[CONTRIBUTION FROM THE RESEARCH LABORATORIES OF THE GLIDDEN COMPANY, SOYA PRODUCTS DIVISION]

Sterols. III. A Method for the Dehalogenation of Steroids

BY PERCY L. JULIAN, WAYNE COLE, ARTHUR MAGNANI AND EDWIN W. MEYER

The classical method for removing halogen from 5,6-dibromo-3-keto-steroids by means of zinc dust and acetic acid sometimes gives the unsaturated ketones in relatively poor yield and contaminated with impurities which are frequently difficult to remove. We were impressed by this inadequacy in connection with the preparation of several 3-keto-steroids, and others have described procedures which reveal unsatisfactory applications of the zinc dust method.[1] Although the sodium iodide procedure[2] obviates the undesirable reduction by-products and is occasionally quite suitable, it often fails to yield completely halogen-free products.

In searching for a more practical method of removing bromine in the preparation of the sex hormones, we discovered that chromous chloride solution gave rapid, complete dehalogenation of the 5,6-dibromo-3-keto-steroids. The Δ^4-3-keto-steroid so formed is, in some cases, crystallized directly from the mixture; in other cases, it is recovered by extraction. Further investigation showed that the chromous chloride procedure was applicable to the removal of halogen from any of the 5,6-dibromo-steroids as well as from α,β-dibromo-ketones and certain α-halo-ketones.

The use of ferrous salts for dehalogenating 5,6-dibromo-steroids[1d] is analogous to our method, but in our opinion the ferrous salt procedure is slower and of less general application than the chromous chloride procedure. The use of other reducing salts, such as titanous chloride, vanadous chloride, stannous chloride, ferrous chloride and sodium sulfite, has given us dehalogenation in various instances, but the yields of pure products have been less reliable and frequently lower than when chromous chloride was employed.

Examples given in this paper of the removal of bromine from 5,6-dibromo-3-keto-steroids include preparations of androstenedione, progesterone, desoxycorticosterone, 3-keto-bisnor-4-cholenic acid and 3-keto-etio-4-cholenic acid. Although the intermediate unstable dibromo ketones may be separated and crystallized, this separation is described for only one case, namely, 5,6-dibromo-pregnandione, since in effort and yield it is more economical to debrominate the crude intermediate promptly. Moreover, the desirability of so doing is emphasized by the tendency of 5,6-dibromo-pregnane-3,20-dione to lose bromine spontaneously, followed by random rebromination. An analogous loss of bromine occurs with 5,6-dibromocholestanone.[3]

(1) (a) Butenandt and Westphal, *Ber.*, **67**, 2087 (1934); (b) Fernholz, *ibid.*, **67**, 2027 (1934); (c) Steiger and Reichstein, *Helv. Chim. Acta*, **20**, 1177 (1937); (d) Bretschneider and Ajtai, *Monatsh.*, **74**, 57 (1941).

(2) Schoenheimer, *J. Biol. Chem.*, **110**, 461 (1935).

(3) Inhoffen, *Ber.*, **69**, 1136 (1936).

5,6-Dibromo-sterols may be dehalogenated by the chromous chloride method, but frequently there is no advantage over the zinc dust procedure, which often gives very satisfactory results. However, an exception is the application of the reagent to the selective removal of bromine from stigmasteryl acetate tetrabromide giving stigmasteryl acetate 22,23-dibromide. Here a large excess of reagent did not attack the 22,23-dibromide to an appreciable extent.

A useful, although infrequent, application of the reagent is the conversion of an α-bromo-ketone into the parent ketone. The reaction is illustrated by the preparation of propiomesitylene from α-bromopropiomesitylene and by the conversion of 3,12-diacetoxy-23-bromonorcholanyl phenyl ketone into the parent ketone. This bromo-ketone, which was prepared in connection with a degradation of desoxycholic acid, undergoes transformation into a higher melting modification on heating. The reconversion to the parent ketone by chromous chloride together with other data, established that this change did not involve re arrangement of the carbon linkages.

A more subtle application of this replacement of α-halogen by hydrogen probably occurs in the oxidative preparation of various steroid ketones. During the oxidation of 5,6-dibromo-steroids to ketones, some bromine is eliminated and seemingly consumed in converting a portion of the product into α-bromo-ketones, thereby lowering the yield and producing a very undesirable impurity. The ability of the debrominating agent to reconvert these by-products into the parent ketone contributes materially toward obtaining pure reaction products.

