at 3380 cm.$^{-1}$; conjugated ketone at 1682 cm.$^{-1}$; conjugated carbon–carbon double bond at 1602 cm.$^{-1}$, $\lambda_{max}^{alc.}$ 251 mμ, ε 8,350; flexure at 314 mμ, ε 606.

6β-Acetoxy-17α-methyltestosterone (XXI).—Fifty mg. of 6β-hydroxy-17α-methyltestosterone (XVII) was allowed to react with 1.1 equivalents of acetic anhydride in pyridine for 16 hours. The reaction mixture was diluted with water and extracted with ether. The ether extract was washed with *N* hydrochloric acid, sodium bicarbonate solution, and water and dried with sodium sulfate. After evaporation of the ether the residue (59 mg.) was crystallized from a few drops of acetone by adding 1 drop of Skellysolve B to yield 27.5 mg. of starting material XVII. The residue in the mother liquors was subjected to alumina chromatography and the peak fractions (27 mg.) combined. Several recrystallizations from 0.2 ml. of methanol by addition of a few drops of water yielded 16 mg. of crystals, m.p. 125–143°. Recrystallization from 2 ml. of ethyl acetate plus 2 drops of ether did not improve the melting point. The infrared absorption spectrum indicated that the material was 6β-acetoxy-17α-methyltestosterone (XXI).

17β-Hydroxy-17α-methylandrostane-3,6-dione (XXII).—Five drops of 10% sulfuric acid in acetic acid was added to a solution of 26 mg. of 6β-hydroxy-17α-methyltestosterone (XVII) in 2.5 ml. of acetic acid. After 96 hours at room temperature the solution was made slightly alkaline with *N* sodium carbonate solution and extracted 4 times with 25-ml. portions of methylene dichloride. The methylene dichloride extract was washed with water, dried over sodium sulfate and the solvent removed at room temperature to yield 29 mg. of product. This was crystallized from 0.2 ml. of acetone by addition of 3 drops of Skellysolve B to give 9 mg. of 17β-hydroxy-17α-methylandrostane-3,6-dione (XXII), m.p. 180–187.5°. The infrared spectrum showed the following absorption bands: hydroxyl, 3410 cm.$^{-1}$; non-conjugated ketone, 1707 cm.$^{-1}$.

By alumina chromatography of the mother liquors a second material (7.7 mg.) was obtained, m.p. 136–150°. Infrared analysis indicated that this was the 17-anhydro derivative of XXII; non-conjugated ketone, 1712 cm.$^{-1}$; no hydroxyl absorption.

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KALAMAZOO, MICHIGAN

[CONTRIBUTION FROM THE RESEARCH LABORATORIES OF THE UPJOHN COMPANY]

Chemical Studies with 11-Oxygenated Steroids. V. A One-Step Oxidation–Halogenation of 3-Hydroxysteroids

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21-Acetoxy-3α,17α-dihydroxypregnane-11,20-dione is converted to 3-keto-4-halo compounds in one step by reaction with N-haloamides, hypohalous acids and *t*-butyl hypochlorite in aqueous *t*-butyl alcohol.

In the course of work on the synthesis of 11-dehydro-17α-hydroxycorticosterone acetate (cortisone acetate) and of 17α-hydroxycorticosterone (hydrocortisone) it became of interest to develop a procedure for the conversion of 3-hydroxysteroids to 3-ketosteroids in high yields. Since many of the steroids under investigation contained the sensitive dihydroxyacetone side chain at C-17, the use of an oxidizing agent such as chromic acid was not considered suitable since it is known that this type of reagent will degrade the side chain to the 17-ketones.[1] For this reason we directed our attention to the use of N-bromoacetamide (NBA), N-bromosuccinimide (NBS), N-chlorosuccinimide (NCS) and similar oxidants, which are mild oxidants for alcohols.[2]

Similar research was in progress at this time in another laboratory, and recently Hershberg and coworkers[3] reported their findings on the use of two of the above reagents (NBS and NBA) in the oxidation and bromination of 21-acetoxy-3α,17α-dihydroxypregnane-11,20-dione (I) to give 21-acetoxy-4-bromo-17α-hydroxypregnane-3,11,20-trione (IIIa). More recently there was reported the oxidation–chlorination of 3-hydroxysteroids[4] using principally *t*-butyl hypochlorite. We had previously[5] reported the use of this reagent in the oxidation–chlorination of 3α,11α,17α-trihydroxypregnane 20-one to 4-chloro-11α,17α-dihydroxypregnane-3,20-dione and of 3α,17α-dihydroxypregnane-11,20-dione to 4-chloro-17α-hydroxypregnane-3,11,-20-trione. However, since our reaction conditions and results are somewhat different from the above references, we wish to record them at this time.

