[CONTRIBUTION FROM THE DIVISION OF STEROID RESEARCH, THE JOHN HERR MUSSER DEPARTMENT OF RESEARCH MEDICINE, UNIVERSITY OF PENNSYLVANIA]

INVESTIGATIONS ON STEROIDS. XVIII. CHLORIDES AND CYCLIC SULFITES IN THE SERIES OF 3β,5,19-TRIHYDROXYETIOCHOLANIC ACID. A CASE OF ASYMMETRIC SULFUR*[1]

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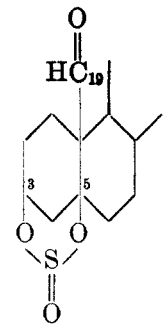
With the aim of preparing steroids of the 19-hydroxypregnane series, 3β,5,19-trihydroxyetiocholanic acid (I) (1) and some of its esters were subjected to various chemical reactions.

The sodium salt (IIa) of 3β,19-diacetoxy-5-hydroxyetiocholanic acid (II) (13) was treated with oxalyl chloride (2) and, without purifying the acid chloride (IV), the product was reacted with diazomethane, followed by treatment of the crude diazoketone with ethereal hydrogen chloride. On account of the rather poor over-all yield of the resulting 21-chloropregnane-3β,5,19-triol-20-one 3,19-diacetate (V) the preparation by this route of the corresponding 21-acetoxy compound was not attempted.

As is known from certain 3,5-diols of the strophanthidin series (lit. *cf.* (3) p. 133; (4) p. 275), reaction with thionyl chloride results in the formation of cyclic neutral 3,5-sulfites.



This behavior was considered to confirm the concept of the *cis* position of the hydroxyl groups at carbon atoms 3 and 5. It is to be noted that in the investigated examples there was no hydroxyl group at carbon atom 19. On the basis of this experience it was interesting to examine compounds of the 3β,5β,19-trihydroxy series. According to views discussed by Dostrovsky, Hughes, and Ingold (5, p. 188) neopentyl halides cannot be prepared by the action of thionyl chloride, or the halides of phosphorus or of hydrogen, on neopentyl alcohol.

* This paper is dedicated to my teacher Prof. Dr. Adolf Windaus in Göttingen on the occasion of his 75th birthday (December 25, 1951). M. E.

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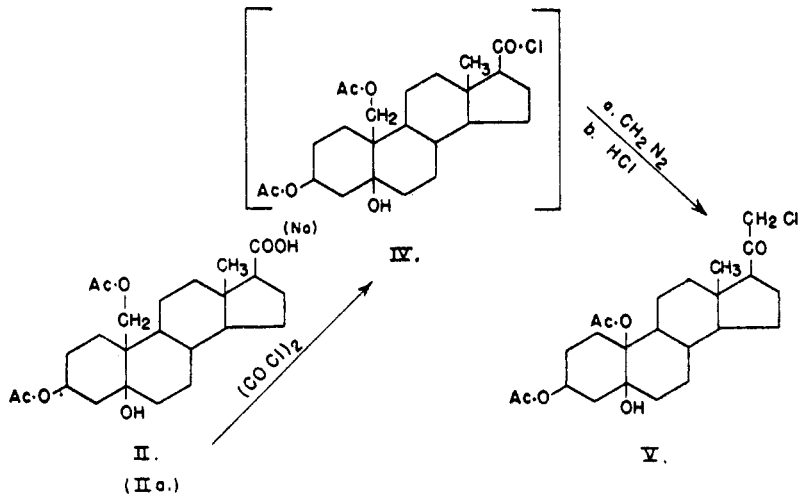
Steroids substituted at carbon atom 19 by a hydroxyl group represent compounds of neopentyl alcohol type.

Thus the question arose whether 3β,5β,19-trihydroxy steroids react with thionyl chloride in such a fashion that 3,5-sulfites are formed with retention of the primary alcohol group at carbon atom 19. Such a behavior would have been of practical consequence because it would have permitted in one operation the transformation of 3β,5,19-trihydroxyetiocholanic acid (I) into the 3,5-sulfite of the acid chloride. This in turn could have served as an intermediate in the preparation of pregnane-3β,5,19-triol-20-one and of several products derived from it by substitution at carbon atom 21.

In a model experiment, ethyl 3β,5,19-trihydroxyetiocholanate (III) was subjected to treatment with thionyl chloride in the presence of pyridine under various conditions. In any case two pure neutral crystalline compounds were

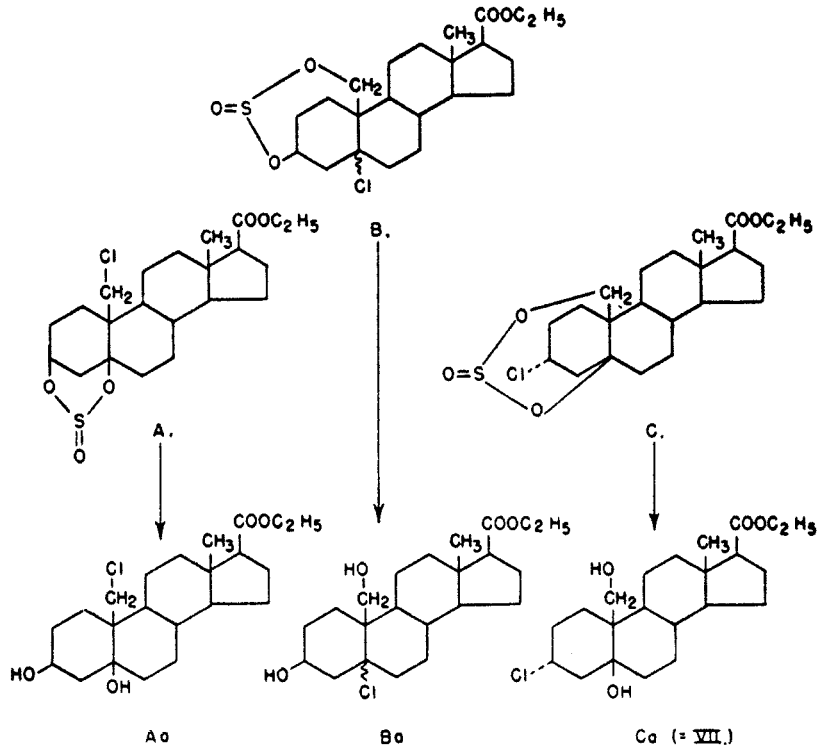


isolated from the reaction mixture after chromatography. Analysis showed that both products are monomolecular and possess the identical composition, namely that of a monochlorosulfite. Accordingly any of the formulas A, B, and C had to be considered, although formula A appeared unlikely because of the reasons presented above.

