THE JOURNAL OF Organic Chemistry®

Volume 24, Number 11 December 29, 1959

[CONTRIBUTION FROM THE MERCK SHARP & DOHME RESEARCH LABORATORIES, DIVISION OF MERCK & CO., INC.]

Syntheses of Hormones from 5,6-Dichloro Steroids. I. Addition of Chlorine to Pregnenolone Acetate

FRANK A. CUTLER, JR., LEON MANDELL, DANIEL SHEW, JAMES F. FISHER, AND JOHN M. CHEMERDA

Received May 20, 1959

Chlorine has been added to pregnenolone acetate to give in 84% yield a dichloride assigned the 5α,6β-configuration. The chlorination is readily effected by bubbling chlorine into a benzene solution of pregnenolone acetate containing a small amount of pyridine. Small amounts of an isomeric dichloride, assigned the 5α,6α-configuration, and of a 7-hydroxypregnenolone acetate are also formed.

Reichstein's Substance S (17α,21-dihydroxy-4-pregnene-3,20-dione) has been the target of many syntheses, particularly since it can be converted by suitable microbiological processes into the 11-oxygenated cortical hormones.[1] Because of the availability of 3β-hydroxy-5-pregnen-20-one from sapogenins and soya sterols, we became interested in the conversion of this steroid into Substance S.

Our intent was to introduce the 17α-hydroxyl group *via* the general method of Gallagher,[2] involving peracid treatment of the enol acetate of the 20-ketone; subsequent bromination and metathesis with acetate would introduce oxygen at position 21. In several of these operations, competing reactions at the 5,6 double bond were anticipated. We indeed found that 5,17-pregnadiene-3β,20-diol diacetate[3] on treatment with peracid or bromine showed virtually no evidence of selectivity between the 5,6 and the 17,20 double bonds. It seemed essential to protect the 5,6 double bond prior to enol acetylation. Ideally, this protecting group should serve to advantage in the final transformation to a Δ^4-3-keto derivative.

Addition of bromine was attractive; however, 5,6-dibromo-3β-acetoxypregnan-20-one was found to suffer loss of bromine at the elevated temperature required for enol acetylation.[4] Moreover, 5,6-dibromides are prone to undergo mutarotation.[5] For these reasons protection by the addition of chlorine was investigated, and proved admirably suited in all respects. The addition of chlorine to 3β-acetoxy-5-pregnen-20-one I forms the subject of the remainder of this paper.[6] The further conversion of the dichloride to Reichstein's Substance S and related hormones is described in the subsequent papers.[7]

The addition of chlorine to the 5,6 double bond of sterols has been investigated by many workers,

(1) For references to published syntheses of Reichstein's Substance S and to its microbiological transformations see H. J. Ringold, G. Rosenkranz, and F. Sondheimer, *J. Am. Chem. Soc.*, **78**, 820 (1956).

(2) T. H. Kritchevsky and T. F. Gallagher, *J. Biol. Chem.*, **179**, 507 (1949).

(3) L. F. Fieser and Huang-Minlon, *J. Am. Chem. Soc.*, **71**, 1840 (1949).

(4) At the time this work was done, the method of enol acetylation at room temperature of D. H. R. Barton, R. M. Evans, J. C. Hamlet, P. G. Jones, and T. Walker, *J. Chem. Soc.*, 747 (1954), had not been published.

(5) For a discussion of the mutarotation of 5,6-dibromides, see D. H. R. Barton and E. Miller, *J. Am. Chem. Soc.*, **72**, 1066 (1950).

(6) Certain details of the chlorination of pregnenolone acetate I and the further transformation to Reichstein's Substance S have already been described: F. A. Cutler and J. M. Chemerda, U. S. Patents **2,786,856-7** (March 26, 1957), **2,884,417** (Apr. 28, 1959).

