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

STEROLS. XIV. REDUCTION OF EPOXY KETONES BY CHROMOUS SALTS[1]

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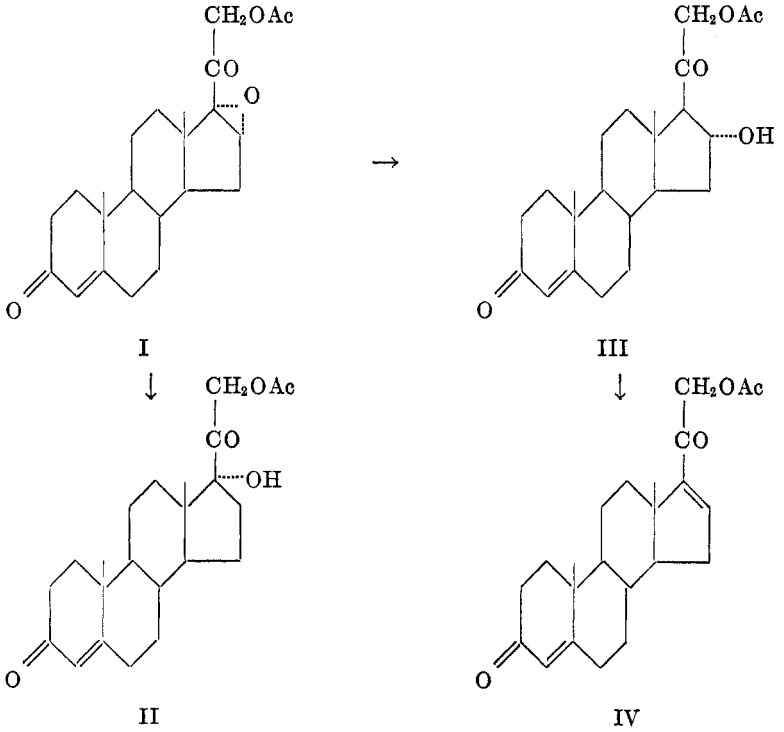
The reduction of certain epoxy ketones in the steroid series to the physiologically active 17α-hydroxy-20-keto steroids utilizes a metal hydride reduction (1) or a dehalogenation of the corresponding bromohydrins (2, 3). These epoxy ketones are rapidly reduced by chromous salts, but the 17α-hydroxy steroids are not formed; instead the reaction takes a different course and yields almost exclusively the 16α-hydroxy steroids and their dehydration products, the α,β-unsaturated ketones.

Thus, although the known reduction methods convert the epoxy ketone (I) into Reichstein's substance S acetate (II), chromous chloride led to the 16α-hydroxy isomer (III) and its dehydration product (IV). The formation of IV is attributed to the high acidity of the chromous chloride reagent, since when chromous acetate was used, only a small amount of IV was obtained, and the



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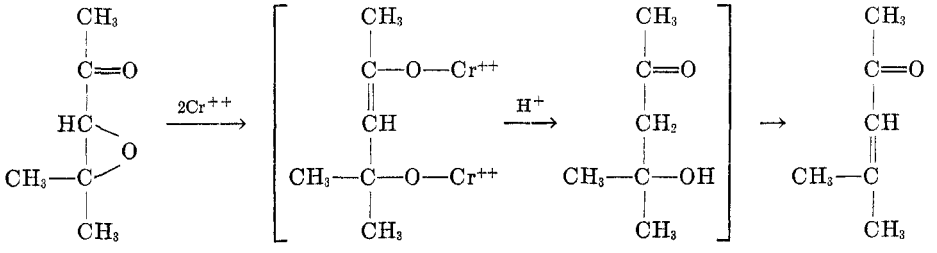
yield of III was improved to about 70%. These desoxycorticosterone derivatives (III and IV) were desired for testing and for further syntheses of 16-oxygen and 16-nitrogen derivatives.

