[CONTRIBUTION FROM THE RESEARCH LABORATORIES OF THE UPJOHN COMPANY]

CHEMICAL STUDIES WITH 11-OXYGENATED STEROIDS. IV[1,2] THE REACTION OF HYPOHALOUS ACIDS WITH STEROID ENOL ACETATES

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Received July 22, 1955

Bedoukian has reported the synthesis of several α-bromoketones by the addition of bromine to the enol acetates of the parent ketones (1). This method was used in the steroid field by Fieser and Huang-Minlon to introduce a 17-bromine atom in the synthesis of 3-acetoxy-5,6,17-tribromopregnan-20-one from 3-acetoxy-5-pregnen-20-one (2). Similarly, by treating the Δ^{20} enol acetate of 3-acetoxy-5-pregnen-20-one with bromine, Moffett and Weisblat introduced bromine at C-21, obtaining 3-acetoxy-5,6,21-tribromopregnan-20-one (3). Reich and Lardon added hypobromous acid (N-bromacetamide in aqueous acid solution) to the enol acetates of cholestenone and methyl 3-keto-4-etiocholenate and obtained the respective 6-bromo-Δ^4-3-ketones (4). This reaction involves 1,4 addition to the conjugated diene system of the enol acetates. Djerassi and Lenk treated a number of enol acetates with N-iodosuccinimide under anhydrous conditions to obtain the α-iodoketones (5).

We have prepared several steroid α-haloketones by adding hypohalous acids to the enol acetates of the corresponding ketones, and have dehydrohalogenated them to conjugated ketones.

Hypochlorous or hypobromous acid adds readily to the enol acetates of pregnan-20-ones or -3,20-diones dissolved in aqueous acetone or *tert*-butyl alcohol, forming α-haloketo steroids. Specifically, 3α,11α,20-triacetoxy-17-pregnene (I) reacts with hypochlorous and hypobromous acids to give, respectively, the 17-halo-3α,11α-diacetoxypregnan-20-ones, IIa and IIb. The 21-chloride (V) was obtained in a yield of 80% by the addition of hypochlorous acid to the 3β,20-diacetoxy-9,11-oxido-5,7,20-pregnatriene-maleic anhydride adduct (IV) (3). The dienol acetate VI (6) reacted with hypobromous acid only at the Δ^{17} position, forming the bromide VII. Similar selectivity is reported for the reaction of peracids with VI (7). The preparation of the bromide VII from the mono enol acetate VIII was previously described in a publication from these laboratories (8).

Dienol acetates of 11-substituted pregnane-3,20-diones readily add 2 moles of hypobromous acid to give 4,17-dibromopregnane-3,20-diones. The conversions X $\rightarrow$ XI and XV $\rightarrow$ XVI illustrate this reaction. In the first example, pregnane-3,11,20-trione (IX) was converted to the trienol acetate X with acetic anhydride and *p*-toluenesulfonic acid. Hypobromous acid was added to

[1] Preceding paper in this series, Levin, Magerlein, McIntosh, Hanze, Fonken, Thompson, Searcy, Scheri, and Gutsell, *J. Am. Chem. Soc.*, **76**, 546 (1954).

[2] Presented in part before the Organic Division of the American Chemical Society at the Spring meeting, Kansas City, March 24, 1954.

crude X in dilute *tert*-butyl alcohol solution to give 4,17-dibromopregnane-3,11,20-trione (XI) in 41% yield based on trione (IX). In a similar manner 11α-hydroxypregnane-3,20-dione (XIV) was converted to 3,11,20-triacetoxy-3,17-pregnadiene (XV) which was isolated and purified (yield 44%). When this material was treated with hypobromous acid, essentially pure 4,17-dibromo-11α-acetoxypregnane-3,20-dione (XVI) was obtained in 80% yield. 11-Keto- and 11α-acetoxy-4,17-dibromopregnane-3,20-dione (XI, XVI) were

