was taken up in benzene and dried over calcium chloride. After filtration and removal of benzene the residue was distilled under reduced pressure to give 45.1 g. (43%) of desired product.[6]

(6) W. Schneider, *Ann.*, **375**, 207 (1910), reported the preparation of this compound by a different procedure, but failed to isolate it from the reaction mixture.

1-(3-Methylmercaptopropyl)-pyridinium Bromide.—A solution of 22 g. (0.13 mole) of 3-bromopropyl methyl sulfide in 31.6 g. (0.4 mole) of pyridine was refluxed for five hours. The solid which formed was recrystallized several times with the least amount of hot *n*-propyl alcohol. The yield of pure product was 10 g. (31%).

RENSSELAER, NEW YORK

[CONTRIBUTION FROM THE RESEARCH LABORATORIES OF THE GLIDDEN CO.]

Sterols. XV.[1] Cortisone and Analogs. Part 1. 16α-Hydroxy and 16α,17α-Epoxy Analogs of Cortisone

BY PERCY L. JULIAN,[2] WAYNE COLE, EDWIN W. MEYER AND BERNARD M. REGAN

RECEIVED FEBRUARY 11, 1955

The partial synthesis of 16α,17α-epoxy-21-acetoxy-4-pregnene-3,11,20-trione and 16α-hydroxy-21-acetoxy-4-pregnene-3,11,20-trione (16α-hydroxy-11-dehydrocorticosterone acetate) is described. The conversion of the key intermediate in this synthesis, 16β-bromocortisone acetate, into cortisone acetate by reductive dehalogenation is likewise detailed. 4,16-Pregnadiene-3,11,20-trione was obtained as a co-product in the preparation of 16α-hydroxy-11-dehydrocorticosterone acetate from the 16α,17α-epoxysteroid.

The partial synthesis of cortisone acetate from 3α-acetoxy-16-pregnene-11,20-dione[3] has already been reported.[4,5] The present paper describes the essential experimental details of this synthesis, and specifically describes our preparation of the 16α,17α-epoxy analog of cortisone acetate, and its reduction products, 16α-hydroxy-21-acetoxy-4-pregnene-3,11,20-trione (16α-hydroxy-11-dehydrocorticosterone acetate) and 17α-hydroxy-21-acetoxy-4-pregnene-3,11,20-trione (cortisone acetate).

For the synthesis of the epoxy analog, 3α-hydroxy-16α,17α-epoxypregnane-11,20-dione (I) may be represented, for this paper, as starting material. It was prepared in excellent yield by the alkaline peroxide epoxidation and hydrolysis of 3α-acetoxy-16-pregnene-11,20-dione.[3,6] Bromination of the epoxy steroid I at C-21, followed by acetolysis with potassium acetate, afforded the desired 3α-hydroxy-16α,17α-epoxy-21-acetoxypregnane-11,20-dione. The latter substance also was prepared in a more circuitous fashion by treating 3α-acetoxy-16α,17α-epoxypregnane-11,20-dione with hydrogen bromide in acetic acid to form the corresponding bromohydrin, then brominating this substance at C-21, followed by hydrolysis at C-3 with hydrogen bromide in methanol-benzene and finally introducing the necessary C-21 acetoxy group by a potassium acetate acetolysis. The resulting 3α-hydroxy-16α,17α-epoxy-21-acetoxypregnane-11,20-dione gave, upon oxidation with chromic acid in acetic acid–chloroform, 16α,17α-epoxy-21-acetoxypregnane-3,11,20-trione.[7] Our experience has shown that for preparation of the related bromohydrin, 16β-bromo-17α-hydroxy-21-acetoxypregnane-3,11,20-trione (II), it is more expedient to employ the crude oxidation product, since isolation of the 3,11,20-trione results in a substantial crystallization loss. Bromination of the bromohydrin II proceeded rapidly; however, attempts to recrystallize the resulting 4α-bromo derivative (III) proved unsuccessful. Therefore, the crude intermediate was converted in solution to the semicarbazone, which then was cleaved with pyruvic acid to give 16β-bromo-17α-hydroxy-21-acetoxy-4-pregnene-3,11,20-trione (16β-bromocortisone acetate (IV)), melting at 236–237°. The preparation, by total synthesis, of the *dl*-modification of this steroid recently has been reported.[8] Reaction of 16β-bromocortisone acetate with potassium acetate in acetone achieved the necessary dehydrobromination for formation of the 16α,17α-epoxy analog of cortisone acetate, 16α,17α-epoxy-21-acetoxy-4-pregnene-3,11,20-trione (V). The over-all yield in this conversion from II was 50%.