During identification of the new reduction products (III and IV) the presence of the hydroxyl group in III was shown by the infrared absorption at 2.9 μ, and its location at 16 was verified by dehydration by mineral acid to the 21-acetoxy-4,16-pregnadiene-3,20-dione (IV). The *alpha* configuration of the hydroxyl group was indicated by its formation from the 16α,17α-epoxide. Also the thermal stability of the 16α-ol and failure of a Darzens dehydration to give IV encouraged the view that the hydroxyl group was *cis* with respect to a 17α-hydrogen. During the mineral acid treatment it is probable that epimerization at C-17 occurs as part of the dehydration mechanism.

Further confirmation of the course of the reduction was found in a number of analogous examples, including the conversion of 16,17-epoxyprogesterone to 16α-hydroxyprogesterone and 4,16-pregnadiene-3,20-dione. The latter was compared with a known sample. The properties of the 16α-hydroxyprogesterone agree with those described by Perlman, Titus, and Fried (4), who obtained this substance as one of the products of microbiological hydroxylation of progesterone by an unknown actinomycete.

The general nature of this reduction of epoxy ketones is indicated by the conversion of 4-methyl-3,4-epoxy-2-pentanone (V) to mesityl oxide (VIII) by means of chromous chloride. The reaction is rapid and nearly complete in a few minutes at room temperature in acetic acid solution. It is probable that an intermediate chromic alkylate of the type described by Hein (5) is formed. Since two moles of



V VI VII VIII

chromous salt are required to reduce one mole of the epoxide, it is possible that a double complex such as VI is formed and rapidly cleaved by acids. While a part of the final product is formed by dehydration of the hydroxy ketone (VII), it may also be true that some of VIII is formed by loss of hydrated chromic ion from an intermediate such as VI during ketonization in the presence of acids. The intermediate (VII) was not isolated, but in certain of the steroid examples the intermediate hydroxy ketones were isolated.

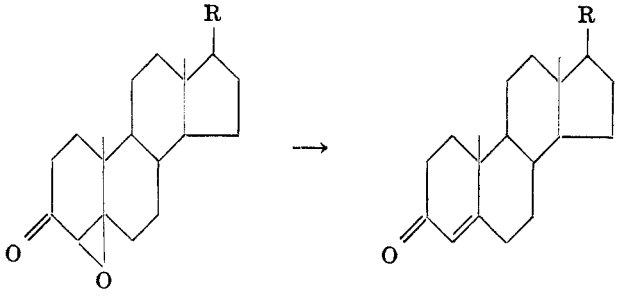
Other unsaturated groups may replace the function of the carbonyl group during the reduction. Thus styrene oxide slowly reacts with chromous chloride and yields styrene. It is expected that epoxy acids, esters and nitriles would be analogously reduced. However, an attempt to extend the reaction to ethylene

oxide and cyclohexene oxide showed that these substances are not readily reduced by the reagent.

Heretofore, α,β-epoxy ketones have been reduced to hydroxy ketones or to unsaturated ketones in special instances by hydrogen iodide (6), by means of the Grignard reagent (7), and by hydrogenation (8). Sodium iodide in acetic acid reacted with 16,17-epoxyprogesterone and iodine was liberated, but the 16-dehydro derivative was not obtained directly nor after dehydration. The Grignard reagent adds to the 20-carbonyl group in the normal way (18), as for example in the preparation of 20-methyl-16,17-epoxy-5-pregnene-3β,20-diol 3-acetate. Direct hydrogenation of an epoxide such as I was not attempted because of the ease of saturating the Δ^4-3-keto system, and hydrogenation of the bromohydrins of the 16,17-epoxy-20-keto steroids is known to yield the 17α-hydroxy-20-ketones (3).

The use of excess chromous chloride in most instances did not damage the α,β-unsaturated ketones, but in the preparation of the 21-acetoxy steroid (IV) some reductive removal of the acetoxy group occurred, in a manner analogous to that described by Nes and Mason (9). Such over-reduction did not occur with chromous acetate. However, in general chromous acetate is a less satisfactory reagent because of its low solubility. Both chromous chloride and chromous acetate caused over-reduction in the treatment of benzalacetophenone oxide, and only a poor yield of benzalacetophenone has been obtained. An interesting by-product of this reduction was 1,4-dibenzoyl-2,3-diphenylbutane (10).