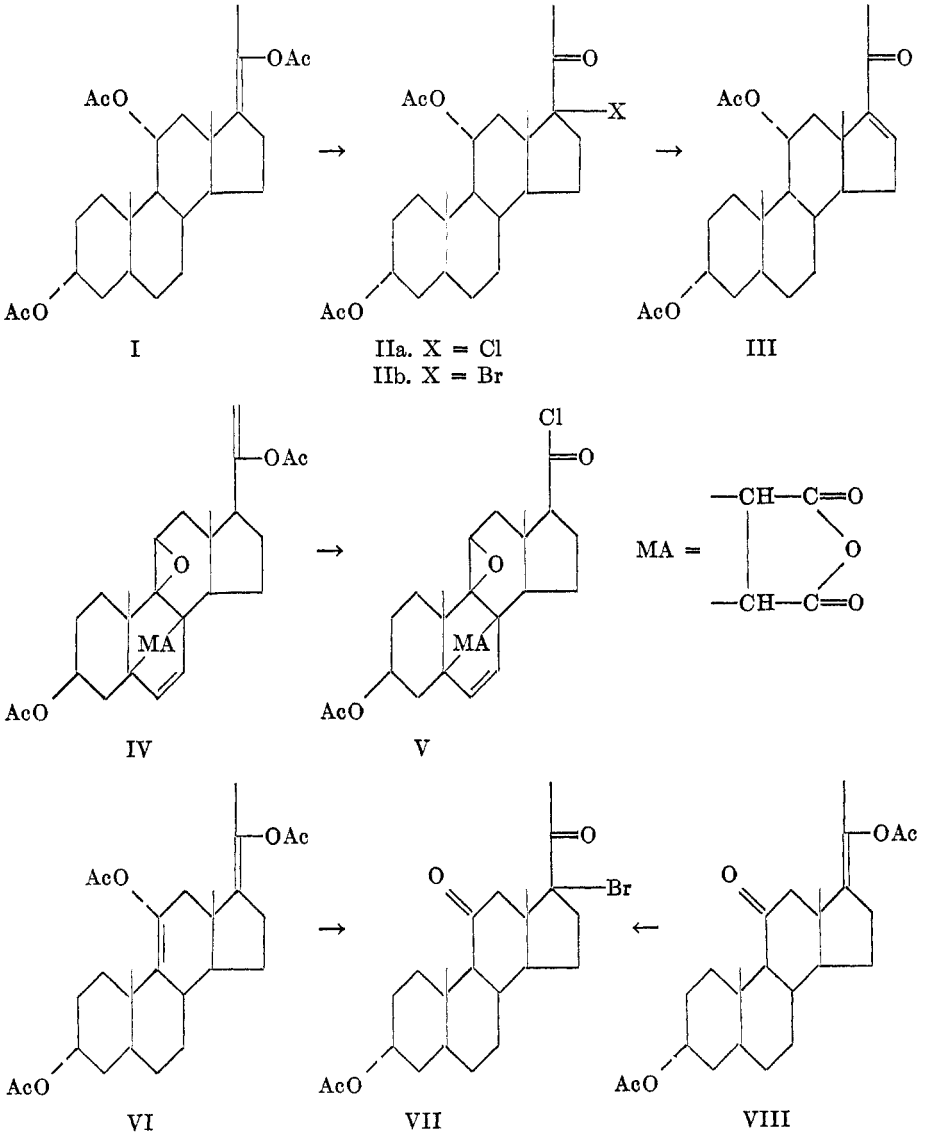

CHART I

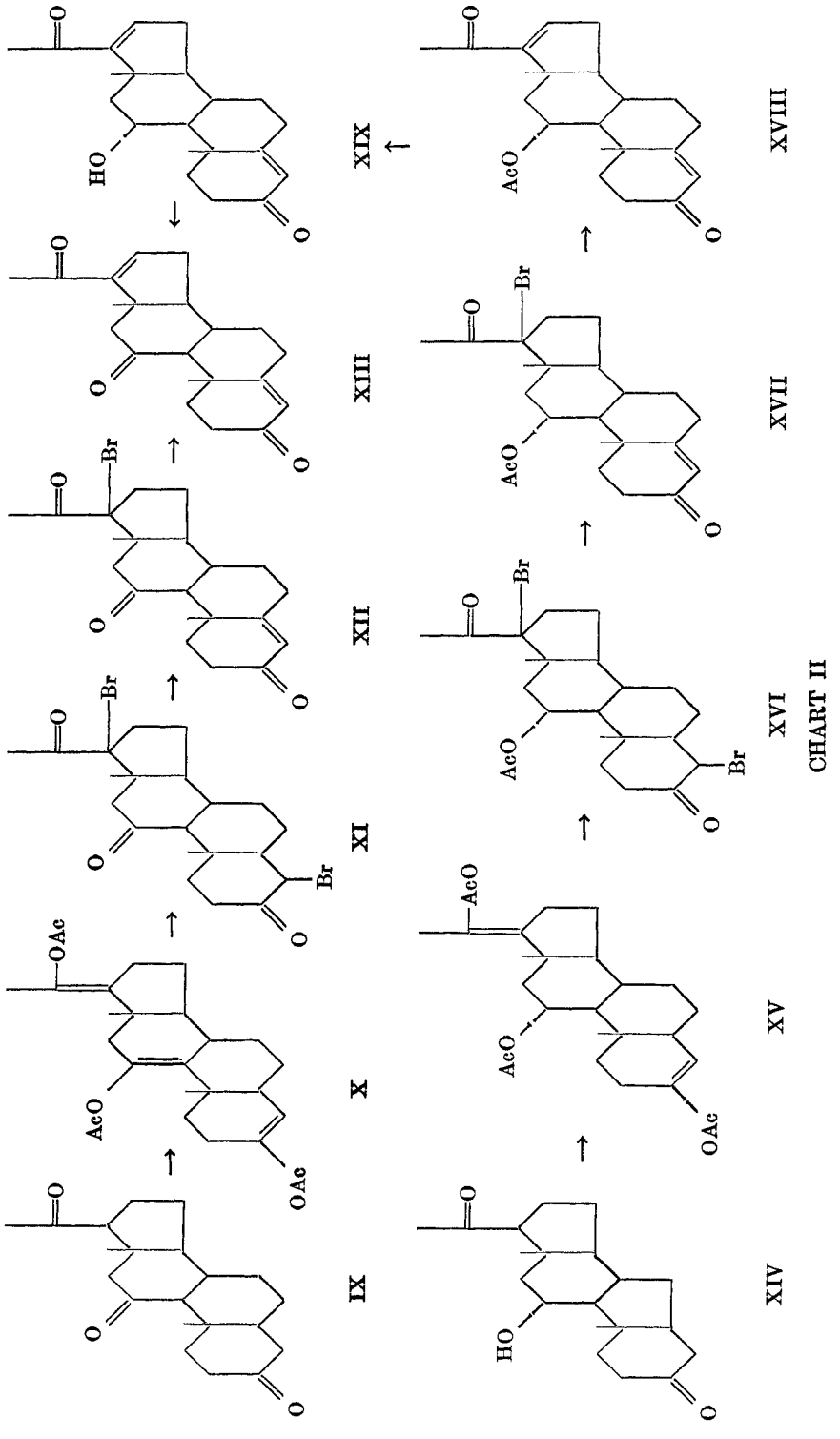

CHART II

dehydrohalogenated at the 4,5 position by treatment with semicarbazide, and the semicarbazide moiety was removed with pyruvic acid (9). The yield of 17-bromo-4-pregnene-3,11,20-trione (XII) was 54% and of 17-bromo-11α-acetoxy-4-pregnene-3,20-dione (XVII) was 62%. The bromine at the 17 position resisted removal under these conditions. It was removed readily by heating under reflux in pyridine solution to give the corresponding 4,16-pregnadiene-3,20-diones (XIII, XVIII) in yields of 77% and 76%, respectively. This method was also used to dehydrohalogenate 17-bromo-3α,11α-diacetoxypregnan-20-one (IIb) to 3α,11α-diacetoxy-16-pregnen-20-one (III) in 70% yield. Dehydrohalogenation of these 17-bromides with collidine (10) was faster but gave lower yields of inferior material.

11α-Acetoxy-4,16-pregnadiene-3,20-dione (XVIII) was hydrolyzed with potassium hydroxide in dioxane to 11α-hydroxy-4,16-pregnadiene-3,20-dione (XIX) which in turn was oxidized to 4,16-pregnadiene-3,11,20-trione (XIII) with chromic anhydride–pyridine (11).