(7) F. A. Cutler, Jr., J. F. Fisher, and J. M. Chemerda, *J. Org. Chem.*, **24**, 1626 (1959); F. A. Cutler, Jr., L. Mandell, J. F. Fisher, D. Shew, and J. M. Chemerda, *J. Org. Chem.*, **24**, 1629 (1959).

notably Wallis[8] and Barton.[9] The presence of the ketone function in our case could well be expected to cause complication, and indeed such proved to be the case.

Our initial experiments involved treating solutions of pregnenolone acetate I in chloroform at low temperatures with a slight excess of chlorine dissolved in carbon tetrachloride. A dichloride II,[10] m.p. 199.5–201°, was obtained in yields up to about 60%. It regenerated the starting pregnenolone acetate on treatment with chromous chloride or zinc dust. By analogy with the work of Barton, Miller, and Young[9] it has been assigned the structure 5α,6β-dichloro-3β-acetoxypregnan-20-one. As shown in the subsequent papers,[7] this compound is well suited to the synthesis of Substance S.

An immediate objective was to improve the procedure both in yield and workability. The use of antimony trichloride as catalyst as described by Barton[9a] and the *N*-chlorosuccinimide–hydrogen chloride couple[11] also gave yields of II of the order of 50–60% and were not further explored. The obvious formation of hydrogen chloride under our original conditions suggested chlorination of the ketonic side chain as the principal side reaction. It was felt that a base would serve to inhibit side chain chlorination by combining with the hydrogen chloride as it was formed and minimize enolization. When our original conditions were modified by adding a mole of pyridine, the yield of II was increased to 73.5%. The procedure was complicated by the formation of an insoluble complex of pyridine and chlorine.

In an experiment designed to produce the 5α,6α-dichloride, pregnenolone acetate was treated with iodobenzene dichloride[12] in dry, refluxing benzene. The product, obtained in 56% yield, proved to comprise largely the same 5α,6β-dichloride observed before.[13]

This unexpected result led us to explore extensively the use of benzene as the solvent for the direct chlorination at room temperature. Initial experiments were directed toward determining the optimum amount of pyridine to be added to the benzene. The results are summarized in Table I. As can be seen, the optimum molar ratio of pyridine to pregnenolone acetate is in the range 0.3 to 0.5, giving first crop yields of II of the order of 77–80%.

It was then found that it was not necessary to add chlorine as a solution, but that chlorine gas could be merely bubbled into the solution of the steroid and pyridine in benzene until the yellow color just persisted. The benzene–steroid ratio was found to play a peculiar role in that at dilutions below 32 ml. per gram, erratic and lower yields were obtained. There was some indication that the efficiency with which the chlorine was distributed into the solution was involved. In large scale work it was found useful to employ a dilution principle: a solution of pregnenolone acetate and pyridine in benzene was introduced alternately with chlorine gas into benzene containing pyridine. In this manner it was possible to use a total benzene to steroid ratio of 12 ml. per gram. The yield of II obtained in several crops was 84%.

The benzene used in these experiments was dried over sodium. With benzene deliberately made wet with sufficient water to form a second phase during the chlorination, the yield was reduced to 42%.

The use of a number of solvents other than benzene in the chlorination was investigated; none was found superior to benzene. The results are tabulated in Table II.

Chromatography of the mother liquor solids from the chlorination of pregnenolone acetate led to the isolation of small amounts of two by-products. The first (III) proved to be an isomeric dichloride. On treatment with zinc in acetic acid it regenerated pregnenolone acetate. However, unlike the major isomer, it resisted the action of chromous chloride. Thus, this minor isomer differs only in configuration, the major isomer having the chlorine atoms disposed in a *trans* axial–axial relationship which facilitates reductive elimination.

Further light was shed on the configuration by comparison of the rate of dehydrochlorination by potassium hydroxide in refluxing dioxane-methanol. In the earlier work with the 5α,6β- and 5α,6α-dichlorocholesteryl benzoates[8,9] it was shown that the 5α,6α-isomer dehydrochlorinated faster than did the 5α,6β-isomer. In our series we have found that the minor isomer dehydrochlorinated some six times as fast as the major isomer. We have therefore assigned the 5α,6α-configuration to the minor isomer III. The 5β,6α and 5β,6β structures are not ruled out, but such dichlorides have never been isolated in other series. In this connection it may be noted that Barton[5] has shown that the 5β,6α-dibromide of cholesteryl benzoate dehydrobrominates even more slowly than the 5α,6β-isomer.

