3α,11α,17α-Triacetoxy-17β-methyl-D-homoetiocholan-17a-one (X). **A.**—A solution of 1.0 g. of 3α,11α,17α-trihydroxypregnan-20-one 3,11-diacetate (IV) in 35 ml. of glacial acetic acid was combined with 2 ml. of acetic anhydride and 2 ml. of boron trifluoride etherate. After standing for 16 hours at 30–35°, the reaction was poured into water, yielding 1.07 g. of a gel. Crystallization from hexane gave 0.94 g. of needles, m.p. 184–186°. The analytical sample, crystallized once more, melted at 186–189°, $[\alpha]_D$ +19.9°.

Anal. Calcd. for $C_{27}H_{40}O_7$: C, 68.04; H, 8.46. Found: C, 68.23; H, 8.82.

B.—A solution of 1.0 g. of IV in 25 ml. of acetic anhydride was refluxed for 12 hours. The solvent was removed under reduced pressure, leaving a crystalline residue. Crystallization from aqueous methanol yielded 0.93 g. of X, m.p. 187–190°. A mixture melting point with the boron trifluoride product showed no depression, and the infrared spectra of the two were identical.

Lithium Aluminum Hydride Reductions. A.—A solution of 1.0 g. of IX in 45 ml. of tetrahydrofuran was added dropwise with stirring to a suspension of 2.0 g. of lithium aluminum hydride in 15 ml. of tetrahydrofuran. The suspension was stirred overnight at 25°, the excess hydride was decomposed by the addition of 10 ml. of ethyl acetate followed by 5 ml. of water, and the mixture poured into ice-water containing 25 ml. of concentrated hydrochloric acid. This was extracted with methylene chloride, the extracts washed with dilute sodium bicarbonate and water, dried and evaporated to give 0.65 g. of a crystalline residue. Two recrystallizations from ethyl acetate yielded 0.22 g. of XII, m.p. 260–275°. The infrared spectrum disclosed the absence of carbonyl or acetate groups.

Anal. Calcd. for $C_{21}H_{36}O_4$: C, 71.55; H, 10.30. Found: C, 71.29; H, 10.65.

B.—The identical procedure was used for the reduction of 1.0 g. of VI; there was obtained 0.12 g. of XI, m.p. 260–270°. This material also did not possess any acetate or carbonyl groups, but its infrared spectrum was not identical with that of XII.

Anal. Calcd. for $C_{21}H_{36}O_4$: C, 71.55; H, 10.30. Found: C, 71.52; H, 10.62.

C.—A solution of 1.0 g. of X in 30 ml. of tetrahydrofuran was added dropwise to a stirred suspension of 2.0 g. of lithium aluminum hydride in 50 ml. of anhydrous ether. The mixture was refluxed for 17 hours, then allowed to stand with stirring at room temperature for 48 hours. The reaction was cooled in an ice-bath, and the excess reagent destroyed by the addition of 2 ml. of water, 2 ml. of 15% sodium hydroxide and 6 more ml. of water. The resulting suspension was allowed to warm up to room temperature and stir for 20 minutes. The solids were removed by filtration and washed thoroughly with tetrahydrofuran and methylene chloride. The solids were stirred with 200 ml. of ice-water containing 20 ml. of concentrated sulfuric acid. Filtration gave 0.27 g. of crystals, m.p. 265–272°.

The original filtrate was evaporated to dryness to yield 0.50 g. of a gum; triturating with acetone gave 0.29 g. of crystals, m.p. 235–275°.

The two crystalline fractions were combined and recrystallized from ethanol–hexane to give 0.34 g. of XIII, m.p. 292–300°. The analytical sample, crystallized once more, melted at 300–307°.

Anal. Calcd. for $C_{21}H_{36}O_4$: C, 71.55; H, 10.30. Found: C, 71.37; H, 10.13.

