(17)-O(17)	108.7 (4)
C(8)-C(9)-C(11)	112.3 (3)	C(17)-C(20)-C(21)	115.3 (4)
C(11)-C(9)-C(10)	114.4 (4)	C(17)-C(20)-O(20)	122.3 (5)
C(9)-C(10)-C(5)	109.3 (3)	C(21)-C(20)-O(20)	122.4 (5)
C(9)-C(10)-C(1)	110.2 (3)	C(20)-C(21)-O(21)	109.5 (5)
C(9)-C(10)-C(19)	111.0 (3)	C(21)-O(21)-C(22)	116.7 (4)
C(5)-C(10)-C(1)	105.9 (3)	O(21)-C(22)-C(23)	111.4 (5)
C(5)-C(10)-C(19)	109.1 (4)	O(21)-C(22)-O(22)	123.4 (5)
C(1)-C(10)-C(19)	111.1 (4)	C(23)-C(22)-O(22)	125.2 (5)

[a] Estimated standard deviation of last significant figures appears in parentheses.

Figure 1 in which it is seen that ring A incorporates a "skew" boat conformation.

Determination of the Crystal Structure.—The positions of the three independent chlorine atoms were obtained from a sharpened three-dimensional Patterson synthesis. One Fourier synthesis, based on the phases calculated for the chlorine atoms, yielded the positions of all carbon and oxygen atoms. Four cycles of full matrix least squares gave a disagreement index (R) of 10.6% for an isotropic model. An additional two cycles of least squares in which the chlorine atoms were assigned anisotropic thermal parameters brought R to 7.7%. The structure was further refined by block-diagonal least squares with anisotropic thermal parameters for all atoms (9 × 9 blocks) to an R of 5.6%. A difference Fourier calculated at this point clearly showed all 27 hydrogen atoms. Refinement was concluded after several additional cycles of least squares (9 × 9 blocks for the nonhydrogen atoms, 4 × 4 blocks for the hydrogen atoms) when all positional parameter shifts were less

than one-tenth of the corresponding parameter's standard deviation. A difference Fourier based on the final parameters has no features greater than 0.25 electron/A^3 in magnitude. The final R value is 3.6%.[21]

Experimental Section

Melting points were determined in capillary tubes and are corrected. Infrared spectra were recorded on a Beckman instrument Model IR-9. Nuclear magnetic resonance spectra were recorded with Varian A-60 or Varian HA-100 instruments using tetramethylsilane as internal reference standard. Optical rotations were measured with a Perkin-Elmer Model 141 polarimeter. Thin layer chromatography (tlc) was run on silica gel G and developed with benzene–ethyl acetate mixtures. The spots were detected by spraying with *p*-toluenesulfonic acid solution followed by heating.

4-Chloro-3-ethoxy-17α-hydroxypregna-3,5-dien-20-one Acetate (2).—A solution of 13 g (0.032 mol) of 4-chloro-17α-hydroxypregn-4-ene-3,20-dione acetate (1)[2] in 135 ml of dioxane (freshly passed over alumina) was treated with 17 ml (16 g, 0.108 mol) of triethyl orthoformate, 8 ml of ethanol, and 1.7 ml of concentrated sulfuric acid. This mixture was stirred at room temperature in the dark. After 15 min the solution had turned green and a large amount of precipitate had formed. After 1 hr tlc showed that only traces of starting material remained and the reaction was poured with stirring into 3 l. of ice and water containing excess sodium bicarbonate. The resulting slurry was stirred for 20 min, and the precipitate was collected by filtration and washed well with water. The damp solid was dissolved in dichloromethane and the organic layer was dried (Na_2SO_4). The solution was concentrated with the simultaneous addition of ether to give 10.30 g (74%) of **2** as yellow crystals, mp 243–247°. Recrystallization from dichloromethane–ether gave the analytical sample as colorless crystals: mp 264–265° (the melting point varies with the rate of heating); $[\alpha]^{25}D$ −104.2° (*c* 1.0, dioxane); uv max (ethanol) 246 mμ (ε 18,000); ir ($CHCl_3$) 1730 and 1715 cm^{-1}; nmr ($CDCl_3$) δ 6.0 (br d, 1, C-6 **H**), 4.07 (q, 2, OCH_2CH_3), and 1.37 (t, 3, OCH_2CH_3).

Anal. Calcd for $C_{25}H_{35}ClO_4$: C, 69.03; H, 8.11; Cl, 8.15. Found: C, 68.85; H, 8.07; C, 8.20.