Reductive dehalogenation of 16β-bromocortisone acetate (IV) with a Raney nickel catalyst produced cortisone acetate (VIII). A similar reduction, the hydrogenolysis of 16β-bromo-4,5-dihydrocortisone acetate in the presence of palladium-on-calcium carbonate, has been reported by Kendall and coworkers.[7]

The 16α,17α-epoxy analog of cortisone acetate (V) also served as a convenient intermediate in the preparation of the hitherto undescribed 16α-hy-

(1) For paper XIV in this series, see W. Cole and P. L. Julian, *J. Org. Chem.*, **19**, 131 (1954).

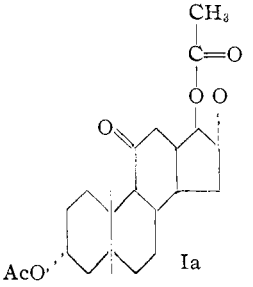
(2) The Julian Laboratories, Inc., Franklin Park, Ill.

(3) For preparation of this 16-dehydropregnane, see P. L. Julian and W. J. Karpel, U. S. Patent 2,671,794; R. U. Schock and W. J. Karpel, U. S. Patent 2,684,963; see also discussion in reference 5, particularly p. 199; see further W. R. Nes and H. L. Mason, THIS JOURNAL, **73**, 4765 (1951).

(4) Presented at the Symposium on Steroids of the 118th National Meeting of the American Chemical Society, Chicago, Ill., September 5, 1950.

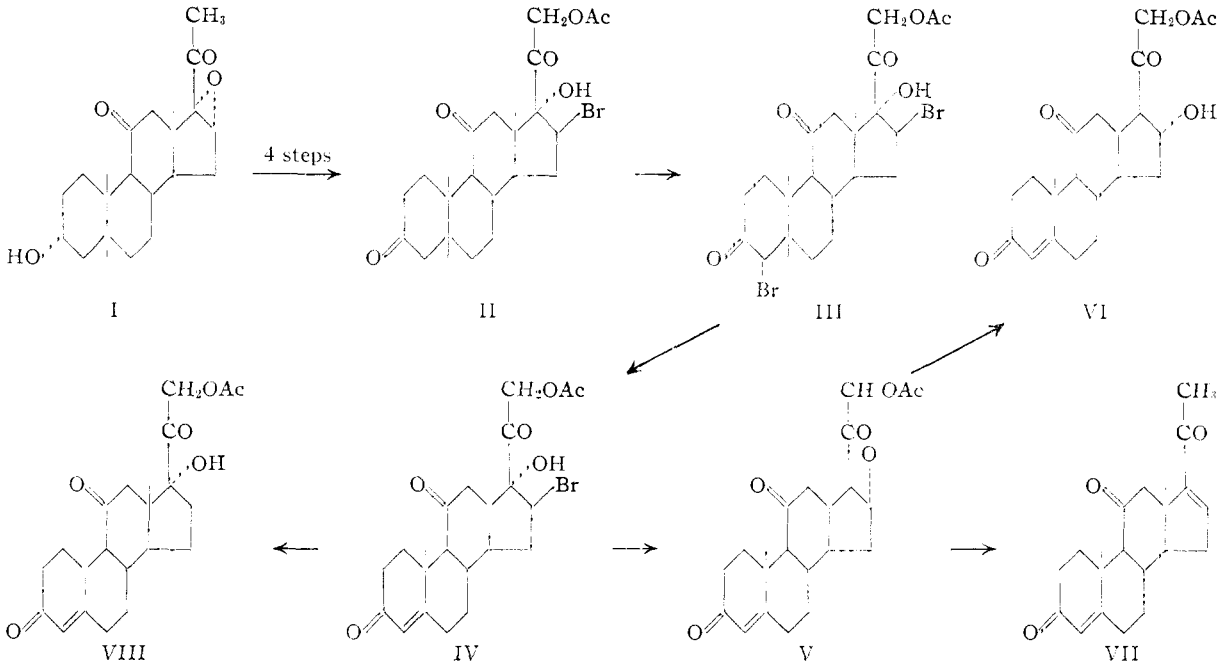
(5) P. L. Julian, *et al.*, in G. Pincus, "Recent Progress in Hormone Research," Vol. VI, Academic Press, Inc., New York, N. Y., 1951, p. 195.