(8) C. J. Berg and E. S. Wallis, *J. Biol. Chem.*, **162**, 683 (1946); D. E. A. Rivett and E. S. Wallis, *J. Org. Chem.*, **15**, 35 (1950).

(9) (a) D. H. R. Barton and E. Miller, *J. Am. Chem. Soc.*, **72**, 370 (1950); (b) D. H. R. Barton, E. Miller, and H. T. Young, *J. Chem. Soc.*, 2598 (1951).

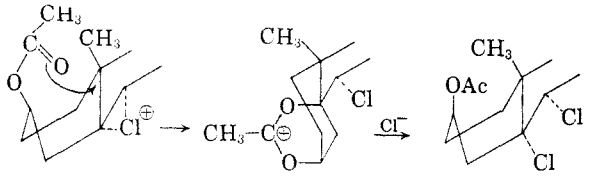
(10) This same dichloride has also been obtained by the catalytic hydrogenation of 5,6-dichloro-3β-acetoxy-16-pregnen-20-one; J. M. Chemerda, U. S. Patent **2,739,162** (March 20, 1956). Also P. L. Julian and W. J. Karpel, U. S. Patent **2,696,490** (Dec. 7, 1954), describe a reaction of a dichloride of pregnenolone acetate without giving details of its preparation or its properties.

(11) *Cf.* J. B. Ziegler and A. C. Shabica, *J. Am. Chem. Soc.*, **74**, 4891 (1952).

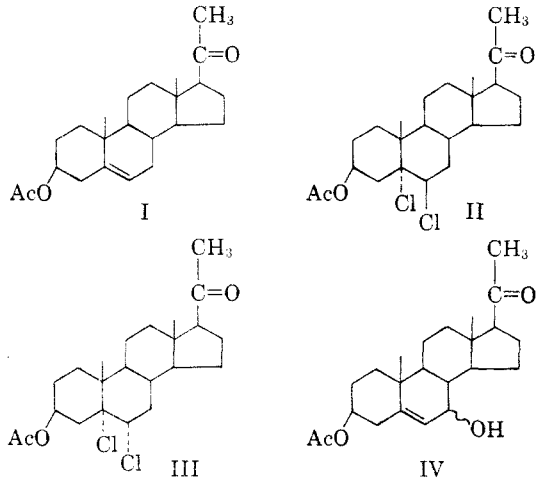
(12) Barton[9] has shown that this reagent produces the 5α,6α-dichloride of cholesterol benzoate.

(13) The circumstances under which iodobenzene dichloride leads to the same products as elemental chlorine have recently been discussed by L. J. Andrews and R. M. Keefer, *J. Am. Chem. Soc.*, **80**, 1723 (1958).

The formation of a 5α,6α-dichloride may be rationalized by noting that when the A-ring takes a boat form, the 3β-acetoxy group may participate at position 5 in the opening of the initial 5,6α-chloronium ion.[14] Subsequent attack by chloride at position 5 would lead to the 5α,6α-isomer.



The second by-product in the chlorination was a 7-hydroxylated pregnenolone acetate IV, apparently arising by action of the alumina used in the chromatography on an allylic chloride.[15]



The hydroxyl group was indicated by infrared analysis and by acetylation. On oxidation with chromium trioxide, an α,β-unsaturated ketone was obtained whose spectral characteristics and melting point agree with those of the known[16] 7-ketopregnenolone acetate.[17]

In conclusion we may note that our experience in forming 5,6-dichlorides has been found in these laboratories to have rather general application. Details of the chlorination of other Δ^5-steroids in inert solvents containing a tertiary amine have recently been disclosed by another laboratory.[19]

EXPERIMENTAL

Melting points were measured on samples in open capillaries with total immersion thermometers and are not corrected. Rotations were measured in chloroform, except as noted, and at concentrations of about 1 g. per 100 ml.