Acknowledgment. The authors are indebted to V. R. Shellman for technical assistance; to Dr. J. L. Johnson, J. E. Stafford, and Mrs. G. S. Fonken for infrared and ultraviolet absorption studies; to W. A. Struck and associates for microanalyses and optical rotations; and to L. M. Reineke and associates for papergram analyses.

EXPERIMENTAL[3]

17-Chloro-3α,11α-diacetoxypregnan-20-one (IIa). An aqueous solution of 0.85 millimole of hypochlorous acid was added to a solution of 350 mg. of 3α,11α,20-triacetoxy-17-pregnene (I) (6) in 15 ml. of acetone. The hypochlorous acid was consumed in 3–5 minutes. The solution was concentrated under a vacuum, diluted with water, and the crystals were collected. They weighed 330 mg. (94% yield), m.p. 208–210°. Several recrystallizations from acetone gave crystals m.p. 211–212°, $[\alpha]_D^{24}$ −38° (chloroform).

Anal. Calc'd for $C_{25}H_{37}ClO_5$: C, 66.28; H, 8.23; Cl, 7.83.
Found: C, 66.52; H, 8.66; Cl, 7.96.

17-Bromo-3α,11α-diacetoxypregnan-20-one (IIb). To a solution of 140 mg. of enol acetate I in 5 ml. of *tert*-butyl alcohol was added 59 mg. of N-bromosuccinimide in 5 ml. of *tert*-butyl alcohol and 2 ml. of 0.8 *N* sulfuric acid. After 2 hours the excess hypobromous acid was destroyed by the addition of a few drops of sodium bisulfite solution. The solvent was evaporated and the crystals were washed with water. Recrystallization from ethanol gave 100 mg. (71%) of product, m.p. 191–200°. Several recrystallizations gave a product melting 204–206°, $[\alpha]_D^{23}$ −67.1° (chloroform).

Anal. Calc'd for $C_{25}H_{37}BrO_5$: C, 60.36; H, 7.50; Br, 16.07.
Found: C, 60.74, 60.60; H, 7.39, 7.56; Br, 16.01, 15.95.

3α,11α-Diacetoxy-16-pregnen-20-one (III). A solution of 650 mg. of 17-bromo-3α,11α-diacetoxypregnan-20-one (IIb) in 30 ml. of pyridine was heated under reflux for 8 hours. The cooled solution was diluted with ether, washed with dilute hydrochloric acid, dried, and concentrated. There was thus obtained 480 mg. of crystals, m.p. 188–192°. This material was chromatographed over alumina and the main fraction, which weighed 472 mg., was recrystallized from ethanol to give 440 mg., m.p. 194–197°. The yield was 81%. Several recrystallizations from ethanol gave an analytical sample, m.p. 196–198.5°.

[3] All melting points are uncorrected. Infrared absorption spectra were secured on all compounds and are consistent with the assigned structures. Optical rotations were taken at a steroid concentration of 1%.

Anal. Calc'd for $C_{25}H_{36}O_6$: C, 72.08; H, 8.71.

Found: C, 72.36, 72.77; H, 8.96, 8.57.

21-Chloro-3β-acetoxy-9,11-oxido-5,7-pregnadien-20-one maleic anhydride adduct (V). Reaction of the enol acetate IV (3) with hypochlorous acid in the manner described above gave 80% yield of V, m.p. 229–233° dec. Recrystallization from methylene dichloride-ether raised the melting point to 244–245.5° dec.

Anal. Calc'd for $C_{27}H_{31}ClO_7$: C, 64.47; H, 6.21; Cl, 7.05.

Found: C, 64.47, 64.23; H, 6.37, 6.52; Cl, 7.15.

17-Bromo-3α-acetoxypregnane-11,20-dione (VII). The addition of hypobromous acid to 3α,11,20-triacetoxy-9(11),17-pregnadiene (VI) (7) in the manner previously described gave 61% yield of VII, m.p. 134–151°. Two recrystallizations from ether and one from ethyl acetate-Skellysolve B[4] gave material melting 174–175°, $[\alpha]_D^{23}$ −7° (chloroform).

Anal. Calc'd for $C_{23}H_{33}BrO_4$: Br, 17.63.