Sodium–Alcohol Reductions. A.—Ten portions of sodium totalling 2 g. were added to a refluxing solution of 0.50 g. of IX in 75 ml. of isopropyl alcohol; the total reaction time was 5 hours. The solution was then poured onto ice and 10 ml. of acetic acid was added to lower the *p*H to *ca.* 7. The solution was then extracted with methylene chloride, and the organic extracts were washed with water, dried and evaporated to yield 0.45 g. of a crystalline residue. Trituration with ethyl acetate left 0.17 g. Recrystallization from aqueous methanol gave 85 mg. of XIII, m.p. 230–237° with bubbling. Its infrared spectrum was identical with that of the $LiAlH_4$ reduction product of X.

B.—A similar sodium reduction of 0.50 g. of X gave 95 mg. of XIII, m.p. 265–278° with bubbling, identical in its infrared spectrum with the two other samples of XIII. The wide variation in m.p. between the three samples of compound XIII might possibly be due to varying degrees of solvation, but this could not be proven definitely.

3α,17α-Diacetoxypregnane-11,20-dione (XIV). A.—A solution of 2.0 g. of 3α,17α-dihydroxypregnane-11,20-dione-3-acetate (II) in 40 ml. of C.P. acetic anhydride was refluxed for 12 hours. The excess anhydride was decomposed at reflux by the slow addition of water, the solution poured into ice and water and the resulting precipitate filtered and dried: 1.67 g., m.p. 160–180°. Crystallization from methanol yielded 0.66 g., m.p. 195–199°, and 0.20 g. m.p. 192–197°.

B.—Repetition of the above experiment, with 1.2 g. of acetic acid added, gave 0.80 g. of XIV, m.p. 196–199°, $[\alpha]_D$ +50.4°; lit.[2] m.p. 203–204°, $[\alpha]_D$ +46.7° ($CHCl_3$).

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[CONTRIBUTION FROM THE CHEMICAL RESEARCH AND DEVELOPMENT DIVISION OF THE SCHERING CORPORATION]

Some Transformation Products of Cortisone Acetate

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Addition of HOBr to cortisone acetate, followed by treatment with potassium acetate, gave the 4,5α- and 4,5β-epoxides III and IV. Reaction of either of these with HBr, or warming the intermediate bromohydrins with acetic acid, gave 4-bromocortisone acetate (V). 4-Chlorocortisone acetate (VI) was prepared by the action of HCl on the β-epoxide. Compound VI was also the main product from the addition of HOCl to cortisone acetate. Opening the β-epoxide with acid gave the 4,5-glycol IX.

Relatively simple changes in the structure of cortisone have resulted in marked increase in corticoid activity. For example, introduction of a 9α-fluorine atom increases the glucocorticoid activity by a factor of about 9 with an even greater enhanced mineralocorticoid activity.[1] Even more startling, the introduction of an added double bond to produce 1-dehydrocortisone enhances the glucocorticoid activity three- to fourfold, without increasing the salt-retaining properties.[2] It seemed desirable, therefore, to prepare other simple derivatives of cortisone.

Addition of hypobromous acid (N-bromoacetamide and perchloric acid) to the 4,5-double bond of cortisone acetate, followed by treatment with potassium acetate, resulted in the formation of two epoxides: The major one had m.p. 224–227°, $[\alpha]_D$ +142°, and the minor product, m.p. 248–255°, $[\alpha]_D$ +34.9°. In order to help assign configurations, 4-cholesten-3-one was converted to its two epimeric epoxides; the β-epoxide[3] had $[\alpha]_D$

(1) J. Fried and E. Sabo, THIS JOURNAL, **76**, 1455 (1954).

(2) H. Herzog, A. Nobile, S. Tolksdorf, W. Charney, E. B. Hershberg, P. Perlman and M. Pechet, *Science*, **121**, 3136 (1955).

(3) P. Plattner, H. Heusser and A. Kulkarni, *Helv. Chim. Acta*, **31**, 1822 (1948).

+123.8°, and the α-epoxide (prepared from cholestenone with H_2O_2 and an acid resin) had $[\alpha]_D$ −33.4°. The lower-melting epoxide with a more positive rotation derived from cortisone acetate is therefore assigned the β-configuration, and the higher-melting, lower-rotation epimer the α-configuration. Recently, Ringold, *et al.*,[4] prepared the 4α,5α-epoxide of cortisone by alkaline hydrogen peroxide treatment of the 3-keto-Δ^4-system and reported m.p. 235–237°, $[\alpha]_D$ −13°. This is in agreement with our assignment of the α-configuration to our acetate of m.p. 248–255°, $[\alpha]_D$ +34.9°.