Reaction of 5,17-pregnadiene-3β,20-diol diacetate. (a) *With perbenzoic acid.* Eight grams (20 mm.) of 5,17-pregnadiene-3β,20-diol diacetate[3] (mixed isomers, m.p. 126–138.5°, $[\alpha]_D^{24}$ −53.5°) was dissolved in 67.1 ml. of 0.298*M* (20 mm.) perbenzoic acid in benzene. The solution was held at 27–30° for 30 min. at which time a test for peracid was negative. The solution was washed with sodium hydroxide solution and water, dried, and evaporated under reduced pressure. The residual sirup was dissolved in 100 ml. of ethanol and saponified by adding a solution of 4.0 g. of sodium hydroxide in 50 ml. of water. After an hour at 25–30°, a crop of crystals (1.67 g., m.p. about 220–250°) was collected. The filtrate was diluted with ether (500 ml.) and the aqueous layer was separated. The ether layer was washed with four 100-ml. portions of 5% sodium chloride solution and evaporated to dryness. Trituration of the residue with ether gave 3.64 g. of crystals, m.p. 187–206°. Specimens of both portions of crystals were chromatographed on 20 parts of acid-washed alumina, giving in each case many fractions with wide melting-point ranges. No pure products were identified.

(b) *With bromine, then perbenzoic acid.* To a stirred solution of 4 g. (10 mm.) of 5,17-pregnadiene-3β,20-diol diacetate in 75 ml. of chloroform at −60° was added 25.5 ml. (10 mm.) of 0.392*M* bromine in chloroform. The bromine was rapidly consumed. The solution was allowed to warm to 0° and 38.7 ml. (11 mm.) of 0.284*M* perbenzoic acid in benzene was added. The solution was allowed to stand overnight, then was washed with three 100-ml. portions of cold 0.5*N* sodium hydroxide and three 100-ml. portions of water. Evaporation of the solvent and slurrying of the residue in 30 ml. of hot methanol gave after chilling 2.46 g. of solid, m.p. 155–160° dec. This material was evidently 5,6,17-tribromo-3β-acetoxypregnan-20-one (lit.[3] m.p. 167–168° dec.), for on treatment with sodium iodide it formed in good yield 17-bromo-3β-acetoxy-5-pregnen-20-one as plates, m.p. 146.5–149° (lit. 147–148°[20]; 146–148°[21]). Thus, attack by an equimolar amount of bromine was not selective.

Attempts to use pregnenolone acetate dibromide. (a) Pregnenolone (10 g.) was treated with one molar equivalent of bromine in chloroform and after removal of solvent, the residue was treated with acetic anhydride (300 ml.) containing 3 g. of *p*-toluenesulfonic acid at the boiling point with slow distillation as described by Gallagher.[22] The distillate was found to contain bromide ion. Further processing with perbenzoic acid and hydrolysis with sodium hydroxide at room temperature gave only dark amorphous materials, even after zinc debromination.

(b) Pregnenolone acetate (20 g.) in chloroform (200 ml.) at −60° was treated with 38.5 ml. of 1.45*M* bromine in chloroform and gave after recrystallization from ethyl acetate 13.7 g. (47%) of 5,6-dibromo-3β-acetoxypregnan-20-one, m.p. 144–148.5° dec. A solution of dibromide (11.09

(14) *Cf.* J. B. Ziegler and A. C. Shabica[11] and D. H. R. Barton, E. Miller, and H. T. Young.[9b]

(15) The similar hydrolysis of 7-bromocholesterol benzoate by action of alumina during chromatography was first observed by J. A. K. Buisman, W. Stevens, and J. v. d. Vliet, *Rec. trav. chim.*, **66**, 83 (1947). The reaction has been used in preparative work by H. J. Ringold, G. Rosenkranz, and C. Djerassi, *J. Am. Chem. Soc.*, **74**, 3318 (1952) and by R. H. Lenhard and S. Bernstein, *J. Am. Chem. Soc.*, **78**, 989 (1956). The latter two groups have shown that principally the 7α-hydroxy configuration is obtained.