Together with the known methods for epoxidation of α,β-unsaturated ketones (11) the presently described method for removal of epoxide oxygen provides a means for protecting such unsaturation during operations on other parts of the molecule. This is the case with the preparation of IV, where the 21-acetoxy group is more easily introduced in the 16,17-epoxy series than in the Δ^{16} series. Such blocking of the 4,5-double bond in steroids is illustrated by the reduction of 4,5-epoxycoprostan-3-one (IX) to cholestenone (X) and by the conversion of 4,5-epoxypregnane-3,20-dione (XI) to progesterone (XII).



IX (R = C_8H_{17}) X (R = C_8H_{17})
XI (R = $COCH_3$) XII (R = $COCH_3$)

16,17-Epoxy-5-pregnen-3β-ol-20-one acetate led to a 16α-ol, which on dehydration gave the well known 16-dehydropregnenolone acetate. These 16α-hydroxy and 16-dehydro derivatives of pregnenolone acetate form beautiful mixed

crystals, which aggravates their separation by crystallization. The 16α-ol is more strongly adsorbed on silica, however, and can be purified easily by such means.

The 16α-hydroxypregnenes have been of recent interest because of their relation to adrenal tumor metabolism, and a method for the preparation of the 3,16,20-triols has been developed by Hirschmann, Hirschmann, and Daus (12). The chromous salt reduction of the epoxy ketones, however, offers the first general method for preparing the 16α-hydroxy-20-keto steroids.

EXPERIMENTAL PART[2]

Chromous acetate was prepared according to Inorganic Syntheses (13). *Chromous chloride reagent* (containing zinc chloride and hydrochloric acid) was prepared as described by Conant and Cutter (14). The chromous chloride reagent was standardized by titrating a measured sample (about 10 ml.) in a carbon dioxide-filled separatory-funnel with a standard solution of iodine in carbon tetrachloride (about 12 g. of iodine per liter) until the lower layer retained a pink color after shaking. Care was taken to exclude air.

Reduction of 4-methyl-3,4-epoxy-2-pentanone (V). A solution of 2.0 g. of 4-methyl-3,4-epoxy-2-pentanone (11) (b.p. 60–61° at 20 mm.) in 40 ml. of water was added, under carbon dioxide, to 80 ml. of 0.6 *N* chromous chloride reagent at 23°. The blue solution darkened to a deep green during several minutes. After 30 minutes the solution was extracted with three 15-ml. portions of methylene chloride and the extract was washed with distilled water. An aliquot of this extract was diluted with ether for ultraviolet absorption, showing λ_{max} 232 mμ in ether (ϵ = 8,000 based on 0.0175 mole of product), indicating approximately an 80% yield of mesityl oxide. The bulk of the extract was concentrated and distilled, giving 1.1 g. of mesityl oxide, b.p. 123–132°, λ_{max} 232 mμ in ether (ϵ = 8,400). From the boiling point and ultraviolet data it is apparent that both isomers of mesityl oxide are present (15) as would be expected of material formed in an acidic medium.

4,16-Pregnadien-21-ol-3,20-dione acetate (IV). To a solution of 5.8 g. (0.015 mole) of 16,17-epoxy-4-pregnen-21-ol-3,20-dione acetate (2) in 150 ml. of acetic acid at 24° under carbon dioxide, was added a mixture of 65 ml. of 0.6 *N* chromous chloride and 65 ml. of acetic acid. The resulting clear solution at 27° was held for five minutes and then diluted with water and methylene chloride. Three 40-ml. methylene chloride extracts were combined, washed with water, then with bicarbonate solution, and again with water. Concentration gave 5.2 g. of crude product, m.p. 134–160°. This was mixed with 20 ml. of acetone and 200 ml. of anhydrous ether, and the mixture was refluxed for ten minutes. Filtration and washing with 40 ml. of anhydrous ether left 1.1 g. of white powder, m.p. 170–190°. The clear filtrate was passed through 20 g. of silica and rinsed through with 200 ml. of anhydrous ether. The filtrate was concentrated to dryness, and the residue, 3.3 g. of white crystals, was recrystallized from ethyl acetate, giving 2.6 g. of 4,16-pregnadien-21-ol-3,20-dione acetate of m.p. 151–152°. Further recrystallization gave stout needles, m.p. 152°, $[\alpha]_D$ +148° (*c*, 1.0 in chloroform), λ_{max} 234 mμ in ether (ϵ = 27,400); λ_{max} 241 mμ in methanol (ϵ = 25,200).