On hydrolyzing such compounds under mild conditions, one would expect the formation of the monochloro compounds Aa, Ba, and Ca respectively.[2] As will be discussed more fully below, hydrolysis of both monochlorosulfites gave the same monochloro compound. With a view to determining its structure, the latter was subjected to a number of reactions. Acetylation with acetic anhydride in pyridine gave a monoacetate which automatically rules out structure Ba. Another argument against this formula is the fact that the compound did not undergo dehydrochlorination on refluxing with dimethylaniline or quinoline

[2] Hydrolysis of steroid sulfites appears to proceed without inversion (*cf.* 6).

(*cf.* 7). In addition, oxidation of the product with N-bromoacetamide resulted in the isolation of starting material. This behavior not only rules out formula Ba but, in spite of the formation of a monoacetate, also formula Aa, because both of these structures would be expected to yield under these conditions a 3-keto compound (*cf.* 8, 9, 10). On the other hand, treatment of the monochloro compound with 1.3 equivalents of chromic acid yielded an appreciable amount of Beilstein-positive acid material. In view of the fact that formula Ba has to be ruled out because of other reasons (*vide supra*), formula Ca is the only structure which agrees with the chemical behavior of this compound towards oxidizing



agents. In fact, it is the only structure which is in agreement with most of the experimental evidence.[3] It follows, therefore, that this 3-chloro compound (Ca) is derived from two chlorosulfites of type C.

As was mentioned above, the two chlorosulfites were separated by chromatography, the higher-melting one (m.p. 222–224°) being eluted first, the lower-melting one (m.p. 203–205°) thereafter. To rule out the possibility that these were polymorphous forms of the same compound, attempts were made to convert the one into the other by seeding solutions of the one product with crystals of the other. In any case the original material was recovered. Since aluminum

[3] The inertness of a compound of structure Ca towards refluxing with organic bases is surprising (*cf.* 17).

oxide had been used in the chromatographic separation of these compounds, the possible influence of this agent was examined. It was found that both compounds were stable towards aluminum oxide. The mixture melting point of the two compounds showed a definite depression (193–197°). On hydrolysis with ethanolic hydrogen chloride, both products yielded the same monochloro compound. From this one cannot necessarily infer that the configuration of the chlorine atom in both chlorosulfites is the same. It is conceivable, though not probable, that hydrolysis of one of the two chlorosulfites is connected with inversion of the chlorine atom. This possibility is ruled out, however, by the fact that hydrolysis with ethanolic potassium hydroxide of both chlorosulfites likewise yielded the same 3-chloro compound.

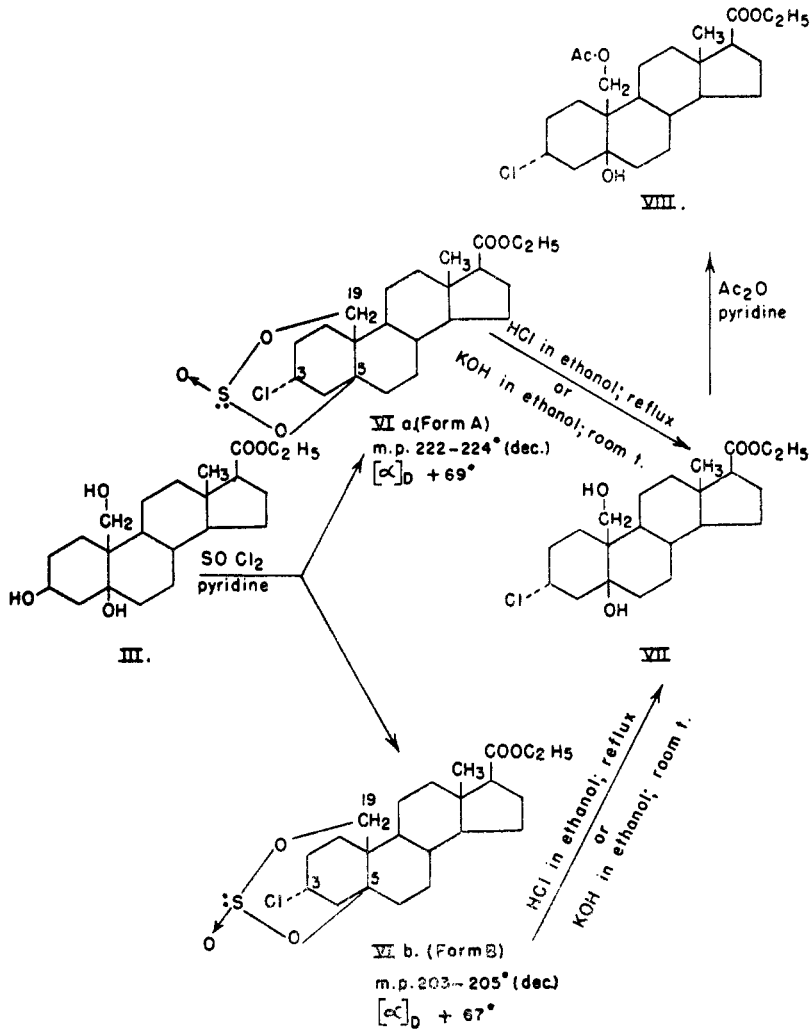
Thus it follows that, in spite of their non-identity, both chlorosulfites have the same stereochemical configurations at the nuclear carbon atoms. Consequently the sulfur atom has to be considered as a center of stereoisomerism. Cases of asymmetric sulfur have been reported in certain sulfinic esters and sulfoxides (lit. *cf.* 11, p. 421). Studies on models indicate that the present instance may represent a similar case of stereoisomerism. Formulas VIa and VIb for ethyl 3α-chloro-5,19-dihydroxyetiocholanate 5,19-sulfite, form A (m.p. 222–224°, decomp.; $[\alpha]_D$ +69°) and form B (m.p. 203–205°, decomp.; $[\alpha]_D$ +67°) respectively are merely a means of formally expressing these stereochemical interrelationships. They are not intended to depict the true configurations at the sulfur atom. To the chlorine atom at carbon 3 is tentatively assigned the α-configuration in accordance with the view that the use of thionyl chloride in the presence of pyridine may lead to inversion of configuration (12, p. 1145). In accordance with the foregoing discussion, hydrolysis of either VIa or VIb leads to ethyl 3α-chloro-5,19-dihydroxyetiocholanate (VII) which was characterized by the monoacetate (VIII). It is understood that also in these compounds the assignment of the α-configuration to the chlorine atom is tentative.