(16) W. Logemann and P. Giraldi, *Gazz. chim. ital.*, **81**, 548 (1951); W. Klyne, *J. Chem. Soc.*, 3449 (1951).

(17) Two alternate structures were considered, namely the Δ^4-6-ketone and the Δ^5-4-ketone. An estimate[18] of the absorption expected of these *cisoid* chromophores is log ε 3.8 and 3.5 respectively, much below that observed, log ε 4.13.

(18) H. Dannenberg, *Abhandl. preuss. Akad. Wiss.*, **21**, 3 (1939); L. F. Fieser and M. Fieser, *Natural Products Related to Phenanthrene*, 3rd ed., Reinhold Publishing Corp., New York, N. Y., 1949, p. 191.

(19) Glidden Company, Brit. Patent **778,334** (July 3, 1957); *Chem. Abstr.*, **52**, 2106 (1958).

(20) H. Heusser, C. R. Engel, P. T. Herzig, and P. A. Plattner, *Helv. Chim. Acta*, **33**, 2229 (1950).

(21) P. L. Julian and W. J. Karpel, *J. Am. Chem. Soc.*, **72**, 362 (1950).

(22) C. W. Marshall, T. H. Kritchevsky, S. Lieberman, and T. F. Gallagher, *J. Am. Chem. Soc.*, **70**, 1837 (1948).

g.) and 1.2 g. of *p*-toluenesulfonic acid monohydrate in 48 ml. of acetic anhydride was heated 5 hr. on the steam bath, and yielded after the usual work-up a black amorphous enol acetate. This was treated with 156 ml. of 0.276*M* perbenzoic acid in benzene at room temperature for 4 hr., at which time an equimolar amount of peracid had been consumed. The solution was washed with alkali and water and evaporated. The residue was debrominated with sodium iodide and then hydrolyzed with sodium hydroxide in ethanol-water at room temperature. Multiple recrystallizations from ethanol finally afforded 0.525 g. of 3β,17α-dihydroxy-5-pregnen-20-one, m.p. 258–268° (lit.[23] 271–273°).

Chlorination of pregnenolone acetate. (a) *In chloroform at −60°.* To a stirred solution of 25 g. of pregnenolone acetate in 940 ml. of chloroform at −60° was added over a period of a minute 116 ml. of 0.63*M* chlorine in carbon tetrachloride. The colorless reaction mixture was concentrated to dryness *in vacuo*, and flushed with acetone. The residue was dissolved in 180 ml. of boiling acetone and 100 ml. was distilled off. After chilling, the suspension of crystals was filtered. After washing with cold acetone and drying, the *5α,6β-dichloro-3β-acetoxypregnan-20-one II* weighed 17.8 g. (59.4%); m.p. 194–197°; $[\alpha]_D$ +6.0°.

Pure 5α,6β-dichloro-3β-acetoxypregnan-20-one is obtained by additional recrystallization from acetone or methanol; m.p. 199.5–201° (bath was heated at 6° per minute, insertion at 190°; at slower rates and with more preheating, slight decomposition was observed); $[\alpha]_D^{25}$ +6.5° (chloroform); −4.2° (benzene).

Anal. Calcd. for $C_{23}H_{34}Cl_2O_3$: C, 64.33; H, 7.98; Cl, 16.51. Found: C, 64.42; H, 8.11; Cl, 16.33.

(b) *In chloroform containing pyridine at −60°.* To a stirred solution of 25 g. of pregnenolone acetate and 6 ml. of pyridine in 940 ml. of chloroform at −60° was added 79 ml. of 0.93*M* chlorine in carbon tetrachloride. A white crystalline precipitate formed (evidently a complex between pyridine and chlorine since it also formed in the absence of steroid) which gradually dissolved as the reaction mixture was allowed to warm to 15°. The solution was then washed successively with 200 ml. of 10% hydrochloric acid, 200 ml. of 5% sodium carbonate solution and two 200-ml. portions of water. Further processing as described above gave 22 g. of II (73.5%), m.p. 193–197°, $[\alpha]_D$ +7.0°.