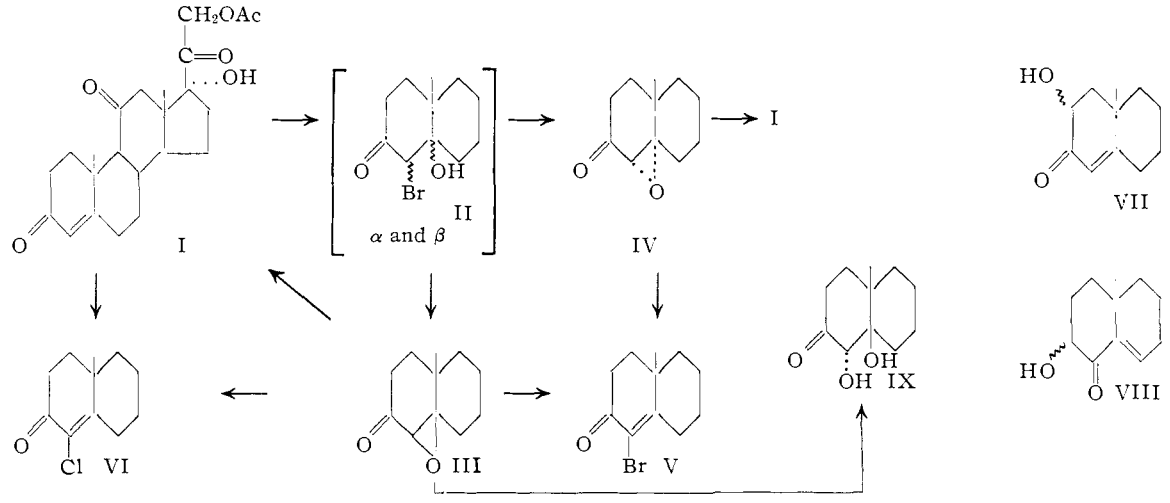
The intermediate bromohydrins could not be isolated in pure state, but treatment of the crudes with hydrogen bromide in acetic acid at room temperature, or warming with acetic acid alone, produced 4-bromocortisone acetate, λ_{max}^{EtOH} 260 mμ (ε 11,200). This latter compound could be prepared from either epoxide by reaction with hydrogen bromide in acetic acid. Debromination by vigorous treatment with zinc and acetic acid regenerated cortisone acetate.

Addition of hypochlorous acid (N-chlorosuccinimide and perchloric acid) to cortisone acetate, followed by potassium acetate treatment, gave, as the main product, 4-chlorocortisone acetate (VI) rather than either epoxide. Compound VI was also prepared readily by the action of hydrogen chloride in acetic acid on the β-epoxide.

Reaction of either epoxide with hydriodic acid in acetic acid readily regenerated cortisone acetate. Zinc dust treatment of the β-epoxide also gave cortisone acetate but in an impure state.

Opening of the β-epoxide with aqueous perchloric or trifluoroacetic acid gave a glycol, which, if our formulation of the epoxide is correct, must be the 4α,5β-diol. The α-epoxide, however, on treatment with trifluoroacetic acid failed to react. These results differ from those obtained with the two epoxides derived from testosterone.[5] In this latter case, the β-epoxide with dilute sulfuric acid in acetone rearranged to 2α-hydroxytestosterone, while the α-epoxide with the same reagent gave the 4β,5α-diol.

In one reaction with the β-epoxide and perchloric acid, the reaction time was extended from 18 to 72 hr., and a small amount of a second product was obtained with an ultraviolet maximum at 236 mμ (ε 13,200) and with an analysis corresponding to $C_{23}H_{30}O_7$. Two possible structures for this compound are VII and VIII: The first might arise by rearrangement and the second by dehydration of the 5-hydroxyl with a hydrogen at C-6, followed by a keto–enol shift. Unfortunately, not enough material was available for further study.