(6) The by-product originally reported as XXXIX in reference 5, p. 200, and formed in part by the action of perbenzoic acid on 3α-acetoxy-16-pregnene-11,20-dione, has since been found by two of us to have the structure of 3α-acetoxy-16α,17α-epoxy-17β-acetoxyetiocholan-11-one (Ia). A more detailed description of it and proof of its structure will appear later (P.L.J. and W.C.).



(7) *Cf.* F. B. Colton, W. R. Nes, D. A. Van Dorp, H. L. Mason and E. C. Kendall, *J. Biol. Chem.* **194**, 235 (1952).

(8) L. B. Barkley, M. S. Farrar, W. S. Knowles and H. Raffelson, THIS JOURNAL, **76**, 5017 (1954).



droxy analog of cortisone acetate. For this conversion, the recently published chromous salt reduction procedure of Cole and Julian[1] was employed. With chromous acetate, the reduction of 16α,17α-epoxy-21-acetoxy-4-pregnene-3,11,20-trione (V) proceeded smoothly to give 16α-hydroxy-21-acetoxy-4-pregnene-3,11,20-trione (16α-hydroxy-11-dehydrocorticosterone acetate (VI)) in a 56% yield. Acetylation of the 16α-hydroxy compound with acetic anhydride in pyridine afforded the corresponding 16α,21-diacetate. A crystalline co-product, m.p. 197–200°, obtained in the reduction reaction, tentatively has been assigned the structure of 4,16-pregnadiene-3,11,20-trione (VII) on the basis of the empirical analysis and ultraviolet absorption spectra. Similar steroids of the 11-desoxy series are formed in analogous chromous salt reductions of 16α,17α-epoxy compounds.[1]

McGuckin, Mason and Higgins have reported that 21-acetoxy-4,16-pregnadiene-3,11,20-trione (VII) and 16α,17α-epoxy-21-acetoxy-4-pregnene-3,11,20-trione (V) are inactive in the deposition of liver glycogen and have no influence upon the glycogen deposition activity of cortisone acetate.[9] The biological activity of 16β-bromocortisone acetate (IV) and 16α-hydroxy-11-dehydrocorticosterone acetate (VI) is under investigation and will be reported at a later date.

Experimental[10]

3α-Hydroxy-16α,17α-epoxypregnane-11,20-dione (I).—A solution of 50 g. of 3α-acetoxy-16-pregnene-11,20-dione[2] in 1500 ml. of methanol was cooled to 15° and treated with 75 ml. of precooled 4 *N* sodium hydroxide, and then, with continued cooling, 150 ml. of cold 30% hydrogen peroxide was added. This mixture was set in an ice-chest at 5° for 40 hours. It then was filtered and the filtrate diluted with 5 l. of salt water containing 1 kg. of sodium chloride. The mixture was cooled in an ice-bath for one hour to complete the crystallization and then filtered. The filter cake was washed with distilled water (about 3 l.) until the filtrate was neutral, and then dried at 50° for ten hours. The yield of epoxide I, m.p. 220–223°, was 42 g. (90%). Recrystallization from methanol gave colorless needles, m.p. 221–223°, $[\alpha]^{25}D$ +99° (*c* 1.0 in chloroform).

Anal. Calcd. for $C_{21}H_{30}O_4$: C, 72.79; H, 8.73. Found: C, 72.55; H, 8.70.