Infrared data were obtained through the courtesy of Drs. Konrad Dobriner and Estella R. Katzenellenbogen of the Sloan-Kettering Institute for Cancer Research in New York. The spectra determined in chloroform solution with a Perkin-Elmer spectrophotometer, model 21, are presented in Fig. 1. The infrared spectra show that VIa and VIb are not identical. The most striking differences of the absorption curves are found in the neighborhood of 980 cm^{-1}, where the spectrum of VIa shows an asymmetric band with a maximum at 977 cm^{-1}, while the spectrum of VIb is characterized by a doublet with maxima at 983 cm^{-1} and 974 cm^{-1}. In addition, the absorption at 977 cm^{-1} and 974 cm^{-1} respectively is much greater for VIa than for VIb.

Infrared spectra of VII were determined in samples obtained from VIa by alkaline hydrolysis and from VIb by acid hydrolysis as well as by alkaline hydrolysis. They were found identical in all regions except that in the spectrum of the product (VII) obtained by alkaline hydrolysis of VIa there was evidence of the presence of a very small amount of unchanged VIa. Also these spectra were determined in chloroform.

In another, similar, series of reactions 3β,5,19-trihydroxyetiocholanic acid

(I) was treated with thionyl chloride. The crude reaction product, which must have contained the acid chloride IX, was successively treated with diazomethane and with hydrogen chloride. Only one form of 3α,21-dichloropregnane-5,19-diol-20-one 5,19-sulfite (X) was isolated after chromatography. Hydrolysis with



methanolic hydrogen chloride yielded 3α,21-dichloropregnane-5,19-diol-20-one (XI). The tentative assignment of the α-configuration to the chlorine atom at carbon atom 3 in IX, X, and XI was made in agreement with the views referred to above.

In an experiment originally designed to transform 3β,19-diacetoxy-5-hydroxy-etiocholanic acid (II) into 21-chloro-Δ^4-pregnene-19-ol-3,20-dione, II was first treated with thionyl chloride in the absence of pyridine. In analogy to experi-

ments described in the preceding paper (13) this must have furnished a mixture of the unsaturated acid chlorides XII and XIII. In order to produce the chloromethyl ketone, the crude reaction product was successively treated with diazomethane and with hydrogen chloride. Subsequent treatment with aqueous ethanolic hydrogen chloride resulted in the elimination of one molecule of acetic acid leading to a 3,5-diene. Hydrolysis of the acetoxy group at carbon atom 19 occurred only in part of the material. Thus chromatographic separation furnished

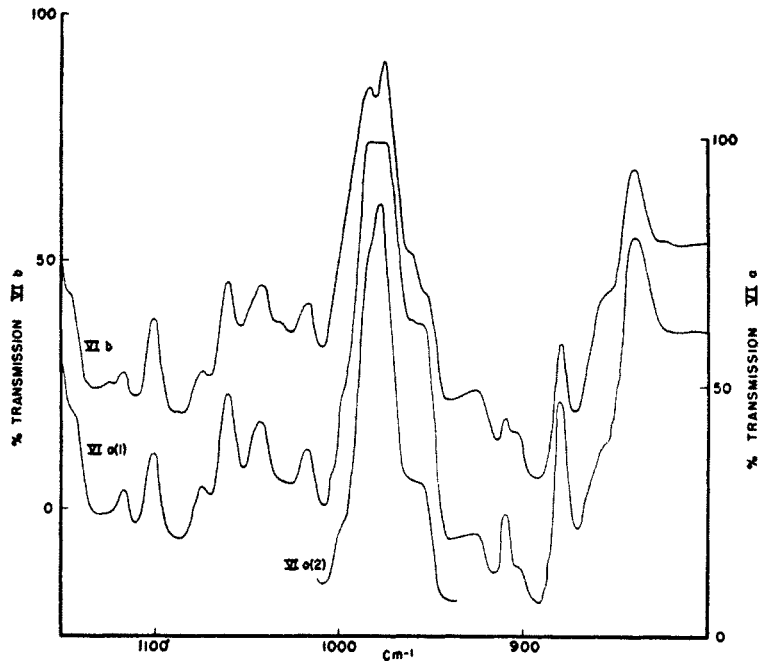


FIGURE 1. INFRARED SPECTRA OF VIa AND VIb IN CHLOROFORM (1-mm. cell). Concentrations per 1 cc.: VIa (1), 1.6 mg.; VIa (2), 0.5 mg.; VIb, 1.5 mg.