The use of chromous chloride as a dehalogenating agent should find more extensive application in other fields. Bromine is readily removed from benzalacetophenone dibromide, and we feel that α,β-dibromo-ketones in general may be so dehalogenated.

Experimental

The 1 *N* aqueous chromous chloride solution (containing zinc chloride and free hydrochloric acid) was prepared as described by Conant and Cutter.[4]

Debromination of 5,6-Dibromoandrostane-3,17-dione.—The dibromide obtained by brominating 2.0 g. of dehydroandrosterone, m. p. 146–148°, in chloroform with 1.1 g. of bromine and then removing the solvent under vacuum, was dissolved in 80 ml. of glacial acetic acid and oxidized with 1.2 g. of chromic anhydride (which was dissolved in 2 ml. of water and 20 ml. of acetic acid) for two hours at 25°. The dibromo-diketone was separated by means of ether, washed free of acids, concentrated, then dissolved in 100 ml. of acetone and treated under carbon dioxide with 60 ml. of 1 *N* chromous chloride solution for two hours. The acetone was partly distilled, and the residue extracted

(4) Conant and Cutter, THIS JOURNAL, **48**, 1023 (1926).

with ether, giving 1.6 g. of colorless 4-androstene-3,17-dione, m. p. 168–170°. This material showed no depression in melting point when melted with the dione prepared in the known manner.[5]

In a comparable androstenedione preparation employing zinc dust and acetic acid as the debrominating method, 2 g. of dehydroandrosterone, brominated and oxidized exactly as above, yielded 1.0 g. of androstenedione, m. p. 152–156°, plus lower-melting material from the mother liquor. Recrystallization from acetone raised the melting point to 167–169°.

5,6-Dibromopregnane-3,20-dione.—A cold solution of 0.95 g. (0.003 mole) of 5-pregnen-3-ol-20-one (m. p. 188°) in 35 ml. of chloroform was treated with 0.48 g. of bromine in 9.6 ml. of chloroform. After twenty seconds all of the solvent was removed by swirling under vacuum. The white amorphous pregnenolone dibromide was dissolved in 30 ml. of glacial acetic acid and treated with a cold solution of 0.25 g. of chromic anhydride in 1 ml. of water and 40 ml. of glacial acetic acid for four hours at 20°. The product was diluted with water, extracted with ether, washed and concentrated *in vacuo* without heating. The residue, 1.4 g. of white wax, readily crystallized from 4 ml. of methanol, giving 1.0 g. of crystals which melted at 78–80° to a red liquid.

Anal. Calcd. for $C_{21}H_{30}O_2Br_2$: Br, 33.7. Found: Br, 33.1, 33.4.

The dibromide is not stable. After standing for five hours in a closed vial at 25° the crystals changed from colorless to pink and gave off bromine vapor, which was identified by odor, color and decolorization by sodium thiosulfate solution. The pink crystals, after washing with sodium thiosulfate solution, were colorless but waxy.

Debrominating the freshly prepared crystals with excess sodium iodide in ethanol solution for ten hours at room temperature gave 65% of the theoretical yield of progesterone plus some material still containing halogen. Treating the freshly prepared dibromide with zinc dust in glacial acetic acid gave waxy progesterone together with a by-product melting at 180–195°.[6]

Progesterone.—A solution of 2.8 g. of 5,6-dibromopregnanedione (prepared from 1.9 g. of pregnenolone as described above, but not crystallized) in 80 ml. of acetone was treated (under carbon dioxide) with 60 ml. of 1 *N* chromous chloride solution at 26° for two hours, and a part of the acetone was distilled. The product was extracted with ether, washed, concentrated and crystallized, yielding first a trace of ether-insoluble crystalline substance melting at 235°, then 1.7 g. (90%) of colorless progesterone melting at 120–123°. Recrystallization from acetone raised the melting point to 128–130°.

