Anal. Calcd. for $C_{27}H_{40}O_4$: C, 75.66; H, 9.41. Found: C, 75.97; H, 9.28.

The corresponding enol acetate, **$\Delta^{7,9(11)}$-22a-5β-spirostadiene-3α,7-diol diacetate** was obtained by slowly concentrating a solution of 0.40 g. of the Δ^8-7-one IX in 25 cc. of benzene containing 2 cc. of isopropenyl acetate and 0.04 g. of *p*-toluenesulfonic acid to a volume of 10 cc. over a period of 6 hours, 1-cc. portions of isopropenyl acetate having been added after 2 hours and 4 hours refluxing. After evaporating to dryness *in vacuo*, the residue was taken up in ether, washed with sodium bicarbonate solution and water, dried and evaporated. Crystallization of the residue from ethyl acetate–pentane yielded 0.39 g. of the enol acetate with m.p. 165–170°. Further crystallization from this solvent pair gave the analytical sample, m.p. 172–174°, 179–181° (Kof.), $[\alpha]^{20}D$ +76°, λ_{max} 242 mμ, log ϵ 4.20, $\nu_{max}^{CHCl_3}$ 1736 cm.$^{-1}$.

Anal. Calcd. for $C_{31}H_{44}O_6$: C, 72.62; H, 8.65. Found: C, 72.93; H, 8.81.

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[CONTRIBUTION FROM THE RESEARCH LABORATORIES OF THE UPJOHN COMPANY]

Preparation and Dehydrohalogenation of 4-Halo-3-ketosteroids

BY R. P. HOLYSZ

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Bromination of 17α-hydroxy-21-acetoxypregnane-3,11,20-trione (dihydrocortisone acetate) in buffered acetic acid solution has been found by subsequent investigators to give lower yields of the corresponding 4-bromo derivative than first reported in the literature. The bromination of dihydrocortisone acetate was improved somewhat by using dimethylformamide as a solvent. Employing this modification 4-bromodihydrocortisone acetate was isolated in 70–80% yields. Brominations of pregnane-3,11,20-trione in the dimethylformamide system and in the buffered acetic acid system were compared. Two monobromopregnanetriones were isolated and characterized. On the basis of analysis, infrared data and dehydrohalogenation studies the two isomers were believed to be relatively pure 4α- and 4β-bromo compounds; the 4α-bromopregnane-3,11,20-trione was obtained in buffered acetic acid solution while the 4β-bromopregnane-3,11-20-trione was obtained in dimethylformamide solution. When certain metal halides, particularly lithium chloride or bromide, and 4-bromo-(or 4-chloro-) dihydrocortisone acetate were heated together in dimethylformamide 60–80% yields of cortisone acetate resulted. Beryllium, magnesium or aluminum chlorides in dimethylformamide or dimethylacetamide dehydrobrominated 4-bromodihydrocortisone acetate almost as well as lithium chloride under the particular conditions investigated; whereas, sodium, ammonium or calcium chlorides in formamide–dimethylformamide, or mercuric chloride in dimethylformamide gave no sigficant amounts of cortisone acetate. Lithium and boron fluorides also failed to effect dehydrohalogenation. Semiquantitative rate studies have been made.

Discussion

The usual method[1] for the bromination of 17α-hydroxy-21-acetoxypregnane-3,11,20-trione in buffered acetic acid solution was reported to give 70% yields of 4-bromo-17α-hydroxy-21-acetoxypregnane-3,11,20-trione. However, later investigators[2,3] reported somewhat lower yields of 4-bromo compound of quality suitable for subsequent dehydrobromination in good yields. In this Laboratory 4-bromo-17α-hydroxy-21-acetoxypregnane-3,-11,20-trione of $[\alpha]D$ +101° was obtained in about 60% yield from dihydrocortisone acetate when the conditions reported by Mattox and Kendall were used.

In view of these results an investigation was undertaken to discover better conditions and/or better solvent systems for this important step in the cortisone synthesis.

Bromination of dihydrocortisone acetate in dimethylformamide gave 70–80% yields of 4-bromo-17α-hydroxy-21-acetoxypregnane-3,11,20-trione; however, the specific rotations of the crude 4-bromo compound varied from +103 to +111°, and the bromine content was generally about 1% below the theoretical value. Purification of the crude bromo compound ultimately yielded an analytical sample having an $[\alpha]D$ +112°, some eight to ten degrees higher than the specific rotation reported in the literature.[1-3] The somewhat low bromine content of the crude reaction product may be attributed to the presence of the amide solvent which was difficult to remove under relatively mild drying conditions. In some instances a small amount (*ca.* 5%) of unreacted starting material was detected in the crude bromination product by means of paperstrip chromatography and infrared spectroscopy. Other isomers of monobromo-17α-hydroxy-21-acetoxypregnane-3,11,20-trione such as described by Mattox[1] and Hershberg[2] have not been isolated; however, their presence in mother liquors was suggested on the basis of bromine assay and specific rotation data. Examination of these 4-bromo-17α-hydroxy-21-acetoxypregnane-3,11,20-triones of $[\alpha]D$ +112 by phase distribution methods[4] has failed to demonstrate the presence of impurities. Dehydrohalogenation by the method of Mattox and Kendall[5] or by methods described in this report has given good yields of cortisone acetate.