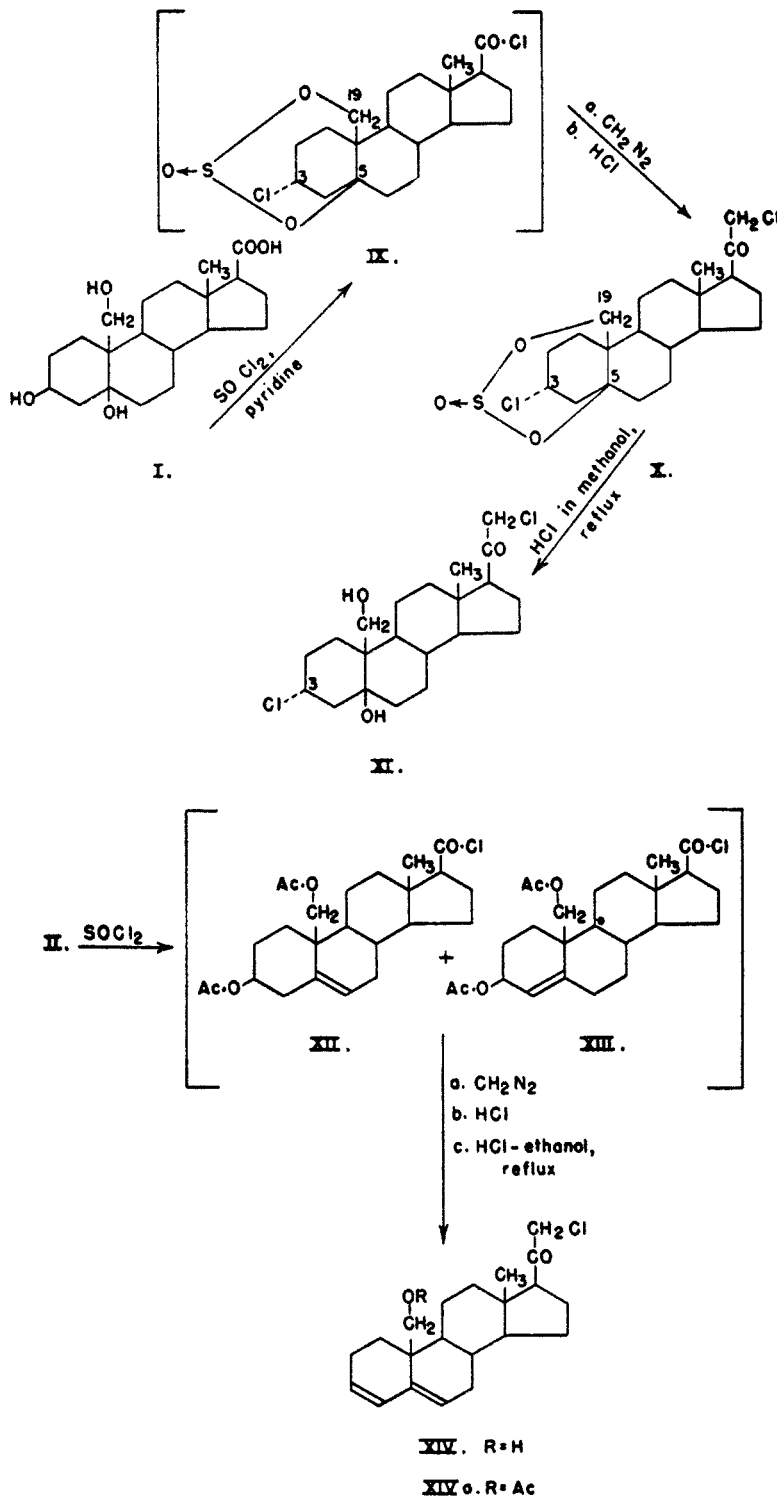
21-chloro-$\Delta^{3,5}$-pregnadiene-19-ol-20-one (XIV) and its acetate (XIVa). The latter was obtained also by acetylation of the former (XIV).

EXPERIMENTAL

The melting points were determined with the Fisher-Johns melting point apparatus. The readings are sufficiently near the true melting points so that no corrections have been made. Unless stated otherwise, the microanalyses were carried out by Dr. E. W. D. Huffman, Denver 2, Colorado, on samples which were dried *in vacuo* over phosphorus pentoxide at 80–90°.

21-Chloropregnane-3β,5,19-triol-20-one 3,19-diacetate (V). A solution of 100 mg. of II (m.p. 154–156°) (13) in 2.15 cc. of 0.106 *N* sodium hydroxide was frozen and lyophylized. To a suspension of the sodium salt in 10 cc. of dry benzene were added three drops of pyridine[4] and then, after cooling in an ice-salt bath, 0.5 cc. of pure oxalyl chloride, causing an instantaneous gas evolution. The mixture was kept in the cold for 5 minutes and at room

[4] Distilled from barium oxide.


CO·Cl
CH3
19
CH2
O
O←S
Cl
3
5
O
a. CH2N2
b. HCl
CH2Cl
CO
COOH
HO
CH2
HO
OH
SO Cl2, pyridine
I.
IX.
X.
HCl in methanol, reflux
XI.
II. SOCl2
Ac·O
Ac·O
XII.
XIII.
a. CH2N2
b. HCl
c. HCl - ethanol, reflux
OR
XIV. R=H
XIV a. R=Ac

temperature for 15 minutes and was then brought to dryness *in vacuo*. The residue was taken up in 2 cc. of benzene and the solution evaporated to dryness. This was repeated twice and the residue was dissolved in 5 cc. of benzene. This solution was slowly added to 5 cc. of cooled 1.8% ethereal diazomethane, and, after keeping the mixture at room temperature for ½ hour, evaporating it to dryness *in vacuo*, dissolving the residue in ether, and filtering through a sintered glass funnel under anhydrous conditions, 2 cc. of absol. ethereal hydrogen chloride (containing 1.5 equiv. of HCl) was added and the reaction mixture was kept at room temperature for ½ hour. After evaporating the solvent *in vacuo*, dissolving the resulting resin in ether, washing the solution with *N* sodium carbonate and water, drying over sodium sulfate, and evaporating, 74.1 mg. of resinous material was obtained which was subjected to chromatographic purification [5 g. of aluminum oxide-Brockmann, activity III (14)]. Only traces of material (4.6 mg.) were eluted by petroleum ether, petroleum ether-benzene combinations, and benzene. With benzene-ether combinations (4:1, 1:1) there resulted a total of 37.6 mg. of resinous material which gave, on repeated crystallization from aqueous ethanol, 21.3 mg. of stout needles; m.p. 118–120°. $[\alpha]_D^{28}$ +115° ±2° (5.440 mg. in 2.0 cc. of chloroform; l, 2 dm.; α +0.63°).