The oxidation of I was initially investigated under two different reaction conditions. In one case the reaction solvent was anhydrous *t*-butyl alcohol containing 3% pyridine, whereas in the other the *t*-butyl alcohol contained 3% water. In both cases the reactions were run in ruby low actinic glassware, a 100% excess of oxidizing agent was used, and the reaction was followed by titration of the iodine liberated by the active halogen in an aliquot of the reaction mixture. In *t*-butyl alcohol–pyridine solution using NBA and NBS the reaction leveled off after 24 hours at one mole equivalent consumed. Crystallization occurred spontaneously and was completed by the addition of water containing sodium sulfite, resulting in 21-acetoxy-17α-hydroxypregnane-3,11,20-trione (II) in 90–93% yield in a high state of purity. When the reaction period was extended, some bromination occurred. However, in aqueous *t*-butyl alcohol solution using NBA or NBS, 1.6 mole equivalents was consumed in 16

(1) T. Reichstein, *Helv. Chim. Acta*, **19**, 402 (1936).

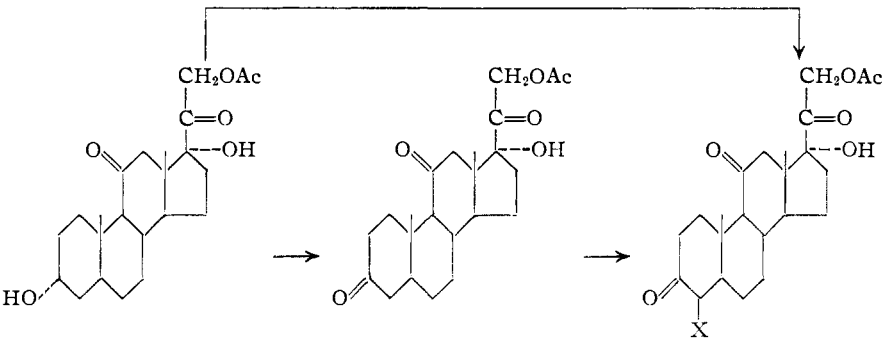
(2) H. Reich and T. Reichstein, *ibid.*, **26**, 562 (1943); L. H. Sarett, THIS JOURNAL, **71**, 1165 (1949); L. F. Fieser and S. Rajagopalan, *ibid.*, **71**, 3935 (1949); **72**, 5530 (1950).

(3) E. B. Hershberg, C. Gerold and E. P. Oliveto, *ibid.*, **74**, 3849 (1952).

(4) J. J. Beereboom, C. Djerassi, D. Ginsburg and L. F. Fieser, *ibid.*, **75**, 3500 (1953).

(5) R. H. Levin, B. J. Magerlein, A. V. McIntosh, Jr., A. R. Hanze, G. S. Fonken, J. L. Thompson, A. M. Searcy, M. A. Scherl and E. S. Gutsell, *ibid.*, **75**, 502 (1953).

hours. Upon working up the reaction products at this time, a mixture of approximately equal amounts of II and brominated II was isolated. When 2.5 mole equivalents of NBA or NBS was used, 21-acetoxy-4-bromo-17α-hydroxypregnane-3,-11,20-trione (IIIa) crystallized in a high state of purity in 60–65% yields after from 24 to 72 hours. Subsequent dilution of the filtrates of the above reaction mixture with water gave mixtures of brominated products which were not investigated *per se* but which presumably contained considerable amounts of the 4,21-dibrominated product.[3] These were treated directly with zinc–acetic acid to give 21-acetoxy-17α-hydroxypregnane-3,11,20-trione (II) in 65–75% yield. Thus the over-all conversion is in the neighborhood of 88% since II can be converted to IIIa either by bromination in acetic acid[6] or by treatment under the same conditions used above for the oxidation–bromination.