Desoxycorticosterone Acetate.—A solution of 4.5 g. of 5-pregnene-3,21-diol-20-one 21-monoacetate in 25 ml. of chloroform was cooled, treated with 1.92 g. of bromine diluted with 20 ml. of chloroform, then concentrated *in vacuo* with little heating to an amorphous residue. This was dissolved in 180 ml. of glacial acetic acid and oxidized with 1.8 g. of chromic anhydride in 3 ml. of water and 35 ml. of acetic acid at 25° for two hours. The dibromo-ketone was extracted with ether, washed free of acids, concentrated, diluted with 300 ml. of acetone and then treated (under carbon dioxide) with 180 ml. of normal chromous chloride solution at room temperature for three hours. A part of the acetone was distilled, the product was extracted with ether, washed, concentrated and crystallized from a small volume of ether, giving 3.6 g. of desoxycorticosterone acetate[10] as colorless prisms (m. p. 157–159°) plus 0.3 g. of low-melting product.

3-Keto-4-bisnorcholenic Acid.[7]—To a suspension of 10 g. of 3-hydroxy-5-bisnorcholenic acid (m. p. 288–290°) in 300 ml. of glacial acetic acid a solution of 4.1 g. of bromine in 25 ml. of acetic acid was added with stirring. The resulting clear solution was oxidized by adding 4 g. of chromic anhydride in 8 ml. of water and 30 ml. of glacial acetic acid at 25°. After two hours, 10 ml. of methanol was added, the solution was covered with carbon dioxide and treated with 150 ml. of normal chromous chloride solution at 25° for two hours. A part of the solvent was removed by vacuum concentration during which 4 g. of 3-keto-4-bisnorcholenic acid (m. p. 269–271°) crystallized directly from the solution. The product remaining in solution was extracted with ether, washed and crystallized from the ether concentrate, giving an additional 2.0 g. (m. p. 269–271°) and 2.0 g. (m. p. 261–265°).

3-Keto-4-etiocholenic Acid.[8]—A suspension of 4.75 g. of 3-hydroxy-5-etiocholenic acid (m. p. 276–278°) in 220 ml. of glacial acetic acid at 25° was treated successively with 2.2 g. of bromine in 22 ml. of acetic acid, with 2.0 g. of chromic anhydride in 4 ml. of water and 30 ml. of acetic acid for two hours, with 10 ml. of methanol for twenty minutes, then (under carbon dioxide) with 160 ml. of normal chromous chloride for two hours. Crystals of the product began to separate from the green solution. Slow addition of 250 ml. of water brought down a first crop of 3.8 g. of colorless crystals of the keto-acid, m. p. 244–248°. Ether extraction of the liquor gave a small additional amount. Recrystallization from benzene or from acetone gave stout needles, m. p. 256–258°.

Stigmasteryl Acetate 22,23-Dibromide.[9]—A suspension of 8 g. of powdered stigmasteryl acetate tetrabromide in 500 ml. of acetone at 34° was covered with carbon dioxide and treated with 140 ml. of 1 *N* chromous chloride solution for five hours at 25–30°. The product crystallized before the tetrabromide had completely dissolved, making it impossible to decide by appearance when the reaction was complete. Diluting with 200 ml. of water and filtering gave 5.9 g. of white powder, m. p. 174–180° with dec. This was dissolved in 30 ml. of benzene, filtered, then diluted with 80 ml. of 95% ethanol to obtain 3.9 g. of white needles, m. p. 211–213°, of the 22,23-dibromide. A second crop weighing 0.2 g., m. p. 207–210°, was obtained.

In a similar manner 5 g. of the tetrabromide in 500 ml. of acetone treated with 150 ml. (four times the theoretical amount) gave 2.8 g. (70% of the theoretical amount) of the 22,23-dibromide melting at 211–213°.

This is an example of the debromination of a relatively insoluble substance, and it is probable that the success of the procedure depends upon using a finely powdered starting material. The 22,23-dibromide is readily distinguished from the tetrabromide by the fact that it does not liberate iodine from hot alcoholic sodium iodide solution.

Debromination of α-Bromopropiomesitylene.—A solution of 12.75 g. (0.05 mole) of α-bromopropiomesitylene in 150 ml. of acetone was treated under carbon dioxide with 100 ml. of 1 molar chromous chloride solution. Heat was liberated and the color quickly changed to deep green. After standing for two hours at room temperature, the solution was diluted with water and extracted with ether. The extract was washed several times with water, once with dilute sodium bicarbonate solution, then with water and dried. The oily residue remaining after removal of solvent was distilled *in vacuo*. The colorless oil which distilled at 120–124° (11 mm.) weighed 8.2 g. (93%) and gave no test for halogen.