The acetate was prepared by dissolving 42 g. of the above product in 126 ml. of pyridine and adding 42 ml. of acetic anhydride. After 12 hours at room temperature, this mixture was filtered for clarification and, while cooling and scratching or seeding, it was diluted with 336 ml. of water. The crystals were collected on a filter, washed with water and dried. The yield of **3α-acetoxy-16α,17α-epoxypregnane-11,20-dione** was 95%. This substance crystallizes from methanol as needles, m.p. 131–133°, or as prisms, m.p. 152–153°, depending on the manner of seeding and the rate of crystallization. A sample of the 152° melting material showed an $[\alpha]^{25}D$ +110° (*c* 0.66 in chloroform).

Anal. Calcd. for $C_{23}H_{32}O_5$: C, 71.11; H, 8.30. Found: C, 71.01; H, 8.28.

3α-Hydroxy-16α,17α-epoxy-21-acetoxypregnane-11,20-dione.[5] **Procedure A.**—Ten grams of 3α-hydroxy-16α,17α-epoxypregnane-11,20-dione (I) in 200 ml. of methylene chloride was treated portionwise with a solution of 5.2 g. of bromine in 60 ml. of methylene chloride. About one hour was required for the addition. After washing with sodium bicarbonate solution and water, the methylene chloride layer was concentrated *in vacuo* to dryness. The residue was stirred with 25 g. of anhydrous potassium acetate and 200 ml. of acetone. This mixture was refluxed for two hours and then concentrated to a small volume (bumping occurs), and cooled to improve crystallization and filtered. The crystals were washed thoroughly with water and then dried, giving 9 g. of crude product. Recrystallization from acetone gave 7.9 g. (68%) of 3α-hydroxy-16α,17α-epoxy-21-acetoxypregnane-11,20-dione, m.p. 234–235°.

Anal. Calcd. for $C_{23}H_{32}O_6$: C, 68.28; H, 7.97. Found: C, 68.16; H, 8.00.

Procedure B.—To a solution of 4 g. of 3α-acetoxy-16α,-17α-epoxypregnane-11,20-dione in 40 ml. of acetic acid and 40 ml. of chloroform, cooled to 20°, there was added 4 ml. of 32% hydrogen bromide in acetic acid. After ten minutes, a solution of 1.76 g. of bromine in 18 ml. of acetic acid was added rapidly and the mixture held at room temperature for 20 minutes until the bromine had been decolorized.

(9) W. F. McGuckin, H. L. Mason and G. M. Higgins, Abstracts, 125th Meeting, Amer. Chem. Soc., 1954, 4 c.

(10) All melting points were determined in capillaries and are uncorrected. We wish to thank Mr. F. Taylor of the Glidden Laboratories for the ultraviolet absorption spectra and the optical rotations. Microanalyses by Micro-Tech Laboratories, Skokie, Ill.

The mixture was concentrated *in vacuo* to a crystalline residue, then slurried with alcohol-free ether, cooled and filtered. There was obtained 3.38 g. of **3α-acetoxy-16β,21-dibromo-17α-hydroxypregnane-11,20-dione**, m.p. 224–230° dec. Recrystallization from chloroform–ether gave crystals melting at 239–240° dec.

Anal. Calcd. for $C_{23}H_{32}O_5Br_2$: C, 50.38; H, 5.88. Found: C, 50.88; H, 5.99.

This material was treated for 12 hours at room temperature with a mixture of 27 ml. of benzene and 72 ml. of methanol containing 1.9 g. of hydrogen bromide. The reaction mixture was diluted with water, extracted with ether and washed with water to neutrality. The ethereal solution was dried and concentrated *in vacuo* to a crystalline residue which then was dissolved in 90 ml. of acetone and refluxed with 15 g. of anhydrous potassium acetate for five hours. The mixture was concentrated to a low volume, precipitated with water and filtered. The dried product, after crystallization from ethanol, afforded 1.78 g. of crude 3α-hydroxy-16α,17α-epoxy-21-acetoxypregnane-11,20-dione, m.p. 230°. Recrystallization from ethyl acetate raised the melting point to 234–235°. This material was identical with that prepared by procedure A.