Found: Br, 17.61, 17.51.

3,11,20-Triacetoxy-3,17-pregnadiene (XV). 11α-Hydroxypregnane-3,20-dione (10.25 g.) and *p*-toluenesulfonic acid monohydrate (4.1 g.) were dissolved in 360 ml. of acetic anhydride. Acetic acid-acetic anhydride was distilled at such a rate that about 200 ml. was collected in 4 hours. Most of the remaining acetic anhydride then was removed by distillation in a vacuum, leaving a viscous syrup. Methylcyclohexane (145 ml.) was added and the remaining acetic anhydride was removed by azeotropic distillation. Benzene (100 ml.) was added and the cooled solution was washed with 50 ml.-portions of cold 4% sodium bicarbonate solution until the last wash remained basic. After one wash with water, the benzene-methylcyclohexane solution was dried over magnesium sulfate and the solvents were removed under reduced pressure. The oil was dissolved in 200 ml. of hot ethanol and 100 ml. was removed by distillation at atmospheric pressure. The solution cooled slowly at room temperature as crystals formed. It was cooled at 4° overnight. The crystals were collected on a filter and washed with a small volume of cold ethanol [wt. 6.18 g. (44%) m.p. 134–142°]. A portion was recrystallized further from methanol and then from acetone to give an analytical sample, m.p. 140–149°[5] $[\alpha]_D^{23}$ −20° (chloroform).

Anal. Calc'd for $C_{27}H_{38}O_6$: C, 70.71; H, 8.35.

Found: C, 71.13, 71.13; H, 8.40, 8.16.

4,17-Dibromo-11α-acetoxypregnane-3,20-dione (XVI). To a solution of 6.18 g. (13.5 millimoles) of the dienol acetate XV in 300 ml. of *tert*-butyl alcohol was added a solution of hypobromous acid prepared by dissolving 5.28 g. (29.7 millimoles) of N-bromosuccinimide in 450 ml. of *tert*-butyl alcohol and adding 155 ml. of 0.8 *N* sulfuric acid. The resulting solution was allowed to stand in the dark at room temperature for 2 hours. A solution of sodium bisulfite in an amount sufficient to destroy the excess hypobromous acid was added and the solvents were removed by distillation under reduced pressure. The solid, after being thoroughly triturated with water, was filtered and washed well with water. The crude product was dried and recrystallized from ethanol. It weighed 5.72 g. (80%), m.p. 207–208°, $[\alpha]_D^{22}$ −32° (chloroform).

Anal. Calc'd for $C_{23}H_{32}Br_2O_4$: C, 51.89; H, 6.06; Br, 30.03.

Found: C, 52.16; H, 5.96; Br, 30.01.

17-Bromo-11α-acetoxy-4-pregnene-3,20-dione (XVII). 4,17-Dibromo-11α-acetoxypregnane-3,20-dione (XVI) (84.4 g., 0.159 mole) was dissolved in 3170 ml. of dioxane and the air in the flask was replaced with nitrogen. To this solution was added a solution prepared by dissolving 35.35 g. (0.317 mole) of semicarbazide hydrochloride and 26.0 g. (0.317 mole) of sodium acetate in 396 ml. of water. The resulting solution was stirred for 2 hours in a nitrogen atmosphere at room temperature. Pyruvic acid (84 ml.) and water (800 ml.) were added and the mixture was stirred overnight at room temperature. The solution was poured

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[4] A saturated hydrocarbon fraction, b.p. 60–71°.

[5] The broad melting range of this compound is probably due to the presence of *cis-trans* isomers of the enol acetate.

into 20 l. of water, and the aqueous mixture was extracted with three 3.5-l. portions of methylene chloride. The methylene chloride solution was washed with two 1750-ml. portions of cold 1% sodium hydroxide and two 3.5-l. portions of water. Magnesium sulfate was used to dry the methylene chloride solution which then was evaporated to dryness under reduced pressure. The oil was dissolved in 150 ml. of hot ethanol. The solution, when cooled, deposited crystals which weighed 44.0 g. (62%), m.p. 162–164°; $\lambda_{max.}^{EtOH}$ 240 mμ, E 16,100. A small sample from a different preparation was recrystallized from acetone-Skellysolve B, and from ethanol $\lambda_{max.}^{EtOH}$ 239 mμ, E 17,000.