Anal. Calc'd for $C_{25}H_{37}ClO_6$ (469.00): C, 64.01; H, 7.95; Cl, 7.56.
Found:[5] C, 63.91; H, 8.00; Cl, 7.56.

The subsequent eluates yielded a total of 11.8 mg. of resinous material which did not crystallize.

Ethyl 3α-chloro-5,19-dihydroxyetiocholanate 5,19-sulfite. Form A and Form B (VIa and VIb). To 100 mg. of III in a mixture of 1.5 cc. of dry pyridine[4] and 7.5 cc. of carbon tetrachloride was slowly added 1 cc. of thionyl chloride.[6] After refluxing the solution for one hour, the solvents were removed *in vacuo* and, after the addition of water, the residue was taken up in ethyl acetate. After washing the solution with *N* hydrochloric acid, *N* sodium carbonate, and water, it was dried over sodium sulfate and evaporated to dryness. The resinous residue (110 mg.), dissolved in 50 cc. of petroleum ether, was chromatographed over 4 g. of aluminum oxide, activity III (14) (diam. of column: 10 mm.; 50-cc. eluates); total recovery: 93.2 mg. By eluting exhaustively with petroleum ether (9 fractions), 32.2 mg. was recovered, of which 30.6 mg., resulting from six successive fractions, represented crystalline material with melting points between 201 and 207°. By recrystallizing twice from ethanol-water, 23.3 mg. of rhombic plates of m.p. 222–224° (decomp.) resulted (Form A). For infrared spectrum see theoretical part. $[\alpha]_D^{28}$ +69° ±2° (6.73 mg. in 2.0 cc. of chloroform; l, 2 dm., α +0.49°). Molecular weight determination (microcryoscopic, camphor): 356.

Anal. Calc'd for $C_{22}H_{33}ClO_5S$ (444.99): C, 59.37; H, 7.47; Cl, 7.96; S, 7.20.
Found:[5] C, 59.31; H, 7.56; Cl, 7.61; S, 7.96.

By elution with petroleum ether-benzene 9:1 (2 fractions) and 4:1 (2 fractions) only 1.6 mg. of resinous material resulted. Elution with petroleum ether-benzene 4:1 (1 fraction) and 3:2 (4 fractions) gave a total of 24.9 mg. of crystalline material with melting points between 190 and 197°. Recrystallization from ethanol-water yielded 18.0 mg. of cubic crystals of m.p. 203–205° (decomp.) (Form B). For infrared spectrum see theoretical part. $[\alpha]_D^{28}$ +67° ±2° (8.31 mg. in 2.0 cc. of chloroform; l, 2 dm., α +0.56°). Molecular weight determination (microcryoscopic, camphor): 362.

Anal. Calc'd for $C_{22}H_{33}ClO_5S$ (444.99): C, 59.37; H, 7.47; Cl, 7.96; S, 7.20.
Found:[5] C, 59.46; H, 7.55; Cl, 7.87; S, 7.23.

A mixture of approx. equal amounts of Form A and Form B had a melting point of 193–197°. Elution with petroleum ether-benzene 3:2 (1 fraction), 1:4 (2 fractions), 1:3 (2 fractions), benzene (2 fractions), benzene-ether 3:1 (2 fractions), 1:1 (2 fractions), and 1:3 (2 fractions) gave a total of 9.4 mg. of resinous material. Elution with ether (2 fractions) yielded 10.5 mg. and 0.7 mg. of resinous residues and finally elution with ether-ethanol

[5] As a precautionary measure special drying (15) was performed though it proved unnecessary.

[6] The thionyl chloride was purified (16, p. 381).

4:1 (3 fractions) gave 10.2 mg., 3.5 mg., and 0.2 mg. of resinous residues. The material contained in the last two peaks of the chromatogram (10.5 mg.; 10.2 mg.) still has to be identified.

The experiment was repeated several times under the described conditions with practically the same results. It was also studied to what extent variations of the conditions influence the yields of the crystalline chlorosulfites. Permitting the reaction mixture to stand at 0° for two days, rather than refluxing it for one hour, gave markedly reduced yields of the crystalline chlorosulfites (yield approx. $\frac{2}{3}$ of the basic experiment) and in turn, somewhat larger amounts of resinous material eluted with benzene-ether and ether-ethanol. In the absence of carbon tetrachloride, when the reaction mixture was kept at room temperature for 16 hours, there resulted a combined yield of crystalline chlorosulfites approximating that of the basic experiment. In keeping the reaction mixture, likewise in the absence of carbon tetrachloride, at a temperature of −20° over a period of two days, there was an appreciable decrease of the yield of the crystalline chlorosulfites (yield about $\frac{2}{3}$ of the basic experiment) and in turn there were somewhat larger amounts of resinous material eluted with benzene-ether and ether-ethanol. In any of those experiments where a reduced yield of the crystalline chlorosulfites had been obtained, the combined benzene-ether, ether, and ether-ethanol eluates were subjected to another treatment under optimal conditions (*vide* basic expt.). In this fashion additional quantities of the crystalline chlorosulfites could be secured.