Bromination of pregnane-3,11,20-trione in cold buffered acetic acid solution yielded a mixture of brominated pregnanetriones, from which a 4-bromopregnane-3,11,20-trione ($[\alpha]D$ +95°) was isolated in approximately 35% yield. Bromination of pregnane-3,11,20-trione in dimethylformamide solution at room temperature also resulted in a mixture of bromopregnanetriones, from which a 4-bromopregnane-3,11,20-trione ($[\alpha]D$ +136°) was isolated in comparable yield. The melting points

(1) V. R. Mattox and E. C. Kendall, *J. Biol. Chem.*, **185**, 593 (1950); **188**, 287 (1951).

(2) E. B. Hershberg, C. Gerold and E. P. Oliveto, THIS JOURNAL, **74**, 3849 (1952).

(3) T. H. Kritchevsky, D. L. Garmaise and T. F. Gallagher, *ibid.*, **74**, 483 (1952).

(4) R. M. Herriott, *Chem. Revs.*, **30**, 413 (1942); A. Findlay, "The Phase Rule and its Applications," Longmans, Green and Co., New York, N. Y., 1938.

(5) V. R. Mattox and E. C. Kendall, THIS JOURNAL, **70**, 882 (1948).

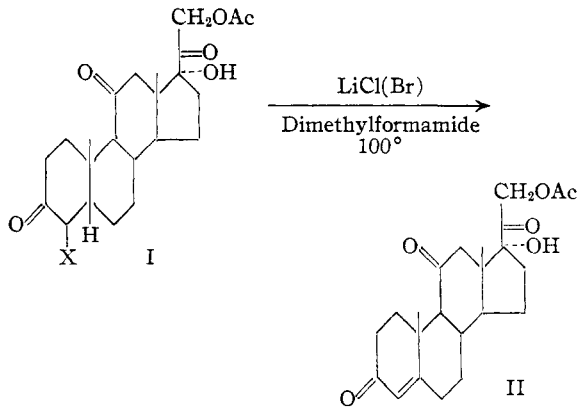
and the mobilities on the paperstrip of these two bromopregnanetriones were the same; a mixed melting point was not significantly depressed. Both compounds dehydrohalogenated to yield 11-ketoprogesterone. A comparison of the infrared spectra revealed that one 4-bromopregnane-3,11,20-trione ($[\alpha]_D$ +95°) exhibited the carbonyl band at 1704 cm.$^{-1}$ and the C–Br band at 719 cm.$^{-1}$; whereas, the other 4-bromopregnane-3,11,20-trione ($[\alpha]_D$ +136°) exhibited a raised ketone band at 1720 cm.$^{-1}$, a carbonyl band at 1698 cm.$^{-1}$ and the C–Br band at 714 cm.$^{-1}$. On the basis of these data the bromo compound having the higher specific rotation and the raised ketone band was believed to be substantially 4β-bromopregnane-3,11,20-trione (bromine equatorial)[6]; while the other bromo compound ($[\alpha]_D$ +95°) was probably predominantly 4α-bromopregnane-3,11,20-trione.

A comparison of the infrared spectrum of 4-bromo-17α-hydroxy-21-acetoxypregnane-3,11,20-trione ($[\alpha]_D$ +112°) obtained by bromination in dimethylformamide with that of the 4-bromo compounds ($[\alpha]_D$ +97° to 103°) obtained by bromination in buffered acetic acid[1] and by oxidation–bromination of tetrahydrocortisone acetate with N-bromosuccinimide in *t*-butyl alcohol[2] was not possible, since interfering absorption of the 20-keto-21-acetoxy system appeared in the region of the raised ketone band. Intensity studies were not made. Nevertheless, these data suggested that the stereochemistry of bromination in buffered acetic acid was different from that in the dimethylformamide system; and, the formation of the 4β-bromo isomer was favored in dimethylformamide.

The action of organic bases such as pyridine, collidine, sodium acetate, etc., on 4-halo-3-ketosteroids generally produces the corresponding Δ^4-3-ketones in poor yields.[7] Mattox and Kendall[5] introduced a novel method for the conversion of 4-bromo-3-ketosteroids into the Δ^4-3-ketones by means of an azone derivative which lost hydrogen bromide spontaneously. Formation of a 2,4-dinitrophenylhydrazone and elimination of hydrogen halide proceeded in excellent yield, and the subsequent cleavage of the resulting Δ^4-3-hydrazone derivative with pyruvic acid was substantially quantitative. The Mayo group[8] have also suggested a plausible mechanism for the activation of the bromine atom and the subsequent elimination of hydrogen bromide.

A third method for the simple conversion of 3-ketosteroids into the corresponding Δ^4-3-ketones has been developed in this Laboratory. 4-Halo-3-ketosteroids were dehydrohalogenated readily by heating them with certain metallic halides, particularly lithium chloride, in an amide solvent such as dimethylformamide, N,N-dimethylacetamide, etc.

The nature of this reaction is uncertain. The original objective was to invert the halogen atom at C-4 from its probable β-configuration to the α-



configuration in order to facilitate *trans* elimination with the β-hydrogen atom at C-5 in the normal series (A/B *cis*). The *cis* relationship between the C-4 bromine and the C-5 hydrogen[9] undoubtedly is an important factor contributing to the difficulty in dehydrobrominating with nucleophilic reagents. Sterically, this configuration is unfavorable for the near approach of an atom or group of appreciable size; thus, an E2 elimination might be expected to proceed with difficulty. Likewise, backside attack by a halide ion in an S_N2 reaction on C-4 would encounter considerable steric interference; and, displacement of halogen on C-4 would be difficult, unless some extraordinary driving force would assist in activating or removing the halogen. Inversion of the configuration of the C-4 halogen was attempted by employing lithium chloride, the cation of which has very small ionic dimensions and has a relatively great tendency to coördinate with nucleophilic centers.