4,6β-Dichloro-17α-hydroxypregn-4-ene-3,20-dione Acetate (3).—To a slurry of 20.2 g (0.045 mol) of **2** in 650 ml of acetone was added a solution of 23 g of sodium acetate dissolved in 190 ml of water, 36 g (0.27 mol) of *N*-chlorosuccinimide, and 26 ml of glacial acetic acid. The suspension was stirred at room temperature until it became homogeneous (2 hr). The reaction mixture was poured slowly into 5 l. of ice and water and the resulting suspension was stirred for 30 min. The precipitate was collected by filtration and washed well with water, and while still damp was dissolved in dichloromethane. The organic layer was dried (Na_2SO_4) and concentrated to a yellow oil which on crystallization from dichloromethane–ether gave 15.13 g (74%) of **3** as light yellow crystals, mp 206–210°. Recrystallization from dichloromethane–ether gave the analytical sample as colorless crystals: mp 216–218°; $[\alpha]^{25}D$ −114.9° (*c* 0.96, $CHCl_3$); uv max (ethanol) 258 mμ (ε 12,300); ir ($CHCl_3$) 1735, 1715, and 1695 cm^{-1}; nmr ($CDCl_3$) δ 5.67 (doublet of doublets, 1, J = 3.8 and 1.8 Hz, C-6 **H**).

Anal. Calcd for $C_{23}H_{30}Cl_2O_4$: C, 62.59; H, 6.85; Cl, 16.07. Found: C, 62.43; H, 7.13; Cl, 16.31.

4α,6,7α-Trichloro-17α-hydroxypregn-5-ene-3,20-dione Acetate (6). A.—A cooled (0°) solution of 5.0 g (0.0123 mol) of 6-chloro-17α-hydroxypregna-4,6-diene-3,20-dione acetate (**5**)[5,8] in 75 ml of chloroform was treated with 12.5 ml of a 1.04 *M* solution of chlorine in carbon tetrachloride. The reaction mixture was stirred at 0° for 30 min and the solvent was then removed under reduced pressure. The residue was treated with hexane (10 ml) and the solvent was again removed under reduced pressure to give a light yellow foam. The residue was triturated with ether (25 ml) and stored at 0° overnight. The precipitate was filtered to give 0.3 g of crude product. In a similar manner, the mother liquor was triturated with ether several times to give a total of 0.9 g of crude **6**. Crystallization from ethyl acetate–cyclohexane gave the analytical sample: mp 205–207° dec (shrinkage at 198°); $[\alpha]^{25}D$ +133.81° (*c* 1.3, $CHCl_3$); uv max (ethanol) 240 mμ (ε 5900); ir (KBr) 1740, 1725, and 1715 cm^{-1}; nmr ($CDCl_3$) δ 4.82 (s, 1, C-4 **H**) and 4.44 (d, 1, J = 3 Hz, C-7 **H**).

Anal. Calcd for $C_{23}H_{29}Cl_3O_4$: C, 58.06; H, 6.14; Cl, 22.35. Found: C, 58.26; H, 6.29; Cl, 22.39.

B.—Five drops of dioxane saturated with hydrogen chloride was added to a solution of 0.405 g (0.001 mol) of **5**, 0.1 g of lithium chloride, and 0.33 g of *N*-chlorosuccinimide in 6 ml of glacial acetic acid. This reaction mixture was stirred at room temperature for 2.5 hr after which time it was added carefully to 150 ml of a 5% sodium bicarbonate solution. The mixture was extracted with ether and the ether solution was washed with 5% sodium bicarbonate solution and dried ($MgSO_4$). The solvent was removed under vacuum and the residue was triturated with ether to give 55 mg of product. Crystallization from ethyl acetate–cyclohexane gave 30 mg of **6**, mp 200–204° dec. The ir, uv, and nmr spectra were identical with those obtained from the preparation described in A.

4,6-Dichloro-17α-hydroxypregna-4,6-diene-3,20-dione Acetate (7). A. By Direct Chlorination of 5 in Propionic Acid.—A cooled (0°) solution of 2.03 g of **5** in 20 ml of dry dimethylformamide and 10 ml of ether was treated with 4.90 ml (10% excess) of a 1.015 *M* solution of chlorine in propionic acid. The solution was allowed to stand at 0° for 16 hr. An extra 0.3 ml of the chlorine solution was then added and the solution was allowed to stand at 0° for an additional 2 hr. The reaction mixture was then poured into 30 ml of water and extracted with ether–methylene chloride (3:1). The organic layer was washed once with 5% sodium bicarbonate solution and once with brine. The dried (Na_2SO_4) organic layers were evaporated and the residue was crystallized from chloroform–ethyl acetate to give 837 mg (38%) of **7**, mp 235–238°. Two further crystallizations from the same solvent system gave the analytical sample: mp 237–239.5°; $[\alpha]^{25}D$ +140.3 (*c* 1, $CHCl_3$); uv max (ethanol) 298 mμ (ε 17,100); ir ($CHCl_3$) 1735, 1715, and 1695 cm^{-1}; nmr ($CDCl_3$) δ 6.30 (d, 1, J = 2.5 Hz, C-7 **H**).