The preparation of this 21-acetoxy-epoxide, m.p. 235–237°, by a related method was described recently by Kendall and co-workers.[7]

16β-Bromo-17α-hydroxy-21-acetoxypregnane-3,11,20-trione (16β-Bromo-4,5-dihydrocortisone acetate) (II).—The procedure for the chromic acid oxidation of **3α-hydroxy-16α,17α-epoxy-21-acetoxypregnane-11,20-dione** was similar to that already recorded by Kendall, *et al.*, but the trione formed from 6.98 g. of the 3α-hydroxy steroid was not crystallized, since purification was inefficient and unnecessary in this case. Instead, the oily oxidation product, after infrared analysis showed an absence of hydroxyl absorptions, was dissolved in 40 ml. of acetic acid, cooled to 10° and treated with 6 ml. of a solution of 25% hydrogen bromide in acetic acid. After standing 40 minutes at room temperature with occasional swirling, the reaction mixture was diluted with water and extracted with methylene chloride. The extracts were washed with sodium bicarbonate solution and water, and then concentrated to about 20 ml. Addition of 50 ml. of ether and cooling gave 6.0 g. of crystalline bromohydrin II, m.p. 187–189° dec. An additional 1.0 g. (total yield, 84%) was obtained from the mother liquor by precipitation with ether and subsequent crystallization from ethyl acetate. Recrystallization from ethyl acetate raised the melting point to 189–190° dec. (reported[7] m.p. 189–190°).

Anal. Calcd. for $C_{23}H_{31}O_6Br$: Br, 16.53. Found: Br, 16.79.

16β-Bromo-17α-hydroxy-21-acetoxy-4-pregnene-3,11,20-trione (16β-Bromocortisone Acetate) (IV).—A solution of 4.83 g. of 16β-bromo-17α-hydroxy-21-acetoxypregnane-3,-11,20-trione in 150 ml. of acetic acid was treated with 1.65 g. of bromine in 50 ml. of acetic acid at 15°. The bromine reacted completely within three minutes. Without delay, the solution was poured into 3.0 l. of cold water and extracted four times with methylene chloride. The combined extract was washed with water, dilute sodium bicarbonate solution and then water. The dried solution was concentrated *in vacuo* with gentle warming to about 85 ml.

Since previous attempts to isolate a crystalline solid at this point failed (an unstable, amorphous solid decomposing at 135° was obtained), the methylene chloride solution of the bromination product was dehydrohalogenated by the semicarbazone procedure.[11] A solution of 2.45 g. of semicarbazide hydrochloride and 1.84 g. of sodium bicarbonate in 8.0 ml. of water was diluted with 100 ml. of *t*-butyl alcohol and this mixture was added, in an atmosphere of carbon dioxide, to the methylene chloride solution previously diluted with 50 ml. of *t*-butyl alcohol. The reaction mixture was allowed to stand for three hours. At the outset an orange color developed; this faded to yellow within the first hour.

In previous runs, attempts to isolate the semicarbazone yielded only about 30% of an impure material (once recrystallized from chloroform–ethanol; m.p. 200–203° dec., λ_{max}^{MeOH} 270 mμ, ε 26,400). Thus the semicarbazone solution was treated with a mixture of 7.5 ml. of 96% pyruvic acid, 15 ml. of acetic acid and 25 ml. of water, and allowed to stand overnight in an atmosphere of carbon dioxide. The reaction mixture was concentrated *in vacuo* to about 75 ml., diluted with water and extracted four times with methylene chloride. The combined extract was washed with water, dilute sodium bicarbonate solution, salt water, and finally with water. The residue (5.0 g. of yellow, amorphous material) remaining after removal of methylene chloride was crystallized from methanol to yield 1.85 g. (39% overall) of 16β-bromocortisone acetate, m.p. 223–224° dec. This material contained a small amount of polybromo impurities. These were best removed by treatment with chromous chloride. A solution of 333 mg. of the impure 16β-bromocortisone acetate in 2.0 ml. of methylene chloride and 10 ml. of acetic acid was treated with 2.0 ml. of 0.33 *M* aqueous chromous chloride in an atmosphere of carbon dioxide. After 30 minutes at room temperature, the product was crystallized by careful addition of water to the reaction mixture. After chilling, filtering and washing with water, 300 mg. of small white needles, m.p. 225° dec., was obtained. Recrystallization from methanol raised the melting point to 236–237° dec. (this varies somewhat with rate of heating), λ_{max}^{MeOH} 238 mμ (ε 15,700); reported[8] for *dl*-16β-bromocortisone acetate, m.p. 238–240° dec., $[\alpha]^{25}D$ +150° (*c* 0.55 in chloroform).