Refluxing 4-bromo-17α-hydroxy-21-acetoxypregnane-3,11,20-trione with a large excess of anhydrous lithium chloride in tetrahydrofuran (b.p. 65°) for 5 hours yielded a reaction product whose bromine and chlorine analyses indicated it to be a mixture of 61% monobromo- and 18.5% monochloro-17α-hydroxy-21-acetoxypregnane-3,11,20-trione along with 7.8% Δ^4-3-ketone (determined by ultraviolet absorption, $\lambda_{max}^{ethanol}$ 238 mμ). Sodium iodide in dimethylformamide at 100° behaved similarly to yield a product consisting of 76% monobromo-, 3.5% monoiodo- and 12% Δ^4-3-ketosteroid. Although these experiments have indicated that some displacement of bromine by other halogen had occurred, the possibility cannot be excluded that the reaction products arose from minor amounts of other monobromo isomers present in the starting material. Unexpectedly, when 4-bromo-17α-hydroxy-21-acetoxypregnane-3,11,20-trione and excess lithium chloride in dimethylformamide solu-

(6) R. N. Jones, D. A. Ramsay, F. Herling and K. Dobriner, THIS JOURNAL, **74**, 2828 (1952).

(7) L. F. Fieser and M. Fieser, "Natural Products Related to Phenanthrene," 3rd ed., Reinhold Publ. Corp., New York, N. Y., 1949, ch. V.

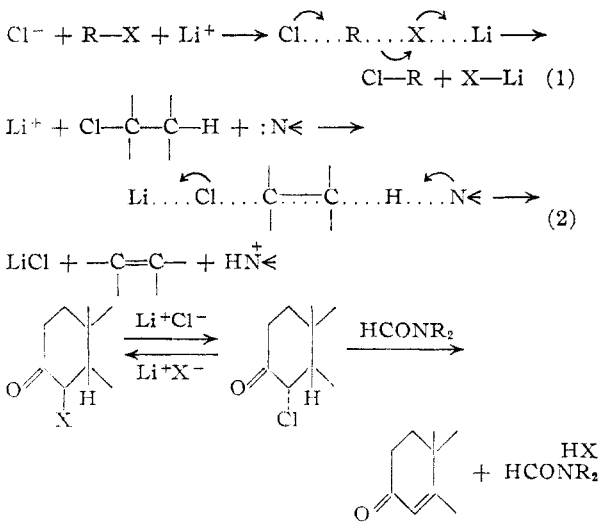
(8) V. R. Mattox and E. C. Kendall, THIS JOURNAL, **72**, 2290 (1950).

(9) L. F. Fieser (120th National Meeting, Am. Chem. Soc., New York, N. Y., Sept., 1951) has shown that the major bromination product of methyl 3-ketocholanate is the 4β-bromo-3-ketocholanate. Sodium borohydride reduction yielded two isomers, 3α-hydroxy-4-bromo- and 3β-hydroxy-4-bromocholanate. Removal of the bromine from the latter by hydrogenation (Pd catalyst) gave 3β-hydroxycholanate; while potassium hydroxide in methanol yielded the original 3-ketone. Reductive removal of the bromine from the 3α-hydroxy-4-bromo isomer gave impure 3α-hydroxycholanate; while potassium hydroxide in methanol yielded the 3,4-α-epoxide. The methyl 4-bromo-3-ketocholanate was dehydrobrominated in very low yield with pyridine but in excellent yield with 2,4-dinitrophenylhydrazine and pyruvic acid.

tion were heated under nitrogen for 5 hours at 60° an 80% yield of cortisone acetate (II) was obtained.

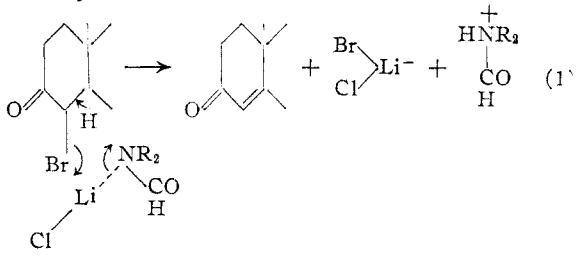
Magnesium, beryllium and aluminum chlorides in dimethylformamide dehydrohalogenated the 4-bromosteroid (I, X = Br) almost as well as lithium chloride; whereas, sodium, ammonium or calcium chlorides in formamide–dimethylformamide, or mercuric chloride in dimethylformamide gave no significant amounts of Δ^4-3-ketone. Lithium fluoride and boron trifluoride also failed to effect dehydrohalogenation. Lithium, beryllium, aluminum and magnesium ions are all of comparable size (very small), and they coördinate readily with water or nucleophilic centers. Semiquantitative rate studies indicated that the rate of cortisone acetate formation from the 4-bromodihydrocortisone acetate (I, X = Br) was dependent upon the concentration of lithium chloride. For a given concentration of lithium salt the rate was greatest with lithium chloride and least with lithium iodide. Dehydrohalogenation of 4-chloro-17α-hydroxy-21-acetoxypregnane-3,11,20-trione (I, X = Cl) was appreciably slower than the dehydrohalogenation of the corresponding bromo compound; however, at higher temperatures (130–135°) a 75% yield of cortisone acetate was obtained from the 4-chloro derivative.