I II IIIa, X = Br IIIb, X = Cl

The conversion of I to IIIa in aqueous *t*-butyl alcohol was greatly accelerated by the addition of hydrobromic acid, and the crystallization of the product was considerably speeded up by stirring the reaction mixture. Amounts of water varying from 1.5 to 18% were tried and, within these limits, seemed to have little effect on the yields. In absolute *t*-butyl alcohol the unbrominated product II crystallized out before bromination occurred. If a base such as potassium acetate was present to remove the hydrogen bromide as it was formed, only II was isolated. The presence of light accelerated the reaction but seemed to have little effect on yield. The same product and yields were obtained using Monobromantin,[7] Dibromantin[7] or hypobromous acid.

Difficulties encountered in attempts to purify the brominated products found in the mother liquors of the above reaction led to the investigation of the preparation of the more stable 4-chloro compounds.

The use of NCS as a reagent for oxidizing alcohols to aldehydes and ketones has already been reported.[8] However, when NCS or hypochlorous acid reacted with I in aqueous *t*-butyl alcohol, 21-acetoxy-4-chloro-17α-hydroxypregnane-3,11,20-trione (IIIb) crystallized out in 55–60% yield. In addition to NCS and hypochlorous acid, *t*-butyl hypochlorite, which has been found by G. S. Fonken and co-workers[9] to be a superior reagent for the oxidation of certain steroid alcohols to ketones, was tried. Although this reagent acts mainly as an oxidizing agent in anhydrous *t*-butyl alcohol, good yields of the α-chlorinated ketones are obtained when water is present, and the latter reaction is greatly accelerated by the addition of hydrochloric acid.

Oxidation studies with NBA in *t*-butyl alcohol–pyridine were also made to determine the relative ease of oxidation of hydroxyl groups in various positions and of different stereochemical configurations. In this regard it was found that, although 11β-hydroxyprogesterone[10] is readily oxidized to give 11-ketoprogesterone, 11α-hydroxyprogesterone[11] is essentially unaffected under the same conditions. It was also found that an 11β-hydroxyl is more labile to oxidation with NBA than a 3α-hydroxyl. Thus 3α,11β,17α-trihydroxypregnane-20-one[12] upon oxidation with 1 mole of NBA in *t*-butyl alcohol–pyridine, gave 3α,17α-dihydroxypregnane-11,20-dione.[13] This same stability of 11α-hydroxyl groups to NBA oxidation was noted by H. L. Herzog and co-workers.[14]

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Experimental[15]

Oxidation of 21-Acetoxy-3α,17α-dihydroxypregnane-11,-20-dione with N-Bromoacetamide.—One gram (2.46 millimoles) of 21-acetoxy-3α,17α-dihydroxypregnane-11,20-dione (I) was dissolved with warming in 48 ml. of *t*-butyl alcohol and 1.5 ml. of pyridine. The solution was cooled to room temperature and 678 mg. (4.92 millimoles) of N-bromoacetamide[16] was added. After remaining at room temperature for 24 hours, titration of an aliquot of the solution indicated that the oxidation was 100% complete. Some crystallization had taken place at this point. Upon the addition of 130 ml. of water to the solution further crystallization took place. The mixture was placed in the refrigerator overnight to complete the crystallization. The mixture was filtered and the product dried to give a 91% yield of 21-acetoxy-17α-hydroxypregnane-3,11,20-trione (II, dihydro E acetate) melting at 226.5–229.5°.

(6) V. R. Mattox and E. C. Kendall, *J. Biol. Chem.*, **188**, 287 (1951).

(7) Monobromantin = 3-bromo-5,5-dimethylhydantoin; Dibromantin = 1,3-dibromo-5,5-dimethylhydantoin; Arapahoe Chemicals, Inc., Boulder, Colo.

(8) C. A. Grob and H. J. Schmid, *Experientia*, **5**, 199 (1949).

(9) G. S. Fonken, J. L. Thompson and R. H. Levin, paper in preparation.

(10) T. Reichstein and H. G. Fuchs, *Helv. Chim. Acta*, **23**, 684 (1940).

(11) D. H. Peterson and H. C. Murray, THIS JOURNAL, **74**, 1871 (1952).

(12) E. P. Oliveto, T. Clayton and E. B. Hershberg, *ibid.*, **75**, 486 (1953).

(13) L. H. Sarett, *ibid.*, **70**, 1454 (1948).

(14) H. L. Herzog, E. P. Oliveto, M. A. Jevnik and E. B. Hershberg, *ibid.*, **74**, 4470 (1952).

(15) Melting points are uncorrected and are taken on a Fisher-Johns block. Rotations are taken in acetone.

(16) Arapahoe Chemicals, Inc., Boulder, Colo.