Anal. Calcd. for $C_{23}H_{29}O_6Br$: C, 57.38; H, 6.07; Br, 16.60. Found: C, 57.54; H, 6.29; Br, 16.57.

In addition, 700 mg. (17%) of 16α,17α-epoxy-21-acetoxy-4-pregnene-3,11,20-trione was isolated following potassium acetate treatment of the mother liquor of the impure 16β-bromocortisone acetate and chromatography on silica (see below).

16α,17α-Epoxy-21-acetoxy-4-pregnene-3,11,20-trione (V).—A mixture of 240 mg. of 16β-bromocortisone acetate and 240 mg. of potassium acetate in 10 ml. of acetone was refluxed for two hours. Concentration to about 5 ml. and slow addition of water gave 190 mg. (95%) of buff colored plates, m.p. 192–195°. One recrystallization from methanol gave the 16α,17α-epoxy steroid as colorless needles melting at 194–196°.

From 1.00 g. of 16β-bromo-17α-hydroxy-21-acetoxypregnane-3,11,20-trione, without isolation of intermediates, there was obtained 410 mg. (50%) of 16α,17α-epoxy-21-acetoxy-4-pregnene-3,11,20-trione. This product was isolated by chromatography on silica. The desired epoxide was found in the benzene–ether (1:1) eluate. Several recrystallizations from methanol afforded colorless needles melting at 195–197°, λ_{max}^{MeOH} 238 mμ (ε 15,500), $[\alpha]^{25}D$ +236° (*c* 1.0 in chloroform).

Anal. Calcd. for $C_{23}H_{28}O_6$: C, 68.98; H, 7.05. Found: C, 69.06; H, 7.00.

16α-Hydroxy-21-acetoxy-4-pregnene-3,11,20-trione (16α-Hydroxy-11-dehydrocorticosterone 21-Acetate) (VI).—Chromous acetate was prepared from 12.5 ml. of 0.33 *M* aqueous chromous chloride and 2.0 g. of sodium acetate in water. The insoluble, red chromous acetate was centrifuged, washed with water and recentrifuged. It was then slurried in 25 ml. of acetone–water (4:1) and added to a solution of 500 mg. of 16α,17α-epoxy-21-acetoxy-4-pregnene-3,11,20-trione in 50 ml. of acetone, to which a solution of 3.6 g. of sodium acetate and 2.5 ml. of acetic acid in 12.5 ml. of water had been added. The whole operation was conducted in an atmosphere of carbon dioxide. The reaction mixture under CO_2 was stirred for six hours at room temperature. It was diluted with 200 ml. of benzene and 600 ml. of salt water. After shaking, the aqueous layer was re-extracted with two successive 100-ml. portions of benzene. The combined benzene extract was washed with 100-ml. portions of salt water, water, 5% aqueous sodium bicarbonate solution, salt water and finally water. The dried solution was concentrated under a stream of carbon dioxide at steam-bath temperature. There remained 510 mg. of off-white crystalline solid, which, when recrystallized from acetone–ether, afforded a first crop of 240 mg., melting at 253–256°. A second crop was obtained from benzene–acetone, 40 mg. melting at 253–256°; total yield 56%. Several recrystallizations of the combined crops from acetone gave colorless needles melting at 259–260°, λ_{max}^{MeOH} 238 mμ (ε 16,326), $[\alpha]^{25}D$ +192° (*c* 0.39 in chloroform containing a trace of pyridine).

(11) B. A. Koechlin, T. H. Kritchevsky and T. F. Gallagher, *J. Biol. Chem.*, **184**, 393 (1950).