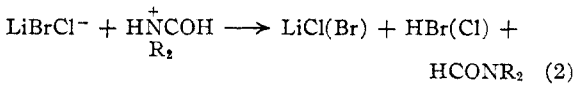
Although a refined kinetic study of this reaction has not been made, the available data suggest a possible mechanism. One may assume that a displacement of the halogen on C-4 by chloride occurs first. Though sterically hindered, this displacement is facilitated by activation (solvation) of the halogen through its coördination with the small lithium ion. The resulting 4α-halosteroid now has a C-4 halogen and a C-5 hydrogen in a *trans* relationship, a configuration seemingly favorable for elimination. The elimination of HX then occurs readily in the presence of the "basic" solvent, $HCONR_2$.



Swain has obtained kinetic evidence for termolecular mechanisms in displacement reactions of methyl and triphenylmethyl halides in benzene solution.[10] Addition of phenols or mercuric bromide solvates the halogen atom; while another molecule solvates the carbon atom. Swain suggests that nucleophilic displacements of anions from saturated carbon atoms are generally of this type, but that they are often masked since the solvent functions as one or two of the three participating molecules.

Another possible and probably more plausible mechanism was suggested in our own laboratory.[11] In the following formulation isomerization prior to elimination is not a necessary stage, and the transition state possesses the geometry of a six-membered ring, all bonds being formed and broken simultaneously.





Inspection of molecular models suggests that the configuration most favorable for the latter mechanism would probably be one in which the 4-bromine was β, *cis* with respect to the 5-hydrogen. The yields of Δ^4-3-ketone obtained by dehydrobromination with lithium chloride in dimethylformamide were significantly better when the 4-bromo compounds were prepared in dimethylformamide. For example, 4-bromo-17α-hydroxy-21-acetoxypregnane-3,11,20-trione prepared in dimethylformamide gave a 73% yield of cortisone acetate of excellent purity; while 4-bromodihydrocortisone acetate prepared in acetic acid gave a 62% yield of cortisone acetate. Similarly, 4β-bromopregnane-3,11,-20-trione (from the dimethylformamide system) afforded 11-ketoprogesterone in better yield than the 4α-bromopregnane-3,11,20-trione (from the acetic acid system).

Experimental[12]

Bromination of 17α-Hydroxy-21-acetoxypregnane-3,11,-20-trione.—A solution of 3.68 g. (23 millimoles) of bromine in 35 ml. of dimethylformamide was added slowly (7–9 hours) at room temperature to a solution of 9.3 g. (23 millimoles) of 17α-hydroxy-21-acetoxypregnane-3,11,20-trione ([α]D +81° in acetone) and 185 mg. of *p*-toluenesulfonic acid monohydrate in 80 ml. of dimethylformamide. When approximately one-fourth of the bromine solution had been added, the 4-bromo compound began to crystallize from the reaction mixture. When addition of the bromine was completed 57 ml. of water was added over a 20-minute period. The reaction mixture was cooled for 30 minutes by means of an ice-bath, after which it was filtered. The precipitate was washed with two 20-ml. portions of cold water, 20 ml. of ice-cold ethanol and two 20-ml. portions of ether. The white crystalline 4-bromo-17α-hydroxy-21-acetoxypregnane-

(10) C. G. Swain, THIS JOURNAL, **70**, 1119, 2989 (1948).

(11) G. Slomp, private communication.

(12) Melting points are recorded as observed on a Fisher–Johns block which had been checked against standard compounds. Molecular extinctions (ϵ) were determined with a Cary Recording Spectrophotometer on solutions in 95% ethanol unless otherwise specified. Infrared spectra were determined with a Perkin–Elmer Model 12C Spectrophotometer equipped with NaCl prisms on mulls of the compounds in liquid petrolatum. [α]D's were determined at temperatures of 22–26°.

3,11,20-trione was dried overnight at room temperature over sulfuric acid in a vacuum desiccator; yield 9.25 g. (83%), m.p. 197–198° (dec.), $[\alpha]_D$ +106° (*c* 2.044 in acetone). The infrared spectrum and paperstrip chromatogram indicated the presence of 7–8% unreacted 17α-hydroxy-21-acetoxypregnane-3,11,20-trione.

Anal. Calcd. for $C_{23}H_{31}BrO_6$: Br, 16.53. Found: Br, 15.79, 15.57.

In approximately twenty such bromination experiments the yields of 4-bromo-17α-hydroxy-21-acetoxypregnane-3,-11,20-trione ranged from 70 to 85%, depending upon the purity of the starting material, dihydrocortisone acetate; specific rotations varied from +103° to +111° (acetone), and the bromine contents were generally 1% below theory. Repeated recrystallization from acetone–ether of a typical sample ($[\alpha]_D$ +106°; Br, 15.4) resulted in a relatively pure substance, m.p. 195–196° (dec.), $[\alpha]_D$ +112° (*c* 0.944 in acetone).

Anal. Calcd. for $C_{23}H_{31}BrO_6$: C, 57.14; H, 6.46; Br, 16.53. Found: C, 57.61, 57.66, 57.45; H, 6.56, 6.54, 6.71; Br, 16.28, 15.97.

Another crude 4-bromo compound was recrystallized several times to yield a product, m.p. 196–197° (dec.), $[\alpha]_D$ +111° (*c* 0.886 in acetone).

Anal. Calcd. for $C_{23}H_{31}BrO_6$: C, 57.14; H, 6.46; Br, 16.53. Found: C, 57.23, 57.26; H, 6.20, 6.54; Br, 16.47, 16.64, 16.40, 16.24.