Anal. Calc'd for $C_{23}H_{31}BrO_4$: C, 61.19; H, 6.92; Br, 17.70.

Found: C, 60.88, 61.14; H, 7.19, 6.75; Br, 17.65, 17.60.

11α-Hydroxy-4,16-pregnadiene-3,20-dione (XIX). 17-Bromo-11α-acetoxy-4-pregnene-3,20-dione (XVII) (1.0 g.) was dissolved in 25 ml. of dry pyridine and the solution was heated under reflux for 24 hours. Most of the pyridine was evaporated under reduced pressure and the residue was dissolved in a mixture of 50 ml. of benzene and 50 ml. of water. The benzene layer was washed with *N*-hydrochloric acid until all the pyridine was removed, then with water until the washes were neutral. The benzene solution was dried over magnesium sulfate and concentrated to dryness under reduced pressure. The residual oil crystallized. Recrystallization of the product from approximately 2 ml. of ethyl acetate and 20 ml. of Skellysolve B gave 0.71 g. (86.3%) of needles. A second recrystallization, from isopropyl alcohol (2.5 ml.), yielded 0.622 g. (76%) of *11α-acetoxy-4,16-pregnadiene-3,20-dione* (XVIII), m.p. 176–178° $\lambda_{max.}$ 239 mμ, E 25,775 (ethanol).

A mixture of 740 mg. (2.0 millimoles) of XVIII, 168 mg. of potassium hydroxide, 7 ml. of water, and 20 ml. of purified dioxane was heated under reflux for 7 hours. The excess alkali was neutralized with 0.1 *N* hydrochloric acid. The volatile solvents were removed under reduced pressure and the last of the water was removed by codistillation with benzene. The oil, which could not be induced to crystallize, was chromatographed over 65 g. of Florisil.[6] Practically all of the material came off the column with 10% acetone in Skellysolve B.

It was crystallized from approximately 15 ml. of ethyl acetate and 20 ml. of Skellysolve B. There was recovered 447 mg. (68% yield), m.p. 179–180°, $\lambda_{max.}$ 241, E 24,100 (ethanol). This material was recrystallized again from ethyl acetate-Skellysolve B to give long needles, m.p. 179–180°, $\lambda_{max.}$ 235, E 25,725 (ether), $[\alpha]_D$ +142° (chloroform).

Anal. Calc'd for $C_{21}H_{28}O_3$: C, 76.79; H, 8.59.

Found: C, 76.92; H, 8.39.

4,16-Pregnadien-3,11,20-trione (XIII). *Method A.* A slurry of the complex of chromic anhydride and pyridine was prepared by slowly adding 250 mg. (2.5 millimoles) of chromic anhydride to 10 ml. of cold pyridine with stirring. A solution of 250 mg. (0.762 millimole) of 11α-hydroxy-4,16-pregnadien-3,20-dione (XIX) in 10 ml. of pyridine was added to the oxidant. The mixture was swirled several times and then was allowed to stand overnight at room temperature. A finely divided dark red solid separated during this period. This was removed by filtration and washed with pyridine. The filtrate and washes were combined and evaporated under reduced pressure at room temperature to a small volume. Benzene (25 ml.) was added and the solution was washed with *N* hydrochloric acid until the washes were acidic. The mixture was filtered. The clarified phases were separated and the benzene layer was washed with water until the washes were neutral. Magnesium sulfate was used to dry the benzene solution which then was concentrated to dryness under reduced pressure. The residual oil crystallized and the solid was recrystallized from ethyl acetate-Skellysolve B to give needles, 151 mg. (60%), m.p. 200.5–202.5°. This material was recrystallized again from ethyl acetate-Skellysolve B, m.p. 202–204°, $\lambda_{max.}$ 231 mμ, E 27,225 (ether), $\lambda_{max.}$ 236 mμ, E 24,875 (methanol).

Anal. Calc'd for $C_{21}H_{28}O_3$: C, 77.27; H, 8.03.

Found: C, 77.36; H, 8.05.

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[6] A synthetic magnesia-silica gel made by The Floridin Co., Warren, Pa.