Both chlorosulfites, Form A and Form B, are stable towards aluminum oxide. A solution of 3.8 mg. of Form A (m.p. 220–221°) in 0.5 cc. of benzene was adsorbed on a column of aluminum oxide [activity III (14)] and, after 1½ hours, the material was eluted with ethyl acetate. Recrystallization from ethanol-water gave 3.4 mg. of rhombic plates; m.p. 220–221°; identical with starting material. When treated in a like fashion, 3.3 mg. of Form B (m.p. 201–203°) gave, after recovery and recrystallization from ethanol-water 2.8 mg. of cubic crystals; m.p. 201–203°; identical with starting material.

The chlorosulfites were also found stable to ethereal hydrogen chloride. Thus, after treating 5.0 mg. of Form B in 5 cc. of dry ether with 2 cc. of dry ethereal *N* hydrogen chloride at room temperature for 30 minutes, 4.5 mg. of starting material was recovered.

Ethyl 3α-chloro-5,19-dihydroxyetiocholanate (VII). *A. From ethyl 3α-chloro-5,19-dihydroxyetiocholanate 5,19-sulfite* (Form A, VIa). (*a*) *By acid hydrolysis.* A solution of 5.3 mg. of VIa in 1.5 cc. of 0.5 *N* hydrogen chloride in 90% ethanol was refluxed for 15 minutes and, after diluting with water, the mixture was extracted with ether. The ethereal solution was washed with *N* sodium carbonate and water, dried over sodium sulfate, and evaporated to dryness. Yield: 4.8 mg. of semicrystalline material which was recrystallized once from acetone-ligroin[7] and twice from ethanol-water furnishing 3.2 mg. of fine needles; m.p. 169–171°; no depression of m.p. when mixed with product obtained under *B*(*a*) (*vide infra*).

(*b*) *By alkaline hydrolysis.* To a solution of 8.0 mg. of VIa in 1.5 cc. of ethanol was added 0.5 cc. of 0.1 *N* potassium hydroxide in ethanol. The reaction mixture was kept at room temperature for three hours, then diluted with water until turbid and permitted to crystallize; yield: 6.5 mg. of needles, m.p. 167–170°; recrystallization from ethanol-water gave 5.3 mg. of needles, m.p. 169–171°. No depression of m.p. when mixed with product obtained under B(a) (*vide infra*). For infrared spectrum see theoretical part.

B. From ethyl 3α-chloro-5,19-dihydroxyetiocholanate 5,19-sulfite (Form B, VIb). (*a*) *By acid hydrolysis.* A solution of 10.0 mg. of VIb in 1 cc. of 0.5 *N* hydrogen chloride in 95% ethanol was refluxed for 30 minutes, then diluted with water and the crystalline precipitate filtered; 8.2 mg. of needles, m.p. 167–169°; by recrystallization from ethanol-water 7.9 mg. of needles, m.p. 169–171°. $[\alpha]_D^{31.5}$ +61° ±1° (8.05 mg. in 2.0 cc. of chloroform; l, 2 dm., α +0.49°).

Anal. Calc'd for $C_{22}H_{35}ClO_4$ (398.95); C, 66.23; H, 8.84; Cl, 8.88.
Found:[5] C, 66.36; H, 8.94; Cl, 8.88.

For infrared spectrum see theoretical part.

(*b*) *By alkaline hydrolysis.* A solution of 8.0 mg. of VIb was treated as described under

[7] The ligroin was purified by shaking with conc'd sulfuric acid.

A (*b*). This yielded 6.8 mg. of needles, m.p. 168–171°. Recrystallization gave 5.2 mg. of needles, m.p. 169–171°. No depression of m.p. when mixed with product obtained under *A* (*b*).

Ethyl 3α-chloro-5,19-dihydroxyetiocholanate (VII) can also be obtained from III without the intermediary isolation of VIa or VIb. In such a case III is reacted with thionyl chloride[6] in carbon tetrachloride as described and then, without chromatographic purification, the reaction product is treated as presented above under *A* (*a*).

Chemical behavior of ethyl 3α-chloro-5,19-dihydroxyetiocholanate (VII). *A. Towards chromic acid.* To 13.1 mg. of VII in 1 cc. of glacial acetic acid was added 2.94 mg. (1.3 equiv.) of chromium trioxide in 90% acetic acid. After keeping the solution at room temperature overnight, the excess chromium trioxide was destroyed with ethanol and the mixture was then diluted with water and extracted with ether. After washing with *N* sodium carbonate and water, the ethereal solution was dried over sodium sulfate and evaporated to dryness; yield: 7.0 mg. of resinous neutral material. The carbonate phase was acidified with *N* hydrochloric acid followed by extraction with ether which was evaporated after washing with water and drying over sodium sulfate; yield 4.7 mg. of acidic material giving a positive Beilstein reaction. On separating the neutral product (7.0 mg.) with Girard's Reagent T, 4.5 mg. of non-ketonic (impure starting material?) and 2.5 mg. of ketonic (aldehydic?) material resulted. Neither product crystallized and both gave positive Beilstein reactions.

B. Towards N-bromoacetamide. To 7.5 mg. of VII in 1 cc. of *tert*-butyl alcohol was added 0.2 cc. of water and 4.7 mg. of N-bromoacetamide. The reaction mixture was kept at room temperature overnight, was then diluted with water and, after the addition of 1 cc. of 10% sodium sulfite, was extracted with ether. After washing with water, drying over sodium sulfate, and evaporating to dryness the ether yielded 7.9 mg. of resinous material which, on crystallization from ethanol-water, gave 7.2 mg. of needles (m.p. 169–171°) consisting of unchanged VII (mixture m.p.).