Bromination of Pregnane-3,11,20-trione in Acetic Acid Solution.—A solution of 3.20 g. (20 millimoles) of bromine and 1.64 g. (20 millimoles) of anhydrous sodium acetate in 20 ml. of acetic acid was added dropwise in approximately 30 minutes to a solution of 6.61 g. (20 millimoles) of pregnane-3,11,20-trione [m.p. 158–160°, $[\alpha]_D$ +116° (acetone)] in 1 ml. of 6% hydrogen bromide in acetic acid and 20 ml. of acetic acid. The reaction mixture was stirred rapidly, and the temperature was maintained at 10–12° throughout addition of the buffered bromine solution. When all the bromine had been consumed, a solution of 1.64 g. (20 millimoles) of sodium acetate in 40 ml. of water was added. White solid precipitated; the thick reaction mixture was stirred for 5 minutes and then filtered. The yield of air-dried solid was 8.20 g.

The crude product was dissolved in 10 ml. of boiling acetone; the solution was diluted carefully with 30 ml. of warm ether. The resulting yellow solution was slurried with 1 g. of activated charcoal (Darco); the mixture was filtered through Celite; the filtrate was concentrated to *ca.* 20 ml., seeded with a similarly prepared sample, and refrigerated 48 hours at 0°. The yield of crystalline material obtained in this manner was 2.82 g. (34.5% yield, calculated for monobromopregnanetrione), m.p. 160–163° (dec.). This material was recrystallized twice from acetone–ether (1:2), the yield of purified bromopregnanetrione being 1.80 g. (22%); m.p. 168–169° (dec.), $[\alpha]_D$ +95° (*c* 0.693 in acetone).

Anal. Calcd. for $C_{21}H_{29}BrO_3$: C, 61.61; H, 7.14; Br, 19.52. Found: C, 61.42, 61.23; H, 7.20, 7.11; Br, 20.21, 20.24.

The carbonyl band at 1704 cm.$^{-1}$ and the C–Br band at 719 cm.$^{-1}$ were observed in the infrared spectrum.

Bromination of Pregnane-3,11,20-trione in Dimethylformamide Solution.—A solution of 3.84 g. (24 millimoles) of bromine in 20 ml. of dimethylformamide was added dropwise in approximately 5 hours to a solution of 6.61 g. (20 millimoles) of pregnane-3,11,20-trione and 120 mg. of *p*-toluenesulfonic acid monohydrate in 20 ml. of dimethylformamide. The reaction mixture was stirred, and the temperature was maintained at 23–25° throughout the reaction. When all of the bromine had been consumed the reaction solution was diluted with 200 ml. of ether; the resulting solution was washed with six 25-ml. portions of water, dried with anhydrous sodium sulfate, filtered and concentrated to 25 ml. Crystals formed during concentration of the ether solution. The solid was separated by filtration, washed with a small amount of ether, and dried in a vacuum desiccator; yield 2.87 g. (35.0%), m.p. 164–166° (dec.), $[\alpha]_D$ +118° (acetone). Recrystallization twice from acetone–ether (1:2) of 1.50 g. of this material yielded 1.02 g. (68% recovery, 24% yield) of pure 4-bromopregnane-3,11,20-trione, m.p. 171–173° (dec.), $[\alpha]_D$ +136° (*c* 0.770 in acetone). The melting point was not depressed on admixing with the 4-bromopregnane-3,11,20-trione ($[\alpha]_D$ +95°) prepared in acetic acid solution.

Anal. Calcd. for $C_{21}H_{29}BrO_3$: C, 61.61; H, 7.14; Br, 19.52. Found: C, 61.65, 61.41; H, 7.08, 7.11; Br, 19.90, 19.94.

A raised ketone band at 1720 cm.$^{-1}$, 11- and 20-ketone band at 1698 cm.$^{-1}$ and C–Br band at 714 cm.$^{-1}$ were observed in the infrared spectrum.

Dehydrobromination of 4-Bromo-17α-hydroxy-21-acetoxypregnane-3,11,20-trione with Lithium Chloride.—A solution of 1.93 g. (4.0 millimoles) of the 4-bromo steroid ($[\alpha]_D$ +106°; Br, 15.79, 15.57) and 0.51 g. (12.0 millimoles) of anhydrous lithium chloride in 20 ml. of dimethylformamide was heated at 100° under nitrogen for 2 hours. Dilution of the reaction solution with 10 ml. of water and cooling of the mixture to ice temperatures resulted in precipitation of crude cortisone acetate. It was separated by filtration, washed with two 5-ml. portions of water, and dried in a vacuum desiccator. Recrystallized from acetone the crude material afforded 1.17 g. (73% yield) of cortisone acetate; m.p. 248–250°, $[\alpha]_D$ +179° (*c* 0.706 in acetone), λ_{max}^{alc} 239 mμ, log ε 4.20. From the mother liquor there was isolated an additional 0.10 g. (6% yield) of somewhat less pure cortisone acetate; m.p. 238–241°, $[\alpha]_D$ +153° (*c* 0.632 in acetone), λ_{max}^{alc} 239 mμ, log ε 4.16.

Dehydrobromination of 4-bromo-17α-hydroxy-21-acetoxypregnane-3,11,20-trione ($[\alpha]_D$ +97°; Br, 16.61; prepared in acetic acid system) afforded a 69% yield of crude cortisone acetate, m.p. 236–243°, λ_{max}^{alc} 238 mμ, log ε 4.18. Recrystallization from acetone yielded two fractions: (1) 56.4% yield, m.p. 247–249°, $[\alpha]_D$ +181° (*c* 0.771 in acetone), λ_{max}^{alc} 238 mμ, log ε 4.19; (2) 6.0% yield, m.p. 240–243°, $[\alpha]_D$ +179° (*c* 0.761 in acetone), λ_{max}^{alc} 238 mμ, log ε 4.19.