(c) *With antimony trichloride as catalyst.* To a solution of 50 g. of pregnenolone acetate in 1875 ml. of chloroform containing 0.5 g. of anhydrous antimony trichloride was added 268 ml. of 0.55*M* chlorine in carbon tetrachloride, keeping the temperature between −60 and −55°. The reaction mixture was washed with three 200-ml. portions of dilute hydrochloric acid, three 200-ml. portions of 10% sodium carbonate solution, and three 200-ml. portions of water. The chloroform extract was then worked up as described above, giving 32.15 g. (53.6%) of II, m.p. 195–198°.

(d) *With N-chlorosuccinimide-hydrogen chloride.* Pregnenolone acetate (10 g.) was dissolved in 100 ml. of chloroform and the solution was saturated with hydrogen chloride at room temperature. The solution was then cooled to −10° and a slurry of 4.15 g. of *N*-chlorosuccinimide in 80 ml. of chloroform was added, keeping the temperature at about −10°. The reaction mixture was washed to neutrality with water and worked up as previously described, yielding 6.45 g. (53.8%) of II, m.p. 193–195°.

(e) *With iodobenzene dichloride.* Five grams of pregnenolone acetate was dissolved in 150 ml. of reagent-grade benzene and the solution was dried by distilling off 50 ml. of benzene at atmospheric pressure. To the hot solution was added 3.88 g. of iodobenzene dichloride with shaking. After 5 min. the yellow reaction mixture gave a negative starch-iodide test. The solution was allowed to reflux for 30 min. during which the yellow color disappeared. The solution was concentrated under reduced pressure, and the residue was recrystallized from 25 ml. of methanol; yield, 3.38 g. (56.4%), m.p. 174–190°. Further recrystallization from methanol gave material whose infrared spectrum was identical with that of II.

(f) *In benzene containing pyridine.* To a stirred solution of 10 g. (28 mm.) of pregnenolone acetate in 320 ml. of benzene (dried over sodium) containing an amount of pyridine indicated in Table I was added 25.4 ml. (28 mm.) of 1.1*M* chlorine in carbon tetrachloride. The reaction was run at room temperature. After discharge of the yellow color, the solution was washed with 250 ml. of 5% hydrochloric acid and 200 ml. of water. After evaporation of the benzene, the residue was crystallized by dissolution in 100 ml. of acetone, distillation of 75 ml. of acetone, and chilling. The yields (first crop) and melting points are given in Table I.

TABLE I

EFFECT OF PYRIDINE ON CHLORINATION IN BENZENE

Pyridine, Ml.	Moles Pyridine per Mole Pregnenolone Acetate	Yield, %	Melting Point, °C.
0.0	0.00	55.2	194.5–197
0.1	0.04	58.2	193.5–196
0.5	0.22	77.5	192–195
0.6	0.27	76.5	196–197
0.65	0.29	79.4	196–198
0.8	0.35	77.5	196–198
1.2	0.53	80.0	195–198
2.4	1.06	75.4	195–196.5

(g) *Using dilution principle.* Chlorine gas was bubbled into a stirred solution of 3.5 ml. of pyridine in 600 ml. of anhydrous benzene until a definite yellow color was obtained. A small portion of a solution of 100 g. of pregnenolone acetate and 3.5 ml. of pyridine in 600 ml. of anhydrous benzene was added from a dropping funnel, discharging the yellow color. Another portion of chlorine was bubbled in to definite excess, followed by another portion of steroid solution until the color was discharged. The cycles were repeated until all the steroid had been added and chlorine was in excess. The solution was washed successively with dilute sodium thiosulfate solution, dilute hydrochloric acid, and with water. The product was isolated from acetone as described previously to give 91.0 g. (76%) of II, m.p. 196–200.5°. The residue from the liquor on crystallization from 60 ml. of acetone afforded a second crop of 7.14 g., m.p. 191–195°. On further concentration a third crop was obtained which after recrystallization from acetone amounted to 1.35 g.; m.p. 192–196.5°. The total direct yield (99.49 g.) corresponds to 83%. A final residue of 15.7 g. was obtained and was chromatographed as described hereafter.