Experimental[6]

4β,5β-Epoxypregnane-17α,21-diol-3,11,20-trione 21-Acetate (IV) and 4α,5α-Epoxyallopregnane-17α,21-diol-3,11,20-trione 21-Acetate.—A suspension of 20.0 g. of cortisone acetate (I) in 1 liter of tetrahydrofuran and 100 ml. of water was chilled in an ice-bath, and 100 ml. of 1 *N* aqueous perchloric acid and 13.8 g. of N-bromoacetamide were added. The ice-bath was removed after the reaction was homogeneous (*ca.* 1 hr.) and then stirred and protected from light for 72 hr. at 25°. At the end of this time, a starch–iodide test was either negative or very weak. The solution was diluted with water containing a small amount of sodium sulfite and extracted with methylene chloride. The combined organic extracts were washed with dilute sodium bicarbonate solution and water, dried over magnesium sulfate and concentrated to dryness under reduced pressure. The resinous residue was taken up in 1 liter of acetone, 40 g. of potassium acetate added and the mixture refluxed with stirring for 5 hr. Water was added, the mixture extracted with methylene chloride, and the organic extracts were washed with water, dried and concentrated under reduced pressure. The crystalline residue was reacetylated by reaction with 100 ml. of pyridine and 15 ml. of acetic anhydride for 1 hr. The excess anhydride was destroyed by the addition of 40 ml. of water and the mixture poured into excess dilute sulfuric acid and ice, then extracted with methylene chloride. The residue obtained from the organic extracts was chromatographed on Florisil. Elution with 50% methylene chloride–benzene yielded a crystalline mixture of the α- and β-epoxides.

Crystallization from acetone–hexane yielded 2.32 g. of α-epoxide, m.p. 240–247°; concentration of the mother liquor yielded 4.40 g. of β-epoxide, m.p. 224–229°. The former was purified by three additional crystallizations from acetone, m.p. 248–255°, $[\alpha]_D$ +34.9° (chlor.).

(4) H. Ringold, E. Batres, O. Mancera and G. Rosenkrantz, *J. Org. Chem.*, **21**, 1432 (1956).

(5) B. Camperino, B. Patelli and A. Vercellone, THIS JOURNAL, **78**, 3540 (1956).

(6) All m.p.'s are corrected. All rotations were taken in a 1-dm. tube at a concentration of *ca.* 1% at 25°. Analyses and optical data were obtained by the Microanalytical and Physical Chemistry Departments of these laboratories.

Anal. Calcd. for $C_{23}H_{30}O_7$: C, 66.01; H, 7.23. Found: C, 66.15; H, 7.33.

The β-epoxide was crystallized from acetone–hexane, m.p. 224–227°, $[\alpha]D$ +142.2° (chlor.).

Anal. Calcd. for $C_{23}H_{30}O_7$: C, 66.01; H, 7.23. Found: C, 65.74; H, 7.16.

Further elution of the Florisil column with methylene chloride, and methylene chloride–methanol gave fractions having increasing ultraviolet absorption at 238 mμ.

Instead of perchloric acid, either trifluoroacetic acid or Amberlite IR-120 ion exchange resin (free acid form) could be used.

The intermediate bromohydrins could not be obtained pure, because of their instability and the ease with which they were converted to 4-bromocortisone acetate. The resinous bromohydrin from the addition of HOBr to 1 g. of cortisone acetate was dissolved in ether, and pentane was then added to yield 1.02 g. of solid, m.p. 125–150° dec. Two recrystallizations from ether gave m.p. 145–148° dec., λ_{max}^{EtOH} 242 mμ (ε 73).

Anal. Calcd. for $C_{23}H_{31}O_7Br$: C, 55.31; H, 6.26; Br, 16.00. Found: C, 56.18; H, 6.72; Br, 16.16.

4β,5β-Epoxycoprostan-3-one and 4α,5α-Epoxycholestan-3-one.—The β-epoxide was prepared by the method of Plattner, *et al.*,[3] using alkaline hydrogen peroxide, and had m.p. 118–120°, $[\alpha]D$ +123.8° (chlor.).