Dehydrohalogenation with Other Lithium Salts, Magnesium, Beryllium and Aluminum Salts in N,N-Disubstituted Amides.—The reactions were carried out essentially as described in the previous experiment. In the reactions involving lithium iodide the reaction mixture was dissolved in chloroform, and the chloroform solution was washed repeatedly with water to remove inorganic salts and the amide solvent. The crude cortisone acetate was isolated by evaporating the chloroform solution to dryness at reduced pressures. The results of these experiments are summarized in Table I.

Rate of Cortisone Acetate Formation.—The 4-bromo-17α-hydroxy-21-acetoxypregnane-3,11,20-trione and three molecular equivalents of the lithium halide were heated together at the desired temperature in dimethylformamide solution. Aliquots were removed at various times for determination of cortisone acetate by ultraviolet absorption ($\lambda_{max}^{ethanol}$ 238–239 mμ). These data are shown graphically in Fig. 1.

The effect of concentration of lithium chloride on the rate of cortisone acetate formation also was investigated. The data are shown graphically in Fig. 2.

Lithium Iodide–Dimethylformamide Coördination Complex.—Solutions of 10.6 g. (0.25 mole) of anhydrous lithium chloride in 100 ml. of dimethylformamide and 37.5 g. (0.25 mole) of anhydrous sodium iodide in 150 ml. of dimethylformamide were mixed at 80–90°. Sodium chloride precipitated immediately; it was separated by filtration (yield 13.1 g.). The filtrate was concentrated at reduced pressures (15–20 mm.) to 100 ml. On cooling to room temperature the liquid solidified. The crystalline solid was recrystallized twice from 150-ml. portions of ethyl acetate; yield 35.2 g. The compound was deliquescent.

Anal. Calcd. for $LiI \cdot C_3H_7NO$: I, 61.33; N, 6.77. Found: I, 62.71, 63.05; N, 6.46, 6.72.

Anhydrous lithium iodide was obtained by heating the coördination complex at 250–300° *in vacuo* to constant weight.

Dehydrohalogenation of 4α-Bromopregnanetrione.—A solution of 1.64 g. (4 millimoles) of 4α-bromopregnane-3,11,20-trione (m.p. 168–169°, $[\alpha]_D$ +95°) and 0.50 g. (12 millimoles) of anhydrous lithium chloride in 8 ml. of dimethylformamide was heated 2 hours at 95–98° (N_2 atm.). The reaction solution was cooled, diluted with 200 ml. of ether. The resulting mixture was washed with 50 ml. of 10% hydrochloric acid solution and four 50-ml. portions of

TABLE I

CORTISONE ACETATE FROM 4-HALODIHYDROCORTISONE ACETATE

Reactants		Reaction conditions				Cortisone acetate					
X in $C_{23}H_{31}O_6X$	MX	Moles of MX per mole of steroid	Solvent	Time, hr.	Temp., °C.	Fraction number	Yield, %	M.p., °C.	$[\alpha]^{23}D$ (acetone)	$\lambda_{max}^{ethanol}$ 238–239 mμ, log ε[a]	Purity,[a] %
Br	LiCl	3	Dimethylformamide	2	100	1	73	248–250	179	4.20	96
						2	6	238–241	153	4.16	89
Br	LiCl	3	Pyridine	2	100	1	37.5	244–247	180	4.19	94.5
						2	41	245–248	177	4.18	92.5
Br	LiCl	3	Dimethylacetamide	2	100	1 + 2	69.5	245–248	183	4.18	93
Br	LiBr	5	N-Formylpiperidine	2	100	Crude	82	213–218	158	4.07	71.5
Br	LiI–C_3H_7NO	3	Dimethylformamide	2	100	1	68	220–230	119	3.37	14
						2	5	217–221	...	3.32	13
Br	$BeCl_2$	5	Dimethylformamide	2	100	1	50	246–249	181	4.18	94
						2	15	230–237	171	4.15	86
Br	$MgCl_2$	4	Dimethylformamide	2	100	1	51	246–249	182	4.18	93
						2	9	236–242	178	4.17	90.5
Br	$AlCl_3$	3	Dimethylformamide	1	100	Crude	57	227–231	159	4.14	84
Cl	LiBr	3	Dimethylacetamide	3	130	Crude	86.5	220–230	178	4.16	88.5
Cl	LiI	3	Dimethylformamide	3	100	Crude	92.5	.....	...	(3.53)	21

[a] Standard of purity for cortisone acetate, $\lambda_{max}^{ethanol}$ 238 mμ, log ε 4.21 (ε 16,300).

water. The colorless ether solution was dried with anhydrous sodium sulfate, filtered and concentrated to 6 ml. Crude 11-ketoprogesterone crystallized spontaneously. The crystals were separated and dried after refrigerating overnight at 0°; yield 0.83 g. (63%), m.p. 159–163°, λ_{max}^{alc} 239 mμ, log ε 4.15. Evaporation of the filtrate to dryness left 0.43 g. of resinous material.