Anal. Calcd. for $C_{23}H_{30}O_6$: C, 68.63; H, 7.51. Found: C, 68.81; H, 7.54.

Chromatography over silica gel (Davison, grade 923, 100–200 mesh) of the mother liquor from the two crops of crystalline material gave 120 mg. of colorless crystals melting at 197–200° dec., in the benzene–ether (1:1) eluate. Recrystallization from ether did not change the melting point. This material, probably **4,16-pregnadien-3,11,20-trione (VII)**, had λ_{max}^{MeOH} 238 mμ (ε 24,552).

Anal. Calcd. for $C_{21}H_{26}O_3$: C, 77.26; H, 8.03. Found: C, 76.84; H, 7.73.

16α,21-Diacetoxy-4-pregnene-3,11,20-trione.—A 63-mg. sample of 16α-hydroxy-21-acetoxy-4-pregnene-3,11,20-trione was acetylated with 0.8 ml. of an acetic anhydride–pyridine mixture (1:3). The reaction mixture was heated at 40° for 15 minutes and then let stand at room temperature for five hours. The product was crystallized by cautious addition of water. There resulted 67 mg. of colorless needles melting at 189–191°. Two recrystallizations from acetone–ether afforded material melting at 190–192° dec.

Anal. Calcd. for $C_{25}H_{32}O_7$: C, 67.55; H, 7.26. Found: C, 67.61; H, 7.43.

17α-Hydroxy-21-acetoxy-4-pregnene-3,11,20-trione (Cortisone Acetate) (VIII).—Commercial Raney nickel catalyst was treated with acetic acid until acidic to phenolphthalein, but basic to litmus. The catalyst was washed by centrifugation with water, followed by methanol. Two grams (wet weight) of the catalyst was suspended in 32 ml. of methanol and refluxed with stirring for one hour. Then 160 mg. of 16β-bromocortisone acetate (m.p. 222–223° dec.) was added and refluxing continued for another hour. The hot mixture was filtered to remove catalyst. The catalyst was washed several times with hot methanol–methylene chloride. The combined filtrate was concentrated *in vacuo* to 10 ml. and then 20 ml. of hot water was added to the residue. The glistening plates which separated upon cooling were filtered, washed with methanol and dried. The crystalline product, 90 mg. (70%), melted at 228–231°. Recrystallization from acetone gave shiny white needles (solvated) melting at 240–242°, λ_{max}^{MeOH} 238 mμ (ε 15,100). Upon admixture with an authentic sample of cortisone acetate (m.p. 245–246°, λ_{max}^{MeOH} 238 mμ (ε 15,700)), no depression in melting point was observed.

NORTH CHICAGO, ILL.

[CONTRIBUTION FROM THE BEN MAY LABORATORY FOR CANCER RESEARCH, UNIVERSITY OF CHICAGO, AND FROM THE DEPARTMENT OF INDUSTRIAL CHEMISTRY, KYÔTO UNIVERSITY]

Preparations of the Synthetic Estrogens. VI.[1] A New Synthesis of 1,1-Bis-(*p*-Alkoxyphenyl)-2-phenyl-2-bromoethylenes

BY KEIITI SISIDO, KÔITI OKANO AND HITOSI NOZAKI

RECEIVED FEBRUARY 23, 1955

Treatment of 1,1,2-triarylethanes with 2 moles of N-bromosuccinimide effected simultaneous dehydrogenation and bromination, giving triarylbromoethylenes in a single operation. 1,1-Bis-(*p*-methoxyphenyl)-2-phenyl-2-bromoethylene and 1,1-bis-(*p*-ethoxyphenyl)-2-phenyl-2-bromoethylene have been prepared in this way in 92 and 91% yields, respectively. The required 1,1-bis-(*p*-alkoxyphenyl)-2-phenylethanes were obtained in fair yields from the condensation of phenylacetaldehyde with anisole or phenetole in the presence of concentrated sulfuric acid as a catalyst.