Anal. Calc'd for $C_{23}H_{30}O_4$: C, 74.55; H, 8.16.

Found: C, 74.26; 74.50; H, 7.94; 8.24.

The yield of 4,16-pregnadien-21-ol-3,20-dione acetate can be increased by dehydration of the high-melting fractions, but in this experiment these were kept separate as described below.

4-Pregnene-16α,21-diol-3,20-dione 21-acetate (III). The 1.1 g. of 170–190° material from the above experiment plus 0.7 g. of similar material obtained by washing the silica column with acetone gave, by acetone recrystallization, 1.2 g. of 4-pregnene-16α,21-diol-3,20-dione

[2] Melting points were taken by the capillary method without corrections. Infrared and ultraviolet patterns were determined by Francis Taylor of this laboratory. Carbon-hydrogen analyses are by Micro-Tech Laboratories, Skokie, Illinois.

21-acetate of m.p. 210–213°. Further recrystallization gave white needles, m.p. 213–214°; $[\alpha]_D$ +123° (*c*, 0.50 in acetone); λ_{max} 241 mμ in methanol (ϵ = 16,300). An hydroxyl group was indicated by the infrared absorption peak at 2.9 μ.

Anal. Calc'd for $C_{23}H_{32}O_5$: C, 71.11; H, 8.30.

Found: C, 70.94; H, 8.22.

The bromohydrin (2) made from 16,17-epoxy-4-pregnen-21-ol-3,20-dione acetate did not react with chromous chloride under the above conditions, but was recovered unchanged.

A sample of the 16α-ol was dehydrated by refluxing for one hour an acetone solution to which was added 0.5% of conc'd hydrochloric acid and 1% water. Concentration and crystallization from aqueous acetone gave the 4,16-diene, m.p. 148–151°.

The yield of the 16α-ol is improved when chromous acetate is used as described below for the hydroxyprogesterone preparation.

Bicarbonate hydrolysis of the 21-monoacetate gave *16α,21-dihydroxyprogesterone*, which crystallized from acetone as prisms, m.p. 203–204°, $[\alpha]_D^{25}$ +109° (*c*, 0.7 in acetone), λ_{max} 241 mμ in methanol (ϵ = 16,600).

Anal. Calc'd for $C_{21}H_{30}O_4$: C, 72.80; H, 8.73.

Found: C, 72.76; H, 9.05.

Reduction of 16,17-epoxy-4-pregnen-21-ol-3,20-dione acetate (I) *with excess chromous chloride.* A solution of 4.0 g. of 16,17-epoxy-4-pregnen-21-ol-3,20-dione acetate in 100 ml. of acetic acid was covered with carbon dioxide and treated with a mixture of 100 ml. of 0.8 *N* chromous chloride, 50 ml. of acetic acid, and 4 ml. of conc'd hydrochloric acid, portionwise, with tap water cooling. The reaction mixture was left at room temperature overnight. Addition of water gave 2.2 g. of white crystals, m.p. 172–184°. Recrystallization from acetone gave 1.2 g. of 4,16-pregnadiene-3,20-dione, m.p. 186–189°, λ_{max} 240 mμ in methanol (ϵ = 25,000).

Anal. Calc'd for $C_{21}H_{28}O_2$: C, 80.73; H, 9.03.

Found: C, 80.74; H, 9.17.

A mixture with 4,16-pregnadiene-3,20-dione prepared by the known method showed no depression in melting point.