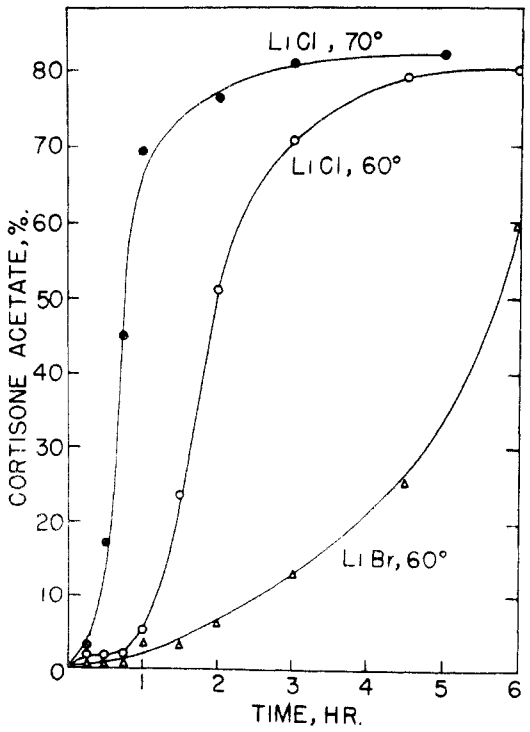


Fig. 1.—4-Bromo-17α-hydroxy-21-acetoxypregnane-3,11, 20-trione heated with lithium salts in dimethylformamide solution.

Recrystallization of the crude 11-ketoprogesterone from 6 ml. of acetone–ether (1:2) yielded 0.51 g. (62% recovery) of 11-ketoprogesterone, m.p. 170–172°, $[\alpha]D$ +216° (*c* 0.808 in acetone), λ_{max}^{alc} 239 mμ, log ε 4.15.

Dehydrohalogenation of 4β-Bromopregnanetrione.—A solution of 819 mg. (2 millimoles) of 4β-bromopregnane-3,-11,20-trione (m.p. 171–173°, $[\alpha]D$ +136°) and 250 mg. (6 millimoles) of anhydrous lithium chloride in 4 ml. of dimethylformamide was heated 2 hours at 95–98° (N_2 atm.). Processing as described above yielded 415 mg. (70%) crude 11-ketoprogesterone, m.p. 160–166° and 135 mg. of semi-solid residue. Recrystallization of 400 mg. of the crude 11-ketoprogesterone from acetone–ether (1:2) yielded 275 mg. (69% recovery) of purified 11-ketoprogesterone, m.p. 173–174°, $[\alpha]D$ +228° (*c* 0.843 in acetone), λ_{max}^{alc} 239 mμ, log ε 4.19.[13]

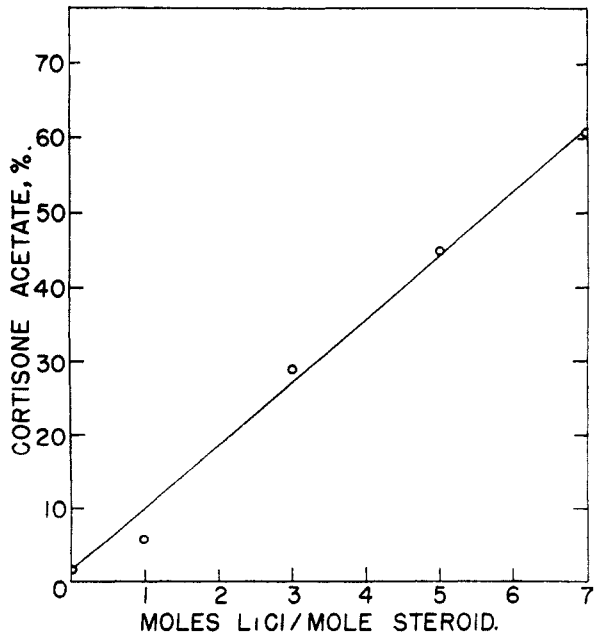


Fig. 2.—4-Bromo-17α-hydroxy-21-acetoxypregnane-3,11, 20-trione heated 2 hours at 60° in dimethylformamide solution with varying concentrations of lithium chloride.

Reaction of 4-Bromo-17α-hydroxy-21-acetoxypregnane-3,11,20-trione with Lithium Chloride in Tetrahydrofuran.—A mixture of 0.97 g. (2.0 millimoles) of the 4-bromo steroid ($[\alpha]D$ +105° in acetone; Br, 15.61, 15.72) and 0.85 g. (20 millimoles) of anhydrous lithium chloride in 20 ml. of anhydrous tetrahydrofuran was refluxed (65°) for 5 hours.

(13) T. Reichstein, *Helv. Chim. Acta*, **23**, 684 (1940); **26**, 721 (1942).

The reaction mixture was diluted with 75 ml. of chloroform; the solid was removed by filtration and rinsed with 25 ml. of chloroform. The solution was washed with four 25-ml. portions of water, dried over anhydrous sodium sulfate at 0°, and concentrated to dryness at reduced pressures. The residue was dried over sulfuric acid in a vacuum desiccator; yield 0.93 g., m.p. 194–195° (dec.), $\lambda_{max}^{ethanol}$ 238 mμ, log ε 3.12 (7.8% Δ⁴-3-ketone).

Anal. Calcd. for $C_{23}H_{31}BrO_6$: Br, 16.53. Calcd. for $C_{23}H_{31}ClO_6$: Cl, 8.08. Found: Br, 10.09, 10.11; Cl, 1.48, 1.53.

Reaction of 4-Bromo-17α-hydroxy-21-acetoxypregnane-3,11,20-trione with Sodium Iodide in Dimethylformamide.—A solution of 1.21 g. (2.5 millimoles) of the 4-bromo compound (Br, 15.61, 15.72) and 1.12 g. (7.5 millimoles) of anhydrous sodium iodide in 10 ml. of dimethylformamide was heated for 2 hours at 100° under nitrogen. Dilution of the deep-red reaction solution with 10 ml. of 5% sodium bisulfite solution precipitated a white solid; yield 0.64 g., m.p. 198–199° (dec.), $\lambda_{max}^{ethanol}$ 238 mμ, log ε 3.37 (14.4% Δ⁴-3-ketone).