A sample of the material was nitrated according to the procedure of Fuson.[10] The product, colorless prisms, melted at 142–144° after several crystallizations from ethanol.[11]

Desoxycholophenone.—Desoxycholic acid was treated with 98% formic acid at 55° for six hours, giving a 95% yield of desoxycholic acid diformate melting at 190–193°.[12] The diformate was converted into the acid chloride by treating 44.8 g. (0.1 mole) with 200 ml. of absolute ether, 100 ml. of benzene, 24 ml. of thionyl chloride and one drop

(5) Ruzicka and Wettstein, *Helv. Chim. Acta*, **18**, 986 (1935).

(6) Another by-product of the zinc dust reaction has been described by Butenandt and Westphal, ref. 1a.

(7) Butenandt and Mamoli, *Ber.*, **68**, 1857 (1935).

(8) Mieschler, Hunziker and Wettstein, *Helv. Chim. Acta*, **23**, 403 (1940).

(9) Fernholz and Stavely, THIS JOURNAL, **61**, 2956 (1939).

(10) Fuson, Ross and McKeever, *ibid.*, **61**, 414 (1939).

(11) Fuson and McKeever, *ibid.*, **62**, 2088 (1940).

(12) Borsche and Feske, *Z. physiol. Chem.*, **176**, 109 (1928).

of pyridine at room temperature for two hours, then removing all of the solvent under vacuum. The crude acid chloride was taken up in 100 ml. of benzene and added to 300 ml. of stirred ether suspension containing 0.2 mole of diphenylcadmium.[13] After stirring for five hours at room temperature the ether–benzene solution was washed and steam-distilled. The residue was hydrolyzed with 400 ml. of 5% methanolic potassium hydroxide and the solution poured into 3 liters of water, giving 32 g. of crystalline product, m. p. 200–203°. For analysis, 1 g. was recrystallized from acetone, giving stout needles, m. p. 203–204°.

Anal. Calcd. for $C_{30}H_{44}O_3$: C, 79.64: H, 9.73. Found: C, 79.69; H, 9.37.

The bulk of the hydroxy-ketone was treated with acetic anhydride and converted into 3,12-diacetoxy-norcholanyl phenyl ketone, which crystallized from acetic acid in prisms, m. p. 136–137°.

Anal. Calcd. for $C_{34}H_{48}O_5$: C, 76.12; H, 8.95. Found: C, 76.19; H, 9.22.

3,12-Diacetoxy-23-bromonorcholanyl Phenyl Ketone.—A solution of 1.6 g. of the diacetate in 35 ml. of acetic acid containing 1 drop of hydrobromic acid was treated with 0.5 g. of bromine. Decolorization occurred during thirty minutes. The product was separated with water and ether, washed, then crystallized from a small volume of acetone, giving 0.8 g. of white crystals; m. p. 106–108°; $[\alpha]^{29}D$ + 91° (57.8 mg. made up to 5 ml. with chloroform gave α + 1.05°; l = 1 dm.). Recrystallization from acetone did not change the melting point. This is the labile form of the bromo-ketone.

Anal. Calcd. for $C_{34}H_{47}O_5Br$: C, 66.34; H, 7.92; Br, 13.0. Found: C, 66.58; H, 7.96; Br, 12.4.

The mother liquor sirup from the above bromination refused to crystallize until it was boiled in alcohol then cooled, whereupon 1 g. of white plates of a second bromo-ketone crystallized; m. p. 165–175°. In another preparation the whole product from 16 g. of the diacetate was boiled in ethanol then crystallized, giving 15 g. of the higher-melting bromo-ketone; $[\alpha]^{28}D$ + 105° (3% solution in chloroform).

Anal. Calcd. for $C_{34}H_{47}O_5Br$: C, 66.34; H, 7.92; Br, 13.0. Found: C, 66.05; H, 7.96; Br, 13.2.

(13) *Cf.* Cole and Julian, THIS JOURNAL, **67**, 1369 (1945).