Reduction of 16,17-epoxy-4-pregnene-3,20-dione. A solution of 5 g. of 16,17-epoxy-4-pregnene-3,20-dione (1) in 100 ml. of acetic acid was covered with carbon dioxide and treated with 60 ml. of 0.8 *N* chromous chloride, added during two minutes. The first portions rapidly turned green. The temperature rose from 26° to 29°. After 30 minutes, water was added to cause crystallization, and the mixture was filtered, giving 3.1 g. of crude pregnadienedione as white crystals, m.p. 179–183°. Recrystallization from acetone raised the melting point to 188–190°, λ_{max} 240 mμ in methanol (ϵ = 25,200). A mixture with 4,16-pregnadiene-3,20-dione prepared by the Oppenauer method (16) showed no depression in melting point.

The aqueous acetic acid filtrate from the above pregnadienedione was extracted with chloroform four times, and the combined extracts were washed with water, bicarbonate solution, and water. Concentration and crystallization from anhydrous ether gave 1.3 g. of white crystals, m.p. 221–225°. Recrystallization from acetone–ether gave prisms of *4-pregnen-16α-ol-3,20-dione (16α-hydroxyprogesterone)*, m.p. 226–227°, $[\alpha]_D$ +119° (*c*, 0.50 in acetone); $[\alpha]_D$ +160° (*c*, 0.50 in chloroform); λ_{max} 241 mμ in methanol (ϵ = 16,400). The infrared absorption pattern showed sharp hydroxyl absorption at 2.9 μ (4).

Anal. Calc'd for $C_{21}H_{30}O_3$: C, 76.32; H, 9.10.

Found: C, 76.30; H, 9.17.

The above experiment illustrates the isolation of both products of the reduction. The 4,16-pregnadiene-3,20-dione was obtained in better yield from a similar run by extracting the whole product with chloroform, and then concentrating the extract to 20 ml. and adding 60 ml. of acetone and 0.5 ml. of 10% hydrochloric acid. This mixture was refluxed for one hour and then concentrated to a volume of 30 ml. The product was extracted with chloroform, washed, and concentrated to a residue, which was recrystallized from acetone, giving 4.3 g. (90% yield) of the pregnadienedione, m.p. 184–188°.

The 16α-hydroxyprogesterone was obtained in better yield by using chromous acetate.

A mixture of 2.0 g. of 16,17-epoxy-4-pregnene-3,20-dione, 4.4 g. of chromous acetate, 45 ml. of acetic acid, and 15 ml. of water was stirred under carbon dioxide at room temperature for 14 hours. The reaction was slow because of the poor solubility of the chromous acetate. Water was added and the product extracted with methylene chloride. An aliquot of this extract showed λ_{max} 241 mμ in methanol (ϵ = 17,500 based on 0.006 mole of product), therefore no large amount of 16,17-unsaturation was present, since the 3-keto-4,5-unsaturation accounts for most of this absorption. The extract was concentrated and crystallized from 6 ml. of acetone, giving 1.35 g. of 16α-hydroxyprogesterone, m.p. 218–222°. Recrystallization from acetone–ether raised the melting point to 226°.

Treatment of 16,17-epoxy-4-pregnene-3,20-dione with stannous chloride in acetic acid under similar conditions gave back the epoxide unchanged.

A sample of 16,17-epoxy-4-pregnene-3,20-dione in acetic acid solution reacted with sodium iodide at steam-bath temperature during 12 hours with liberation of iodine. The product was precipitated by addition of water and then dissolved in ether and washed. The crude product, m.p. 160–175°, dec., contained halogen. None of the 16-dehydroprogesterone could be obtained from it by recrystallization.

Dehydration of 16α-hydroxyprogesterone. A mixture of 200 mg. of 16α-hydroxyprogesterone, 5 ml. of acetone, and 0.1 ml. of 10% hydrochloric acid was refluxed for 30 minutes and then boiled down to a volume of about 2 ml. A few drops of water were added and the solution was scratched to crystallize the product, giving as the first crop 158 mg. of buff-color plates, m.p. 181–184°, which gave no depression in melting point when mixed with authentic 4,16-pregnadiene-3,20-dione of melting point 188–190°, λ_{max} 240 mμ in methanol (ϵ = 25,000).

An attempted dehydration by the Darzens method was not satisfactory.