(h) *Comparison of solvents.* These experiments were run using the following proportions: 10 g. of pregnenolone acetate, 320 ml. of solvent, and 0.7 ml. of pyridine. Chlorinations were conducted at room temperature and worked up as described in (f) or (g). The first crop yields are recorded in Table II. The dichloride obtained generally melted in the range 195–200°.

Isolation of by-products in chlorination of pregnenolone acetate. The mother liquor residue amounting to 15.7 g., which resulted from the chlorination of 100 g. of pregnenolone acetate as described earlier, was chromatographed over 350 g. of acid-washed alumina and eluted with mixtures of ether and light petroleum ether. From the 5% ether–petroleum ether eluate there was obtained 1.79 g. more of II (total, 84.5%). From the 35% ether–petroleum ether cuts after evaporation and crystallization from methanol, there was obtained 1.7 g. of *5α,6α-dichloro-3β-acetoxy-*

(23) P. Hegner and T. Reichstein, *Helv. Chim. Acta*, **24**, 828 (1941).

TABLE II

EFFECT OF SOLVENT ON CHLORINATION

Solvent	Method[a]	Yield
Benzene, sodium-dried	G	77.7%
Benzene plus 10 ml. water	G	42.3[b]
1,1,1-Trichloroethane	G	73.8
Chlorobenzene	S	71.5
Carbon Tetrachloride	S	61.7
Cyclohexane[c]	S	61.9
Dimethylformamide	S	42.5

[a] In experiments labeled "G," chlorine was added as the gas to slight excess; in those labeled "S," an equivalent amount of chlorine dissolved in about 11 ml. of carbon tetrachloride was added. [b] This material melted at 180–189°. [c] Sixty ml. of benzene was present in this run.

pregnan-20-one (III), m.p. 174–175°; mixed m.p. with II, 151–171°.

Anal. Calcd. for $C_{23}H_{34}Cl_2O_3$: C, 64.33; H, 7.98; Cl, 16.51. Found: C, 63.77; H, 8.23; Cl, 16.36.

From the ether eluate there was obtained by concentration and recrystallization from ether 1.7 g. of *3β-acetoxy-7-hydroxy-5-pregnen-20-one* (IV), m.p. 193–195°. The infrared spectrum showed bands at 2.81 (hydroxy), 5.79 (acetate), 5.90 (carbonyl), and 6.00 μ (double bond).

Anal. Calcd. for $C_{23}H_{34}O_4$: C, 73.76; H, 9.15. Found: C, 74.11; H, 9.34.

Acetylation of 50 mg. of IV in 2 ml. of pyridine and 2 ml. of acetic anhydride overnight at room temperature gave after precipitation with water and recrystallization from methanol 40 mg. of *3β,7-diacetoxy-5-pregnen-20-one*, m.p. 207–210°. The infrared spectrum showed the absence of hydroxyl bands and the presence of ester carbonyl at 5.80 μ and of ketonic carbonyl at 5.9 μ.

Anal. Calcd. for $C_{25}H_{36}O_5$: C, 72.08; H, 8.71. Found: C, 71.63; H, 8.85.

Oxidation of IV was carried out as follows: To a solution of 0.1 g. of IV and 0.2 ml. of water in 2 ml. of glacial acetic acid at 5° was added 1.0 ml. of a solution prepared by dissolving 0.27 g. of chromium trioxide in 0.5 ml. of water and 9.5 ml. of glacial acetic acid. Concentrated sulfuric acid (0.015 ml.) was added and the reaction mixture was stirred at 5° for 90 min., then at room temperature overnight. The steroid was then precipitated by the addition of water and recrystallized from methanol, to give 20 mg. of 7-keto-pregnenolone acetate, m.p. 149–151°.[24] The infrared spectrum showed bands at 5.79 (acetoxyl carbonyl), 5.86 (C-20 carbonyl) and 5.99 and 6.1 μ (conjugated carbonyl bands). The ultraviolet spectrum showed $\lambda_{max}^{methanol}$ at 235 mμ, ε 13,450.