C. Towards dimethylaniline and quinoline. After refluxing a solution of 8.0 mg. of VII in 1 cc. of dimethylaniline for 20 minutes it was poured onto ice and, after the addition of ether, the base was extracted with 6 *N* hydrochloric acid. The ethereal solution was washed with *N* sodium carbonate and water, dried over sodium sulfate, and evaporated to dryness. Yield: 7.2 mg. of needles, m.p. 163–165°; by recrystallization from alcohol-water 5.9 mg. of fine needles, m.p. 167–169°; identified as unchanged VII (mixture m.p.). On refluxing a solution of 10.0 mg. of VII in 1 cc. of quinoline for 1 hour and working it up as in the above instance, 9.1 mg. of unchanged VII was recovered.

Ethyl 3α-chloro-5-hydroxy-19-acetoxyetiocholanate (VIII). To 12.9 mg. of VII in 0.5 cc. of pyridine[4] was added 0.25 cc. of acetic anhydride. The mixture was kept at room temperature for 16 hours, then cooled with ice, diluted with *N* hydrochloric acid, and extracted with ether. The ethereal solution was washed with *N* sodium carbonate and water, dried over sodium sulfate, and evaporated to dryness. Yield: 14.8 mg. of resinous material which was chromatographed over 0.5 g. of aluminum oxide, activity II–III (14) (diam. of column: 4 mm.; 30-cc. eluates). By elution with petroleum ether and petroleum ether-benzene combinations (18 fractions) a total of 3.4 mg. of resinous material was obtained. Elution with benzene and benzene-ether, 3:1 (4 fractions) gave 11.4 mg. of crystalline material which on recrystallizing twice from ethanol-water yielded 8.1 mg. of fine plates; m.p. 49–51°, resolidification at 70–76°, remelting at 114–115°. Recrystallization from ether-petroleum ether gave clusters of plates, m.p. 114–115°. $[\alpha]_D^{28}$ +39° ±2° (7.81 mg. in 2.0 cc. of chloroform; l, 2 dm., α +0.31°). The first carbon-hydrogen determination was performed on material recrystallized from ethanol-water, the second on material recrystallized from ether-petroleum ether.

Anal. Calc'd for $C_{24}H_{37}ClO_5$ (440.99): C, 65.36; H, 8.45; Cl, 8.04 (Monoacetate)
$C_{26}H_{39}ClO_6$ (483.02): C, 64.65; H, 8.14; Cl, 7.34 (Diacetate)
Found: C, 64.84,[9] 65.17,[5] H, 8.43,[9] 8.43;[5] Cl, 7.66.[9]

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[8] Special drying (15) was essential.

[9] Dried at room temperature.[8]

3α,21-Dichloropregnane-5,19-diol-20-one 5,19-sulfite (X). Compound I (100 mg.) was added to 0.5 cc. of pure thionyl chloride.[6] After cessation of the gas evolution (2 min.) a mixture of 3 cc. of dry benzene and 1.5 cc. of dry pyridine[4] was slowly added and the solution was then kept at room temperature for 30 minutes and subsequently refluxed for 15 minutes. The mixture was brought to dryness *in vacuo* and the residue freed from excess reagent by repeated evaporation with dry benzene. Finally a solution of the product in dry benzene was filtered and the filtrate was added to 5 cc. of 1.8% ethereal diazomethane. After standing at room temperature for ½ hour the mixture was brought to dryness *in vacuo* and, after dissolving the residue in 5 cc. of dry benzene, 2.5 cc. of dry *N* ethereal hydrogen chloride was added. After standing at room temperature for ½ hour the solvents were removed *in vacuo* and the residue was taken up in ethyl acetate. After washing the extract with *N* sodium carbonate, *N* sulfuric acid, and water it was dried over sodium sulfate and evaporated to dryness yielding 95.7 mg. of a resinous residue. On adding ether, crystals (m.p. 182–185° decomp.) separated which were repeatedly recrystallized from methanol and acetone-petroleum ether yielding 18.5 mg. of needles, m.p. 197–199° (decomp.). The combined mother liquors gave 75.2 mg. of material which was chromatographed over 5 g. of aluminum-Brockmann [Activity III (14)]. From the petroleum ether-benzene eluates there resulted, after recrystallization from ethanol-water, 23.6 mg. of crystalline material, m.p. 194–196° (decomp.), which gave no depression of the m.p. with the material which had crystallized spontaneously (*vide supra*). $[\alpha]_D^{25}$ +105° ±2° (3.975 mg. in 2.0 cc. of chloroform; l, 2 dm.; α +0.42°).

Anal. Calc'd for $C_{21}H_{32}Cl_2O_4S$ (449.42): C, 56.12; H, 6.73; Cl, 15.78; S, 7.13.

Found:[6] C, 56.17; H, 6.71; Cl, 15.70; S, 7.13.

3α,21-Dichloropregnane-5,19-diol-20-one (XI). A solution of 23.6 mg. of X (m.p. 194–196°) in approx. 3 cc. of 0.5 *N* methanolic hydrogen chloride (methanol about 90%) was refluxed for 1 hour and the major part of the solvent was subsequently removed *in vacuo*. The resinous residue was taken up in ether and this solution was washed with *N* sodium carbonate and water, dried over sodium sulfate, and evaporated to dryness. Yield: 19.7 mg. of resinous material which, upon the addition of petroleum ether, gave 16.5 mg. of needles of m.p. 169–171°. Repeated recrystallization from methanol-water furnished 12.8 mg. of fine needles; m.p. 176–178°. According to the analytical figures this material was not quite pure. The optical rotation is therefore reported with reservation. $[\alpha]_D^{25}$ +149° ±10° (1.66 mg. in 2.0 cc. of chloroform; l, 2 dm.; α +0.25°).

Anal. Calc'd for $C_{21}H_{32}Cl_2O_3$ (403.38): C, 62.54; H, 7.99; Cl, 17.58.

Found:[5] C, 63.18; H, 8.11; Cl, 16.94.