A common defect of usual preparations of 1,1,2-triaryl-2-bromoethylenes,[2–4] for the purpose of large-scale production at least, is that the Grignard reaction is utilized for synthesizing the key intermediate, 1,1,2-triaryl-2-ethanol. Though some variations[5] have been reported in which the use of the Grignard reaction is avoided, the yields obtained are rather low. We have observed that the treatment of 1,1,2-triarylethane derivatives with 2 moles of N-bromosuccinimide results in the formation of 1,1,2-triaryl-2-bromoethylenes in good yields. This discovery constitutes a new synthesis which appears suitable for a large scale preparation of these potent estrogens.

The required intermediates, 1,1-bis-(*p*-alkoxyphenyl)-2-phenylethanes, were prepared by the condensation of alkyl phenyl ethers and phenylacetaldehyde in the presence of sulfuric acid. If the acidic catalyst was added dropwise to a solution of the reaction components in glacial acetic acid, there resulted a considerable quantity of tarry matter, which presumably might be composed of a polymer of the aldehyde. Substantially improved yields were realized, however, when the aldehyde was added quite slowly to a mixture of the phenol ether, glacial acetic acid and concentrated sulfuric acid in order to minimize the action of the mineral acid on the unchanged phenylacetaldehyde. 1,1-Bis-(*p*-methoxyphenyl)-2-phenylethane and 1,1-bis-(*p*-ethoxyphenyl)-2-phenylethane were prepared in this way in 51 and 58% yields, respectively. An attempted condensation of phenylacetaldehyde with benzene, fluorobenzene or *o*-fluoroanisole in the presence of concentrated sulfuric acid failed to afford the desired 1,1,2-triphenylethane.

When these 1,1-bis-(*p*-alkoxyphenyl)-2-phenylethanes were treated with 2 moles of N-bromosuccinimide in carbon tetrachloride solution at its boiling point, simultaneous dehydrogenation and bromination of the ethane derivatives occurred and the corresponding 1,1-bis-(*p*-alkoxyphenyl)-2-phenyl-2-bromoethylenes were obtained in excellent

(1) Previous paper: K. Sisido, H. Nozaki and O. Kurihara, THIS JOURNAL, **72**, 2270 (1950).

(2) For the preparation of triarylethanols and triarylhaloethylenes therefrom which utilizes the Grignard reaction between benzylmagnesium halides and benzophenones see (a) C. F. Koelsch, THIS JOURNAL, **54**, 2487 (1932); (b) A. Schönberg, J. M. Robson, W. Tadros and H. A. Fanim, *J. Chem. Soc.*, 1327 (1940); (c) W. Tadros and A. Schönberg, *ibid.*, 394 (1943); (d) W. Tadros and A. Latif, *ibid.*, 3823 (1952); (e) R. S. Shelton, M. G. Van Campen, Jr., D. F. Meisner, S. M. Parmerter, E. R. Andrews, R. E. Allen and K. K. Wyckoff, THIS JOURNAL, **75**, 5491 (1953).

(3) For the preparation utilizing the Grignard reaction between phenylacetic esters and phenylmagnesium bromides see (a) ref. 2a; (b) P. R. Carter and D. H. Hey, *J. Chem. Soc.*, 150 (1948).

(4) For the preparation utilizing the Grignard reaction between desoxybenzoins and phenylmagnesium bromides see (a) F. R. Basford, British Patent 566,415 (Dec. 29, 1944); *C. A.*, **41**, 3929e (1947); (b) F. R. Basford, British Patent 567,807 (Mar. 5, 1945); *C. A.*, **41**, 2753g (1947); (c) Buu-Hoï, *Bull. soc. chim. France*, 117 (1946); *C. A.*, **41**, 5490a (1947); (d) Nguyen-Hoàn and Buu-Hoï, *Compt. rend.*, **224**, 1228 (1947); *C. A.*, **41**, 6571b (1947); (e) ref. 3b.

(5) (a) D. Xuong, P. Cagniant and C. Mentzer, *Compt. rend.*, **226**, 1453 (1948); *C. A.*, **42**, 7279d (1948); (b) C. Mentzer and D. Xuong, French Patent 937,423 (Aug. 13, 1948); *C. A.*, **44**, 2030h (1950).