Anal. Calcd for $C_{23}H_{28}Cl_2O_4$: C, 62.87; H, 6.42; Cl, 16.14. Found: C, 62.87; H, 6.38; Cl, 16.13.

B. By Dehydrochlorination of 6.—A solution of 150 mg of **6** in 0.4 ml of dry pyridine was allowed to stand at room temperature for 2 hr. The pale yellow solution was poured into 50 ml of ether and the ether solution was extracted several times with 1 *N* sulfuric acid solution. The dried ($MgSO_4$) ether solution was evaporated and the residue was triturated with ether to give 125 mg of product, mp 228–235°. Crystallization from methylene chloride–ether gave 100 mg of **7**, mp 238–240°. The melting point was not depressed upon admixture with the sample described in A.

4α,6,7α-Trichloro-17α,21-dihydroxypregn-5-ene-3,11,20-trione 21-Acetate (17). A.—To a cold (3°) solution of 1.0014 g (0.0023 mol) of 6-chloro-17α,21-dihydroxypregna-4,6-diene-3,11,20-trione 21-acetate[7] (**7**) in 58 ml of chloroform (left over alumina for 15 min to remove ethanol) was added 3 drops of chloroform saturated with dry hydrogen chloride followed by 2.5 ml of a 1.0 *M* solution (0.0025 mol) of chlorine in carbon tetrachloride. After 30 min at 3°, 3 more drops of chloroform saturated with dry HCl was added. After 50 min at 3°, tlc and the ultraviolet spectrum indicated that very little reaction had occurred. Dry HCl was bubbled through the reaction mixture for a few seconds at 3°. After 25 min, the ultraviolet spectrum showed the absence of starting material. The colorless solution was washed with 5% sodium bicarbonate solution, dried ($MgSO_4$), and concentrated under reduced pressure to yield a colorless foam (1.4 g). Two crystallizations from ethyl acetate–hexane gave 0.2915 g of pure trichloro compound (**17**): mp 196–199°; $[\alpha]^{25}D$ −23.1° (*c* 1.2, $CHCl_3$); uv max (ethanol) 241 mμ (ε 5350); ir (KBr) 1750, 1727, 1715, and 1707 cm^{-1}; nmr ($CDCl_3$) δ 4.86 (s, 1, C-4 **CH**Cl) and 4.51 (d, 1, J = 3 Hz, C-7 **CH**Cl).

Anal. Calcd for $C_{23}H_{27}Cl_3O_6$: C, 54.61; H, 5.38; Cl, 21.03. Found: C, 54.70; H, 5.23; Cl, 20.98.

B.—A solution of 0.103 g (0.23 mmol) of **7** and 0.0149 g (0.3 mmol) of anhydrous lithium chloride in 5 ml of acetic acid at 25° was treated with 0.0432 g (0.3 mmol) of *N*-chlorosuccinimide (recrystallized from CH_2Cl_2–C_6H_{14}) followed by 2 drops of dioxane saturated with anhydrous HCl. After stirring at 25° for 2 hr, 0.0224 g of lithium chloride and 0.0426 g of *N*-chlorosuccinimide were added and the solution was stirred at 25° for 16 hr. The

(21) Listings of structure factors, coordinates, and anisotropic temperature factors will appear following these pages in the microfilm edition of this volume of the journal. Single copies may be obtained from the Reprint Department, ACS Publications, 1155 Sixteenth Street, N.W., Washington D. C. 20036, by referring to author, title of article, volume, and page number. Remit $3.00 for photocopy or $2.00 for microfiche.

reaction mixture was cautiously poured into 100 ml of saturated sodium bicarbonate. The product was extracted with methylene chloride and the extract was washed with saturated sodium bicarbonate, dried ($MgSO_4$), and concentrated under reduced pressure. Crystallization from dichloromethane–ether gave 0.0369 g of the trichloro compound **17**, mp 198–200°, uv max (ethanol) 240 mμ (ε 5200). The melting point was undepressed upon admixture with the material prepared in A. In addition, the ir and nmr spectra were identical with those obtained from the preparation described in A.