The literature melting point[13] for this compound is 228–230°. The product was determined to be of high purity by infrared analysis and papergram analysis.[17]

Oxidation–Halogenation of 21-Acetoxy-3α,17α-dihydroxypregnane-11,20-dione (I). A. With N-Bromoacetamide.—One gram (2.46 millimoles) of 21-acetoxy-3α,17α-dihydroxypregnane-11,20-dione (I) was dissolved with warming in about 45 ml. of *t*-butyl alcohol, in a 50-ml. low actinic volumetric flask. The solution was cooled and 1.8 ml. of water, 0.3 ml. 48% hydrobromic acid (2.46 millimoles) and 1.2 g. (7.38 millimoles) of NBA were added. The solution was diluted to mark with *t*-butyl alcohol and stirred with a magnetic stirrer. After 43 hours the test for active halogen was negative and copious crystallization had occurred. The mixture was filtered and the crystals washed with a small amount of *t*-butyl alcohol; yield 729 mg. (61.2%), m.p. 202–205° dec., $[\alpha]^{25}D$ +99°. This was shown to be 21-acetoxy-4-bromo-17α-hydroxypregnane-3,11,20-trione by its conversion to cortisone acetate by the semicarbazone procedure.[6,18]

Addition of 100 ml. of water to the filtrate gave 130 mg. (11%) of material with $[\alpha]^{25}D$ +91° (acetone). Recrystallization of this material from acetone–Skellysolve B gave material with $[\alpha]^{25}D$ +101° in a 70% return. Monobromantin[7] and Dibromantin[7] gave similar yields under the same reaction conditions.

B. With Hypobromous Acid.—Hypobromous acid was prepared by adding, dropwise, 8 g. of bromine to a stirred suspension of 5.3 g. of yellow mercuric oxide in 100 ml. of water cooled in an ice-bath. The mercuric bromide was filtered off and the molarity of the hypobromous acid in the filtrate was determined iodometrically. It was found to be 0.565 *M*.

21-Acetoxy-3α,17α-dihydroxypregnane-11,20-dione (1.00 g., 2.46 millimoles) was dissolved with warming in 35 ml. of *t*-butyl alcohol in a 50-ml. low actinic volumetric flask. The solution was cooled to room temperature and 10.9 ml. (6.15 millimoles) of the above hypobromous acid solution was added. The solution was diluted to volume with *t*-butyl alcohol and stirred at room temperature for 4 days. The crystalline precipitate was removed by filtration and dried to yield 705 mg. (59.2%) of IIIa, $[\alpha]D$ +100° (*c* 0.9). Concentration of the filtrate to 20–25 ml. gave a second crop, 160 mg. (13.5%), $[\alpha]D$ +92° (*c* 0.9).

C. With N-Chlorosuccinimide.—To 2.00 g. (4.92 millimoles) of 21-acetoxy-3α,17α-dihydroxypregnane-11,20-dione (I) in 96 ml. of *t*-butyl alcohol in a 100-ml. low actinic volumetric flask was added 3.0 ml. of water and 1.64 g. (12.3 millimoles; 2.5 equivalents) of NCS. The solution was diluted to volume with *t*-butyl alcohol and the reaction allowed to proceed for two days. The crystals of IIIb which precipitated were filtered and dried, yield 1.13 g. (52.1%), m.p. 239–243°, $[\alpha]D$ +100° (*c* 0.74).

Anal. Calcd. for $C_{23}H_{31}ClO_6$: Cl, 8.1. Found: Cl, 8.3.

The filtrate was concentrated to one-half volume and the crystals of crude IIIb which separated were filtered, yield 100 mg. (4.6%), m.p. 232°, $[\alpha]D$ +90° (*c* 0.89).

The first crop was converted to cortisone acetate having λ_{max}^{EtOH} 238 mμ, ε 13,857 in a 83.4% yield *via* the semicarbazone procedure.[6,18]

D. With *t*-Butyl Hypochlorite.—A mixture of 6.00 g. (0.0148 mole) of 21-acetoxy-3α,17α-dihydroxypregnane-11,20-dione (I), 85 ml. of *t*-butyl alcohol, 3 ml. of water and 1.2 ml. of concentrated hydrochloric acid in a low actinic volumetric flask was stirred vigorously and 3.78 ml. (3.61 g., 0.0334 mole; 2.25 eq.) of *t*-butyl hypochlorite[19] was added. The temperature rose to 36° and was brought to 30° with a water-bath. The product precipitated from the reaction mixture and was separated by filtration one hour after addition of the hypochlorite, giving 4.70 g. (72.5%) of 21-acetoxy-4-chloro-17α-hydroxypregnane-3,11,20-trione (IIIb), m.p. 238–243°. This was recrystallized from a mixture of 90 ml. of acetone and 50 ml. of water to give 3.8 g. (59%) of crystals melting at 240–243°. Further crystallization from aqueous acetone gave a sample melting at 242–245°, $[\alpha]^{24}D$ +105° (*c* 0.82).