5,16-Pregnadien-3β-ol-20-one acetate. A solution of 6.6 g. of 16,17-epoxy-5-pregnen-3β-ol-20-one acetate, m.p. 160° (1), in 240 ml. of acetic acid at room temperature was covered with carbon dioxide and treated with 120 ml. of 0.6 *N* chromous chloride reagent. The resulting blue-green solution was held for 30 minutes and then extracted with methylene chloride. The extract was washed with water and concentrated to a small volume. The mixture of 16α-ol and 16-dehydro compounds was treated with 60 ml. of acetone and 0.5 ml. of 10% hydrochloric acid during one hour at the reflux temperature, and then concentrated to 30 ml. A methylene chloride extract was washed and concentrated to dryness. The crystalline residue was recrystallized from ethyl acetate, giving 4.3 g., m.p. 166–170°, plus 1.6 g., m.p. 163–167°, of, 5,16-pregnadiene-3β-ol-20-one acetate. Recrystallization from ethyl acetate gave prisms m.p. 173–174°, λ_{max} 240 mμ in methanol (ϵ = 9200); λ_{max} 233 mμ in isoöctane (ϵ = 9530). This gave no depression in melting point when mixed with a known sample of 5,16-pregnadien-3β-ol-20-one acetate.

5-Pregnene-3β,16α-diol-20-one 3-acetate. A solution of 7.44 g. (0.02 mole) of 16,17-epoxy-5-pregnen-3β-ol-20-one acetate (1) in 150 ml. of acetone and 20 ml. of water, was covered with carbon dioxide and treated at 20° with 80 ml. of 0.6 *N* chromous chloride. The color shifted to green as rapidly as the chromous chloride was run in. After three minutes the mixture was diluted with ether and extracted with methylene chloride four times. The washed extract was concentrated to a crystalline residue, which weighed 7.4 g., m.p. 158–162°. Ultraviolet absorption indicated that it was about one-third 16-dehydro material and two-thirds 16-hydroxy material. The residue was dissolved in a small amount of methylene chloride, adsorbed onto silica, and then eluted with ether, giving first 5,16-pregnadien-3β-ol-20-one acetate, m.p. 169–173°, and then slowly the 16α-ol, m.p. 169–172°. These showed a depression in melting point of about 8°, but ultraviolet absorption served as a better method of identifying the fractions. The last 3.5 g. of material eluted was recrystallized from benzene, giving prisms, m.p. 172°, U.V.-pattern low and flat in the 240 mμ region; sharp hydroxyl absorption at 2.9 μ.

Anal. Calc'd for $C_{23}H_{34}O_4$: C, 73.80; H, 9.09.

Found: C, 74.04; H, 9.21.

A sample (0.25 g.) of the 16α-ol was dehydrated by refluxing a solution in 40 ml. of acetone

and 2 ml. of 10% hydrochloric acid for 20 minutes and then concentrating *in vacuo* to dryness. The white crystalline residue was recrystallized from ethyl acetate, giving rods of 5,16-pregnadien-3β-ol-20-one acetate, m.p. 172–174°, λ_{max} 239 mμ in methanol (ϵ = 9300).

16,17-Epoxy-20-methyl-5-pregnene-3β-20-diol 3-acetate. To a solution of 0.01 mole of methylmagnesium bromide in 80 ml. of ether and 5 ml. of benzene at 0°, was added a cold solution of 1.8 g. of 16,17-epoxy-5-pregnen-3β-ol-20-one acetate in 80 ml. of benzene. After stirring for ten minutes, the mixture was hydrolyzed with ice and dilute hydrochloric acid. The washed and crystallized product was 1.4 g. of 16,17-epoxy-20-methyl-5-pregnene-3β,20-diol 3-acetate of m.p. 169–170°.

Anal. Calc'd for $C_{24}H_{36}O_4$: C, 74.18; H, 9.34.
Found: C, 74.72; H, 9.54.

The identity of the product was determined by reduction with lithium aluminum hydride in ether to form a triol, which was brominated, oxidized with chromic acid in aqueous acetic acid, and debrominated to give the known 4-androstene-3,17-dione, m.p. 169–171°.