21-Chloro-$\Delta^{3,5}$-pregnadiene-19-ol-20-one (XIV) *and its acetate* (XIVa) *from 3β,19-diacetoxy-5-hydroxyetiocholanic acid* (II). To 1.5 cc. of pure thionyl chloride[6] was added at −20° a total of 250 mg. of II. The mixture was kept at this temperature for 15 minutes and was then allowed to warm slowly to 0°. After a total period of 45 minutes it was brought to dryness *in vacuo*. The last traces of thionyl chloride were removed by repeated dissolution of the residue in dry benzene followed by evaporation. Finally a solution of the residue in 5 cc. of dry benzene was added to 5 cc. of a 1.8% ethereal solution of diazomethane. After 30 minutes the mixture was brought to dryness and the residue was dissolved in 5 cc. of dry benzene to which was subsequently added 21 mg. of dry hydrogen chloride in 2.5 cc. of absolute ether. The mixture was kept at room temperature for 30 minutes and was then evaporated to dryness followed by dissolving the residue in 20 cc. of 0.5 *N* hydrogen chloride in 90% ethanol and refluxing for one hour. After bringing the mixture to dryness *in vacuo*, the resinous residue was dissolved in ether which was washed with *N* sodium carbonate, *N* sodium hydroxide, and water. After drying over sodium sulfate, evaporation of the ether gave 169 mg. of a partly crystalline neutral residue. On acidification, the carbonate phase yielded no appreciable material whereas the sodium hydroxide phase furnished, after working up, 65 mg. of a dark yellow resin (phenolic?). The neutral material was chromatographed over 10 g. of aluminum oxide, activity III (14) (diam. of column: 10 mm., 50-cc. eluates). The chromatogram showed two peaks of crystalline material: (a) from petroleum ether-benzene, 3:1; 15.5 mg.; (b) from petroleum ether-benzene, 1:3, benzene (2 eluates)

and benzene-ether, 4:1; total 46.0 mg. A third peak (c), from ether-methanol, 9:1, represented resinous material.

The eluates composing the second peak (b) contained identical material interpreted to be 21-chloro-$\Delta^{3,5}$-pregnadiene-19-ol-20-one (XIV). The combined fractions, 46.0 mg., were recrystallized three times from methanol-water yielding 24.3 mg. of needles of constant m.p. 139–141°. A solution of the substance in chloroform gave a pronounced yellow color with tetranitromethane. The ultraviolet absorption spectrum is in agreement with the assigned structure. (λ_{max}^{alc} 234 mμ; ϵ, 22,800). $[\alpha]_D^{26}$ −38° ±1° (8.64 mg. in 2.0 cc. of chloroform; l, 2 dm.; α −0.33°).

Anal. Calc'd for $C_{21}H_{29}ClO_2$ (348.90): C, 72.29; H, 8.38; Cl, 10.14.
Found:[5] C, 72.78; H, 8.74; Cl, 9.68.

The eluate representing the first peak (a) consisted essentially of material interpreted to be 21-chloro-$\Delta^{3,5}$-pregnadiene-19-ol-20-one acetate (XIVa). The fraction, 15.5 mg., was recrystallized twice from methanol-water yielding 8.2 mg. of needles of constant m.p. 119–121°. A solution of the product in chloroform gave a marked yellow color with tetranitromethane. The ultraviolet absorption spectrum is in agreement with the assigned structure. (λ_{max}^{alc} 234 mμ; ϵ, 17,400). $[\alpha]_D^{29}$ −61° ±1° (5.47 mgs. in 2.0 cc. of chloroform; l, 2 dm., α −0.34°).

Anal. Calc'd for $C_{23}H_{31}ClO_3$ (390.94): C, 70.66; H, 7.99; Cl, 9.07.
Found:[5] C, 70.38; H, 8.08; Cl, 8.87.

Proof of the structure of the acetate (XIVa) was rendered also by acetylation of 21-chloro-$\Delta^{3,5}$-pregnadiene-19-ol-20-one (XIV): To 1.0 mg. of XIV (*vide supra*) in 0.1 cc. of pyridine[4] was added 0.05 cc. of acetic anhydride and the mixture was kept at room temperature overnight. After the addition of ice-cold water the mixture was extracted with ether which was washed with *N* hydrochloric acid, *N* sodium carbonate, and water. After drying over sodium sulfate the ether was evaporated leaving 2.1 mg. of resinous material which did not crystallize. It was chromatographed over 100 mg. of aluminum oxide, activity II–III (14). The petroleum ether eluate gave 0.8 mg. of a greasy residue, whereas the benzene eluate yielded 0.75 mg. of a crystalline residue, m.p. 110–112°, which on recrystallization from ethanol-water furnished 0.5 mg. of needles, m.p. 114–116°. No depression of m.p. when mixed with acetate described in preceding experiment.

The whole experiment was repeated with essentially identical results.

SUMMARY

1. 3β,19-Diacetoxy-5-hydroxyetiocholanic acid (II) was converted into 21-chloropregnane-3β,5,19-triol-20-one 3,19-diacetate (V).

2. Treatment of ethyl 3β,5,19-trihydroxyetiocholanate (III) in pyridine with thionyl chloride gave two forms of ethyl 3α-chloro-5,19-dihydroxyetiocholanate 5,19-sulfite (VIa and VIb) which are different compounds with identical configurations at the nuclear carbon atoms. The sulfur atom has been discussed as the source of asymmetry. Hydrolysis with ethanolic hydrogen chloride or potassium hydroxide of VIa or VIb gave the identical ethyl 3α-chloro-5,19-dihydroxyetiocholanate (VII) which was characterized by the acetate VIII. The behavior of VII towards several reagents has been discussed.

3. 3β,5,19-Trihydroxyetiocholanic acid (I) was converted into 3α,21-dichloropregnane-5,19-diol-20-one 5,19-sulfite (X) which by hydrolysis was transformed into 3α,21-dichloropregnane-5,19-diol-20-one (XI).

4. By a complex series of reactions II was converted into a mixture containing 21-chloro-$\Delta^{3,5}$-pregnadiene-19-ol-20-one (XIV) and its acetate (XIVa).

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