Anal. Calcd. for $C_{23}H_{31}ClO_6$: Cl, 8.08. Found: Cl, 8.18.

The filtrate of the reaction mixture was diluted with water to give 1.3 g. of an amorphous powder, m.p. 173–185°. A crystallization from aqueous acetone gave 0.8 g. (12%) of crystals, m.p. 208–215°, shown to be mainly IIIb by papergram analysis.[17]

E. With Hypochlorous Acid.—A solution of 0.845 *N* hypochlorous acid was made by adding solid carbon dioxide to a suspension of 10 g. of 70% calcium hypochlorite (HTH, Mathieson Chem. Corp., New York, N. Y.) in 100 ml. of water, followed by filtration. Using 2.5 molar equivalents of the hypochlorite solution a first crop yield of 46% with $[\alpha]^{25}D$ +100° (*c* 0.9) and a second crop of 17% with $[\alpha]^{23}D$ +93° (*c* 0.85) was obtained using the reaction conditions given in (C).

Oxidation of 11β-Hydroxyprogesterone.—To 812 mg. (2.46 millimoles) of 11β-hydroxyprogesterone[10] in 48 ml. of *t*-butyl alcohol and 1.5 ml. of pyridine in a 50-ml. low actinic volumetric flask was added 678 mg. (4.92 millimoles) of NBA. The flask was diluted to mark with *t*-butyl alcohol and the reaction allowed to proceed until an iodometric titration of an aliquot showed one equivalent of NBA to have been consumed (*ca.* 24 hours). Water (50 ml.) containing sodium sulfite (0.25 g.) was added and the whole concentrated under reduced pressure to remove *t*-butyl alcohol. Filtration of the resultant slurry gave 735 mg. (91.3%) of material melting at 145–150°, shown to be 11-ketoprogesterone by infrared spectrogram. Recrystallization from methanol gave material melting at 166–170° which gave no depression of melting point on admixture with a known sample of 11-ketoprogesterone, m.p. 173–176°.

Under identical conditions 11α-hydroxyprogesterone was recovered in 95% yield.

Oxidation of 3α,11β,17α-Trihydroxypregnane-20-one.—To 300 mg. (0.853 millimole) of 3α,11β,17α-trihydroxypregnane-20-one[12] in 24 ml. of *t*-butyl alcohol and 0.5 ml. of pyridine in a 25-ml. low actinic volumetric flask was added 130 mg. (0.94 millimole) of NBA. Iodometric titration of an aliquot showed the reaction to be essentially complete in 20 hours. Water (50 ml.) was added and the *t*-butyl alcohol removed under reduced pressure. The crystalline product (194 mg.) was filtered off and melted at 202–204°. It was identified as 3α,17α-dihydroxypregnane-11,20-dione by its mobility on a paper chromatogram and by its infrared spectrum which was identical to that of an authentic sample, m.p. 203–204°.

Bromination of 21-Acetoxy-17α-hydroxypregnane-3,11,20-trione.—To 404 mg. (1.0 millimole) of 21-acetoxy-17α-hydroxypregnane-3,11,20-trione in 48 ml. of *t*-butyl alcohol was added 0.75 ml. of water containing 0.122 ml. of 48% hydrobromic acid (1 millimole of HBr) and 276 mg. (2.0 millimoles) of NBA. Crystallization began after approximately 24 hours at room temperature. The solution was filtered after 49 hours and the filtrate was concentrated under nitrogen to one-half its volume. On standing overnight, a second crop was obtained. The first crop (162 mg., 33.4%), $[\alpha]^{25}D$ +101° was shown to be IIIa by paper chromatographic analysis and infrared spectrum while the second crop (135 mg., 28.0%), $[\alpha]^{25}D$ +96° (*c* 0.8), consisted largely of IIIa by similar measurements.

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