The α-epoxide was prepared in low yield by the following procedure: A mixture of 0.45 g. of Amberlite IR-120 ion exchange resin (free acid), 1.0 g. of 4-cholesten-3-one, 50 ml. of C.P. chloroform and 3.0 ml. of 30% hydrogen peroxide was refluxed with stirring for 3 hr. The resin was removed by filtration and washed with acetone and methylene chloride. The combined filtrate and washings were washed with dilute sodium sulfite solution, dilute sodium bicarbonate solution and water, dried and evaporated. The residue was chromatographed on Florisil. From the hexane eluates there was obtained 100 mg. of crystalline material. Recrystallization from methanol gave 35 mg., m.p. 120–121°, $[\alpha]D$ −42.5° (chlor.), with no ultraviolet absorption and an epoxide band at 7.91 μ in the infrared.

Anal. Calcd. for $C_{27}H_{44}O_2$: C, 80.94; H, 11.07. Found: C, 80.62; H, 10.98.

4-Bromocortisone Acetate (V).—The crude bromohydrins obtained from 1 g. of cortisone acetate were dissolved in 10 ml. of acetic acid and heated on the steam-bath for 30 minutes. Dilution with water gave crystals contaminated with a dark oil. The mixture was extracted with methylene chloride, the organic extracts washed with dilute sodium bicarbonate and water, dried and evaporated. The residue was reacetylated in the usual manner, and the resulting 1.02 g. of crystalline material was chromatographed on Florisil. The material eluted with 50% benzene–methylene chloride was recrystallized from acetone–hexane to give 0.22 g. of V, m.p. 170–173° dec., $[\alpha]D$ +196.2° (diox.), λ_{max}^{EtOH} 260 mμ (ε 10,400). Two crystallizations from acetone–hexane gave a m.p. of 178–181° dec.

Anal. Calcd. for $C_{23}H_{29}O_6Br$: Br, 16.60. Found: Br, 16.20.

The crude bromohydrins also could be converted to V by treatment with hydrogen bromide. The resin from the addition of HOBr to 2.5 g. of cortisone acetate was dissolved in 25 ml. of acetic acid, and 5 ml. of acetic acid saturated with hydrogen bromide added. After standing for 1 hr. at 25°, the reaction was diluted with water, extracted and chromatographed in the usual way to give 0.46 g., m.p. 183–185° dec., λ_{max}^{EtOH} 260 mμ (ε 11,200).

Reaction of either epoxide III or IV with HBr in acetic acid by the following procedure also gave V.

A mixture of 0.3 g. of III in 10 ml. of acetic acid was combined with 0.6 ml. of 4 *N* hydrogen bromide in acetic acid. After 1 hr. at 25°, water was added, the precipitated solids were removed by filtration, dried and recrystallized from acetone–hexane to yield 0.23 g. of V, m.p. 189–191° dec. All samples of V were identical in their infrared spectra. The reported[3,7] ultraviolet absorption for 3-keto-Δ^4-4-bromo-steroids is λ_{max} 258–261 mμ (ε 10–12,000).

4-Chlorocortisone Acetate (VI).—A solution of 0.20 g. of the β-epoxide III in 5 ml. of glacial acetic acid was combined with 1 ml. of glacial acetic acid saturated with hydrogen chloride. The solution was allowed to stand for 1 hr. at 25° and was then poured into water. The resulting white gel (0.18 g.) was recrystallized from acetone–hexane to yield 0.13 g. of VI, m.p. 227–231° dec., $[\alpha]D$ +223.8° (chlor.), λ_{max}^{MeOH} 253 mμ (ε 11,200); lit.[8] m.p. 232–234° dec., $[\alpha]D$ +214° (diox.), λ_{max} 253 mμ (ε 12,900).

The same product, 4-chlorocortisone acetate, was obtained *via* the addition of hypochlorous acid to cortisone acetate. This compound formed with such great ease that it was impossible to obtain any reasonably pure epoxide on potassium acetate treatment of the supposed chlorohydrin. The reaction of 1 g. of cortisone acetate and N-chlorosuccinimide (instead of N-bromoacetamide) gave, after potassium acetate treatment and chromatography, 0.3 g. of VI, m.p. 218–224° dec., λ_{max}^{EtOH} 252 mμ (ε 8,500).