When the 106–108° form is boiled in ethanol solution then cooled, plates of the 175°-bromo-ketone separate. The lower-melting form seems to be the primary bromination product, but it could be obtained in good yield only when small quantities of the diacetate were brominated and the product crystallized promptly.

In order to show that the 175°-bromo-ketone did not represent a rearrangement product, a sample was reconverted to the parent ketone. Two grams of the bromide in 200 ml. of acetone was covered with carbon dioxide, then treated with 25 ml. of 1 *N* chromous chloride solution at room temperature for three hours. Extraction and crystallization gave 1.4 g. of 3,12-diacetoxynorcholanyl phenyl ketone, m. p. 133–136°.

Debromination of Benzalacetophenone Dibromide.—A solution of 9.2 g. of benzalacetophenone dibromide[14] in 150 ml. of acetone was treated, under carbon dioxide, with 75 ml. of 1 molar chromous chloride solution. Heat developed and the color turned green immediately. After standing for one and one-half hours, the solution was diluted with water and extracted with ether. The halogen-free oily residue from the washed and dried ether solution gave 0.6 g. of white solid crystallizing from ethanol, m. p. 168–178°. This material which may be one of the dimerides of benzalacetophenone was not studied further. The remainder of the reaction product was distilled *in vacuo*. The fraction distilling at 160–170° air-bath temperature, 1 mm., weighed 2.9 g. (55%). The benzalacetophenone solidified upon moistening with methanol and scratching, and showed m. p. 54.5–57.5°.

Summary

A method for the dehalogenation of steroids by means of chromous chloride is described. By this method 5,6-dibromo-3-keto-steroids are converted into the corresponding Δ^4-3-keto-steroids, 5,6-dibromo-sterols give the Δ^5-sterols, and α-bromo-ketones are reduced to the parent ketone. The method may be useful in other fields.

(14) "Organic Syntheses," Coll. Vol. I, 2nd ed., p. 205.

CHICAGO, ILLINOIS RECEIVED JULY 26, 1945

[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY, THE UNIVERSITY OF TEXAS]

Allylic Chlorides. I. Catalytic Hydrolysis of Allyl Chloride

BY LEWIS F. HATCH AND REEDUS RAY ESTES[1]

Only recently has brief mention been made in the literature[2,3] of the catalytic hydrolysis of allyl chloride by a hydrochloric acid solution of cuprous chloride, although the preparation of the chloride from the alcohol using hydrochloric acid and cuprous chloride has been known for some time.[4] This method of acid hydrolysis was reported to give yields of both allyl alcohol and diallyl ether comparable to those obtained by hydrolysis using a basic medium. Because the reaction is of unusual interest from a theoretical standpoint and is potentially of wide application to the hydrolysis of other allylic chlorides as well, a series of investigations has been made on the catalytic hydrolysis of allyl chloride and various substituted allyl chlorides.

Experimental

Allyl Chloride.—Commercial grade allyl chloride was furnished us for this work by the Shell Development Company. It was fractionated through a 4-ft. helix-packed column and the material boiling constantly at 44.9° (751 mm.) was used.

Cuprous Chloride.—Merck "Reagent Grade" cuprous chloride was purified by the usual method.[5] Electrodeposition analysis indicated a cuprous chloride content of 99.8% assuming the impurity to be cupric chloride.

Continuous Hydrolysis of Allyl Chloride.—A diagram of the apparatus used in all the hydrolysis runs except those involving added sodium chloride is given in Fig. 1. The hydrolysis column *N* was made of three concentric Pyrex tubes 48 in. long and having outside diameters of 20 mm.,

(1) Present address: The Armour Laboratories, Chicago, Illinois.

(2) Williams, *Trans. Am. Inst. Chem. Engrs.*, **37**, 157 (1941); *Chem. Met. Eng.*, **47**, 834 (1940).

(3) British Patent 549,001 to Shell Development Co. (1942).

(4) (a) Dewael, *Bull. soc. chim. Belg.*, **39**, 40 (1930); (b) Breckpot, *ibid.*, **39**, 462 (1930).

(5) Henderson and Fernelius, "Inorganic Preparations," McGraw-Hill and Co., New York, N. Y., 1935, p. 24.