Anal. Calcd. for $C_{23}H_{31}BrO_6$: Br, 16.53. Calcd. for $C_{23}H_{31}IO_6$: I, 23.93. Found: Br, 12.03; I, 0.91.

Dilution of the filtrate with 50 ml. of water precipitated more solid; yield 0.33 g., m.p. 205–206° (dec.), $\lambda_{max}^{ethanol}$ 238 mμ, log ε 3.09 (7.5% Δ⁴-3-ketone).

Anal. Calcd. for $C_{23}H_{31}BrO_6$: Br, 16.53. Calcd. for $C_{23}H_{31}IO_6$: I, 23.93. Found: Br, 13.63; I, 0.77.

Phase Distribution Study.[4]—The solubility of 4-bromo-17α-hydroxy-21-acetoxypregnane-3,11,20-trione [m.p. 195–196° (dec.), $[\alpha]_D$ +112 and 111°] was measured in diethyl ketone at 24° in the presence of varying quantities of solid phase. A plot of the ratios, mg. of solid/mg. of solvent *versus* mg. of solid/ml. of solution, resulted in a well-defined curve characteristic for a pure substance, the maximum solubility being 19.30 mg. per ml.

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KALAMAZOO, MICHIGAN

[CONTRIBUTION FROM THE EASTERN REGIONAL RESEARCH LABORATORY][1]

Steroidal Sapogenins. VIII. Markogenin (22b-Spirostane-2ξ,3β-diol). A New Sapogenin Isolated from Yucca[2]

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22b-Spirostane-2ξ,3β-diol, a new steroidal sapogenin, has been isolated from certain Yucca species. The structure of the compound has been determined from chemical and infrared data. The new sapogenin is distinctly different from the previously reported texogenin which is stated to have the same structure.

During a survey of sapogenaceous plants, a dihydroxy sapogenin, normal at carbon 22, was isolated from several *Yucca* species. Preliminary examination indicated that the compound was a new sapogenin. Chemical and infrared studies proved conclusively that the dihydroxy sapogenin had the structure assigned by Marker[3] to texogenin. However, as shown in Table I, a comparison of the melting points of the new sapogenin and its derivatives with those given by Marker, *et al.*, for texogenin, show obvious discrepancies. In particular the new sapogenin melts some 80° higher than "texogenin."

TABLE I

COMPARISON OF THE MELTING POINTS OF MARKOGENIN AND ITS DERIVATIVES WITH THOSE OF TEXOGENIN, AND SPECIFIC ROTATIONS OF THE NEW GENIN

	M.p., °C.	$[\alpha]^{25}D$ Chloroform
22b-Spirostane-2ξ,3β-diol	256–257	−70.3
Texogenin	172–175[3]	....
22b-Spirostane-2ξ,3β-diol 2,3-diacetate	185–186	−84.2
Texogenin acetate	172–173[3]	....
2,3-seco-22b-Spirostane-2//3-dioic acid	244–246	−46.8
Texogenic acid	268–269[3]	....

The method used by Marker, *et al.*,[3] for the isolation of texogenin was complex[4] in that it was necessary to separate the compound from six other sapogenins. In fact the entire history of texogenin is perplexing.[5]

In view of these facts we therefore wish to present the details of an unequivocal isolation and structure proof of the new steroidal sapogenin. In order to avoid confusion with texogenin, we have named the new sapogenin Markogenin.[6]

We have isolated Markogenin (22b-spirostane-2ξ,3β-diol) from the leaves of *Yucca faxoniana*, *Y. schidigera* and a yucca by-product leaf powder[7]

(1) One of the laboratories of the Bureau of Agricultural and Industrial Chemistry, Agricultural Research Administration, United States Department of Agriculture. This work was done as part of a coöperative arrangement between the Bur. of Plant Industry, Soils and Agricultural Engineering and Bur. of Agricultural and Industrial Chemistry of the U. S. Department of Agriculture and the Natl. Institute of Health, Department of Health, Education and Welfare. Article not copyrighted.

(2) Paper VII, M. E. Wall, *et al.*, *J. Am. Pharm. Assoc., Sci. Ed.*, in press.

(3) R. E. Marker, *et al.*, THIS JOURNAL, **69**, 2167 (1947).

(4) R. E. Marker, *et al.*, *ibid.*, **69**, 2226 (1947).

(5) Marker, *et al.*, *ibid.*, **69**, 2226 (1947), stated that texogenin was isolated by conversion to pseudotexogenin = pseudosamogenin (20(22)-furosten-2ξ,3β,26-triol), followed by acid isomerization back to texogenin. This was in contradiction to statements in another section of this paper, p. 2197, in which it was stated that pseudosamogenin reverts to samogenin. Marker, *et al.*, resolved this difficulty by assuming that some of the texogenin did not form the pseudo derivative and hence was recovered unchanged. Later, Marker and Lopez, *ibid.*, **69**, 2373 (1947), stated that acid isomerization of pseudosamogenin results in the formation of an 80-20 mixture of samogenin and texogenin, respectively. They concluded that *texogenin does not occur naturally* but is an artifact arising from samogenin. In a following paper, *ibid.*, **69**, 2383 (1947), Marker and Lopez treat texogenin = neosamogenin as a naturally occurring product. Consequently the status of this sapogenin is indeed dubious.

(6) In honor of Russell Marker.

(7) Anonymous, *Chem. Eng. News*, **30**, 2822 (1952).