The crude "chlorohydrin" from another 1-g. reaction was taken up in 20 ml. of glacial acetic acid and heated for 30 minutes on the steam-bath. The mixture was diluted with water, extracted and chromatographed as previously described to give 0.26 g. of VI, m.p. 210–222° dec., λ_{max}^{EtOH} 253 mμ (ε 10,000).

Regeneration of Cortisone Acetate.—A mixture of 0.15 g. of the β-epoxide, 15 ml. of glacial acetic acid and 150 mg. of zinc dust was refluxed with stirring for 30 minutes.[9] At 10-minute intervals thereafter additional 80-mg. portions of zinc dust were added (5 additions in all). The mixture was then cooled, filtered and the filtrate diluted with water and extracted with methylene chloride. The organic extracts were washed with water, dilute sodium bicarbonate solution and water, dried and evaporated. The residue (0.13 g.) was recrystallized from acetone–hexane to yield 0.07 g. of I, m.p. 196–202°, λ_{max}^{EtOH} 238 mμ (ε 12,500). The infrared spectrum indicated this was impure cortisone acetate.

A solution of 0.20 g. of the α-epoxide IV in 5 ml. of glacial acetic acid was cooled to 15° and combined with a mixture of 0.5 ml. of 48% hydriodic acid and 2.3 ml. of acetic anhydride, also at 15°. An immediate iodine color appeared. The dark solution was allowed to warm up to 25° and stand for 1.5 hr., then poured into aqueous sodium sulfite and filtered. The solid was recrystallized from acetone–hexane to yield 0.14 g. of I, m.p. 235–240°, λ_{max}^{EtOH} 238 mμ (ε 14,800). The infrared spectrum of this material matched that of cortisone acetate. The β-epoxide behaved similarly with hydriodic acid.

A solution of 0.20 g. of 4-bromocortisone acetate (V) in 20 ml. of ethanol and 5 ml. of glacial acetic acid was brought to reflux with stirring, and eight portions of zinc (200 mg. each) were added, one every 15 minutes. The solids were removed by filtration and washed with methylene chloride. The combined washings and filtrate were diluted with water and the organic extract washed with dilute sodium bicarbonate solution and water, dried and evaporated. Recrystallization of the residue from acetone–hexane yielded 0.12 g. of cortisone acetate (I), m.p. 225–231°. λ_{max}^{MeOH} 238 mμ (ε 13,000), identical in its infrared spectrum with an authentic sample.

4α,5β,17α,21-Tetrahydroxypregnane-3,11,20-trione 21-Acetate (IX).—A solution of 0.50 g. of the β-epoxide, 25 ml. of acetone, 5 ml. of water and 5 drops of trifluoroacetic acid was allowed to stand for 18 hr. at 25°. The solution was diluted with water and extracted with methylene chloride. The combined extracts were washed with dilute sodium bicarbonate solution and water, dried and evaporated. Crystallization of the residue from acetone–hexane gave 0.34 g. of IX, m.p. 228–234°. The analytical sample, crystallized twice more, had m.p. 230–235°, $[\alpha]D$ +203.0° (chlor.).

Anal. Calcd. for $C_{23}H_{32}O_8$: C, 63.28; H, 7.39. Found: C, 63.34; H, 7.12.

An 18-hr. run using perchloric acid as the catalyst and chromatographing the crude reaction product gave the same result. However, a 72-hr. run with perchloric acid followed by chromatography gave, besides the expected glycol, 50 mg. (from 0.50 g. of III) of a second product. Crystallization from acetone yielded 35 mg., m.p. 265–270°, λ_{max}^{MeOH} 236 mμ (ε 13,200). Compounds VII and VIII are possible structures.

Anal. Calcd. for $C_{23}H_{30}O_7$: C, 66.01; H, 7.23. Found: C, 65.91; H, 7.11.

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(7) D. Kirk, D. Patel and V. Petrow, *J. Chem. Soc.*, 627 (1956).

(8) D. Kirk, D. Patel and V. Petrow, *ibid.*, 1184 (1956).

(9) *Cf.* H. Heusser, G. Saucy, R. Anliker and O. Jeger, *Helv. Chim. Acta*, **35**, 2090 (1952).