4,6-Dichloro-17α,21-dihydroxypregna-4,6-diene-3,11,20-trione 21-Acetate (18). A. By Direct Chlorination in Propionic Acid.—To a cooled (0°) solution of 1.50 g of 6-chloro-17α,21-dihydroxypregna-4,6-diene-3,11,20-trione 21-acetate[5] in 16 ml of dry dimethylformamide and 10 ml of ether was added 4.0 ml (20% excess) of a 1.05 *M* solution of chlorine in propionic acid. The resulting solution was allowed to stand at 0° for 10 hr and then at room temperature for 5 hr. The reaction mixture was poured into 100 ml of water and extracted with methylene chloride. The organic layer was washed twice with 5% sodium bicarbonate and once with brine. The dried (Na_2SO_4) organic layer was evaporated and the residue was crystallized from methylene chloride–ether to give 600 mg (37%) of **18**, mp 255–257.5°. An additional crystallization from the same solvent system gave the analytical sample: mp 257.5–259.5°; $[\alpha]^{25}D$ +398.4° (*c* 0.5, $CHCl_3$); uv max (ethanol) 295 mμ (ε 15,750); ir ($CHCl_3$) 1750, 1730, 1720, and 1697 cm^{-1}; nmr ($CDCl_3$) δ 6.30 (s, 1, C-7 H).

Anal. Calcd for $C_{23}H_{26}Cl_2O_6$: C, 58.86; H, 5.58; Cl, 15.11. Found: C, 58.85; H, 5.79; Cl, 15.22.

B. By Dehydrochlorination of 17.—The trichloro compound **17** (0.044 g) was dissolved in 1 ml of pyridine and was allowed to stand at 25° for 75 min. The reaction mixture was then poured into 25 ml of 1 *N* hydrochloric acid and the product was extracted with ethyl acetate. The combined organic layers were dried ($MgSO_4$) and evaporated under reduced pressure to give 0.033 g of colorless solid, uv max (ethanol) 296 mμ (ε 19,700). Crystallization from methylene chloride–ether gave 0.0207 g (51%) of **18**, mp 258.5–261°, undepressed upon admixture with the sample described in A.

Crystallography.—Crystals of 4α,6,7α-trichloro-17α,21-dihydroxypregn-5-ene-3,11,20-trione 21-acetate (**17**, $C_{23}H_{27}Cl_3O_6$, mol wt 505.84) were grown from an ethyl acetate–hexane mixture. The crystal data are $a = 12.915 \pm 0.003$, $b = 15.310 \pm 0.005$, $c = 6.073 \pm 0.002$ Å, $\beta = 105.04 \pm 0.02°$ (at 21°, Cu $K_\alpha = 1.5418$ Å), $V = 1159.7$ Å, $D_m = 1.47$ g cm^{-3}, $D_c = 1.45$ g cm^{-3}, $Z = 2$, F(000) = 528; space group $P2_1$, (C_2^2, No. 4) (0*k*0 absent for *k* odd).

The intensities of 2266 independent X-ray diffraction maxima with $2\theta \leq 140°$ were measured on a Hilger and Watts Model Y290 four-circle diffractometer by a moving crystal-moving detector technique, using Ni-filtered Cu K_α radiation. Of these data, 410 were not significantly greater than background and were excluded from the structure analysis. The data were corrected for absorption (μ 39.1 cm^{-1}) by the method described by Coppens, *et al.*[22] as well as for the usual Lorentz and polarization effects. The crystal used was a rectangular prism with dimensions 0.14 × 0.18 × 0.24 mm.

All calculations were performed on a GE-635 computer. The Fourier program used is a local revision of one originally written at the University of Wisconsin.[23] Local modifications of the Busing–Martin–Levy ORFLS[24] crystallographic least squares program were used for the refinement in which the function $\Sigma w (|F_o| - |F_c|)^2$ was minimized. In the final cycles of least squares refinement, the weights were taken as $w = 1/(6.25 + F_o + 0.02 F_o^2)$.

The scattering curves of Cromer and Waber[25] were used for Cl, O, and C and that of Stewart, Davidson, and Simpson[26] for H. The C scattering curve was corrected for both the real and imaginary parts of the anomalous dispersion.[27]

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Migration of the Double Bond in the Side Chain of Sterols with Iodine[1a]

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Several papers including our reports on fucosterol[2] and kauren[3] have already been published on the double bond migration with iodine wherein such behavior was presumed to be similar to acid migrations, but detailed investigations on this reaction have not been reported. When a solution of fucosterol acetate (**1**) or 24-methylene cholesterol acetate in benzene with iodine was refluxed, the $\Delta^{24(25)}$ isomer in a yield of *ca.* 50% and other unknown products were obtained.[2] Details of the double bond migration of sterol side chains are described in this paper.

Gas chromatographic analysis of the products of fucosterol acetate indicates that the product consists of at least three components.[4] By alumina chromatography and recrystallization, stigmasta-5,24-dien-3β-ol acetate (**3**) was obtained pure, but the other products could not be successfully separated by tlc or column chromatography. Catalytic reduction of the products with PtO_2 gave single compound which was identified as 24-ethylcholestanol acetate by mass spectrometry and glc. Thus, the by-products are assumed to be double bond isomers of fucosterol.

It was found by glc analysis of the ozonization products at periodic intervals that only the first component eluted from the glc is attacked by ozone very slowly.

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