Reactions of 5α,6β-dichloro-3β-acetoxypregnan-20-one II. (a) *With zinc.* Five grams of II was dissolved in 100 ml. of glacial acetic acid. To the stirred solution was added 10 g. of zinc dust in portions over 2.5 hr., beginning at 35° and increasing finally to 80°. The mixture was filtered and the zinc cake was washed with 100 ml. of acetic acid. Water (800 ml.) was added to the combined filtrate. The suspension was chilled and the pregnenolone acetate was collected, washed with water and dried; yield, 4.0 g. (96%); m.p. 148–149.5°.

(b) *With chromous chloride.* To a solution of 500 mg. of II in 100 ml. of acetone at room temperature was added 40 ml. of chromous chloride solution.[25] The reduction was virtually instantaneous. The acetone was then removed under reduced pressure, additional water (200 ml.) was added, and the mixture was chilled and filtered. The pregnenolone acetate was washed and dried; yield, 0.41 g. (98%); m.p. 145–148°.

(c) *With potassium hydroxide.* To a solution of 0.5 g. (1.17 mm.) of II in 50 ml. of dioxane (purified by distillation over sodium) was added a solution of 0.5 g. of potassium hydroxide in 25 ml. of methanol. The solution was heated at the reflux temperature for 1 hr., after which the steroid was precipitated by the addition of water (300 ml.) and filtered off. The filtrate and washings were acidified with nitric acid and the chloride ion, as determined by titration by the Volhard method, amounted to 0.17 me.

Reactions of 5α,6α-dichloro-3β-acetoxypregnan-20-one III. (a) *With zinc.* A solution of 0.24 g. of III in 5.2 ml. of glacial acetic acid was heated on the steam bath and three 0.3 g.-portions of zinc dust were added at 20-min. intervals with shaking. The mixture was filtered and the zinc cake was washed with a small amount of acetic acid. The combined filtrate was diluted with water (about 30 ml.) and after chilling, the crystals of pregnenolone acetate were collected, washed with water and dried; weight, 0.19 g. (95%); m.p. 142–144.5°. There was no depression in melting point on admixture with authentic pregnenolone acetate and the infrared spectra were identical.

(b) *With chromous chloride.* To a solution of 50 mg. of III in 35 ml. of acetone was added 30 ml. of chromous chloride solution.[25] The solution was refluxed for 30 min., then concentrated under reduced pressure to remove acetone. The residue was extracted into chloroform and the chloroform extract was washed with water and then concentrated to dryness under reduced pressure. Recrystallization of the residue from methanol afforded 40 mg. of unreduced starting material, m.p. 168–175° alone and 172–175° when mixed with III.

(c) *With potassium hydroxide.* To a solution of 0.5 g. (1.17 mm.) of III in 36 ml. of purified dioxane was added a solution of 0.4 g. of potassium hydroxide in 18 ml. of methanol. The solution was heated at the reflux temperature for 1 hr. The steroid was precipitated by the addition of water and filtered off. The filtrate and washings were acidified with nitric acid and the chloride ion was determined to be 1.13 me.

Acknowledgment. We are indebted to the staff of the Physical and Inorganic Research Dept. for many analyses and spectral determinations.

RAHWAY, N. J.

(24) W. Logemann and P. Giraldi, *Gazz. chim. ital.*, 81, 548 (1951), give m.p. 152–153°; W. Klyne, *J. Chem. Soc.*, 3449 (1951), gives m.p. 151–153°.

(25) Prepared as described by G. Rosenkranz, O. Mancera, J. Gatica, and C. Djerassi, *J. Am. Chem. Soc.*, 72, 4077 (1950).