Progesterone. 4,5-Epoxypregnane-3,20-dione[3] (0.5 g., m.p. 173–175°, *Anal.* Calc'd for $C_{21}H_{30}O_3$: C, 76.32; H, 9.10. Found: C, 76.85; H, 9.14) in 25 ml. of acetic acid was covered with carbon dioxide and treated with 10 ml. of 0.8 *N* chromous chloride. The first portions of chromous chloride promptly turned from blue to green on contacting the solution. After one hour at 30°, the mixture was diluted with water and extracted with methylene chloride, yielding 0.39 g. of crude crystalline residue, λ_{max} 240 mμ (ϵ = 15,100) in methanol. This was recrystallized from ethanol, giving prisms of progesterone, m.p. 128–129°, λ_{max} 240 mμ in methanol (ϵ = 16,900). These showed no depression in melting point when mixed with a standard progesterone sample.

Cholestenone. A solution of 0.9 g. of 4,5-epoxycoprostan-3-one (17) in 60 ml. of acetic acid was covered with carbon dioxide and treated with a mixture of 12 ml. of 0.8 *N* chromous chloride and 3 ml. of 10% hydrochloric acid. After one hour at 30°, extraction with methylene chloride and water gave 0.77 g. of waxy cholestenone, λ_{max} 240 mμ in methanol (ϵ = 13,300). Crystallization from ethanol gave a sample, m.p. 77–80°.

Reduction of benzalacetophenone oxide. A solution of 2.2 g. (0.01 mole) of benzalacetophenone oxide (18) in 50 ml. of acetone at 20° was stirred under carbon dioxide while a mixture of 40 ml. of 0.5 *N* chromous chloride and 4 ml. of 10% hydrochloric acid was added. The mixture rapidly turned green. After five minutes, watering gave only a gum. This showed an ultraviolet maximum at 307 mμ of about half of the benzalacetophenone intensity. The gum was extracted with ether and, after separation of an ether-insoluble by-product, crystallization from methanol gave 0.3 g. of benzalacetophenone.

The use of more chromous chloride gave still poorer yield of benzalacetophenone. The use of chromous acetate at room temperature for ten hours was also unsatisfactory, giving both benzalacetophenone and the ether-insoluble by-product.

The by-product, after recrystallization from acetone–ether, was white needles, m.p. 272–273°. Its properties agree with those of 1,4-dibenzoyl-2,3-diphenylbutane, which has been obtained from benzalacetophenone by zinc reduction (10) and by chromous chloride reduction (14).

Behavior of cyclohexene oxide with chromous chloride. A mixture of 12 g. of cyclohexene oxide, 40 ml. of acetic acid, and 300 ml. of 0.8 *N* chromous chloride was swirled at 22–26° for several minutes. No green chromic salt formed; instead a slow separation of red crystals of chromous acetate occurred, indicating a decrease in hydrochloric acid content of the solution. This behavior was consistent with the isolation, on work-up, of cyclohexene chlorohydrin.

Reduction of styrene oxide. A solution of 5 g. of styrene oxide in 80 ml. of acetic acid under carbon dioxide was treated with 110 ml. of 0.8 *N* chromous chloride. The mixture became warm but did not turn green promptly as did the epoxy ketone reactions. After standing

[3] We are indebted to J. G. Klein of this laboratory for the sample of 4,5-epoxypregnane-3,20-dione.

overnight, oily droplets had separated from the green solution. The mixture was watered, cooled in a separatory-funnel for several hours, and the upper layer was separated. The 3 ml. of liquid so obtained was washed with water and dried by centrifuging. It showed the ultraviolet pattern of styrene and λ_{max} 247 mμ in methanol (ϵ = 10,100), indicating about 80% purity. The starting material (styrene oxide) showed only low flat ultraviolet absorption in the same region.

SUMMARY

α,β-Epoxy ketones are reduced by chromous salts to the corresponding β-hydroxy ketones or their dehydration products. This method has served for the preparation of several new steroids, including 4-pregnene-16α,21-diol-3,20-dione and 4,16-pregnadiene-21-ol-3,20-dione acetate.

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