Method B. 17-Bromo-4-pregnene-3,11,20-trione (XII) (2.60 g.) in 50 ml. of pyridine was heated under reflux for 24 hours. The pyridine was removed by concentration under reduced pressure, and the product was dissolved in methylene chloride and washed with 2 *N* hydrochloric acid and then with water. The crystalline residue which remained after drying and removal of methylene chloride was recrystallized from ethyl acetate-Skellysolve B to give 1.519 g. (77% yield), m.p. 198–203°. A mixture melting point with material prepared by *Method A* was not depressed.

4,17-Dibromopregnan-3,11,20-trione (XI). Pregnane-3,11,20-trione (10 g., 0.030 mole) was dissolved in acetic anhydride (350 ml.) containing 3 g. of *p*-toluenesulfonic acid monohydrate. The solution was heated and distillation was allowed to proceed at such a rate that 200 ml. of distillate was collected over a 4 hour period. Most of the acetic anhydride was removed by concentration under reduced pressure and the remaining anhydride was removed by distillation as an azeotrope with methylcyclohexane (250 ml.). Benzene (250 ml.) was added and the resulting solution was washed with cold sodium bicarbonate solution until the wash was alkaline and then was washed twice with water. The organic layer was dried with magnesium sulfate. This was followed by 5 g. of Magnesol[7] to decolorize the solution. A light yellow solution was obtained by filtration. The solvent was removed under reduced pressure to give crude *3,11,20-triacetoxy-3,9,17-pregnatriene* (X) which was not purified. The crude enol acetate X, was dissolved in *tert*-butyl alcohol (300 ml.).[8] To this was added a solution of N-bromsuccinimide (10.68 g., 0.060 mole) in *tert*-butyl alcohol (900 ml.) followed by 362 ml. of 0.8 *N* sulfuric acid. A clear solution resulted which was protected from light for 2 hours at room temperature. At the end of this period no hypobromous acid remained. The solvents were removed under reduced pressure and the crystalline residue was slurried with 250 ml. of water. The product was collected, washed with water, and dried *in vacuo*. It was recrystallized by dissolving in methylene chloride, adding ethanol (150–250 ml.), and distilling the solvent until crystallization began. The flask was refrigerated overnight, and the crystals were collected, washed with cold ethanol, and dried *in vacuo* (41% yield); the crystals weighed 5.99 g., m.p. 195–196° (dec.). Several recrystallizations gave an analytical sample, m.p. 196–197° (dec.), $[\alpha]_D^{23}$ +27° (chloroform).

Anal. Calc'd for $C_{21}H_{28}Br_2O_3$: C, 51.65; H, 5.78; Br, 32.74.

Found: C, 51.86; H, 5.83; Br. 32.87.

17-Bromo-4-pregnene-3,11,20-trione (XII). 4,17-Dibromopregnane-3,11,20-trione (XI) (5.99 g.) was treated with semicarbazide as described above for XVI to introduce the double bond at the 4 position. In this manner 2.72 g., m.p. 172–175° (54%) of XII was obtained. A sample was purified by recrystallization, first from isopropyl alcohol and then from ethyl acetate-Skellysolve B. It melted at 174–176°, $\lambda_{max.}^{EtOH}$ 239 mμ, E 16,625.

Anal. Calc'd for $C_{21}H_{27}BrO_3$: Br, 19.63. Found: Br, 19.64.

SUMMARY

The reaction of steroid enol acetates with hypohalous acids to form steroid α-haloketones is described. Dehydrohalogenation of 17-bromo-3α,11α-diacetoxypregnan-20-one (IIb) gave 3α,11α-diacetoxy-16-pregnen-20-one (III). Dehydrohalogenation of 4,17-dibromo-11-keto- (or 11α-acetoxy) pregnane-3,20-dione by the semicarbazide-pyruvic acid method selectively removed the 4-bromide leaving the 17-bromine intact. Treatment of the compounds with pyridine gave 11-keto- (or 11α-acetoxy)-4,17-pregnadiene-3,20-dione.

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[7] Westvaco brand of magnesium silicate.

[8] It was necessary to heat this mixture in order to obtain a solution which was quickly cooled before adding immediately to the solution of enol acetate.

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