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Approaches to the Total Synthesis of Adrenal Steroids. XI. Dehydrocorticosterone and Cortisone

BY G. I. POOS, R. M. LUKES, G. E. ARTH AND L. H. SARETT

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The final steps of the present total synthesis of cortisone involving the conversion of the 3-dioxolane of *dl*-11-ketoprogesterone (I) to cortisone acetate are described. The 21-oxalyl acid of *dl*-I is resolved *via* its strychnine salt. The resulting optically active steroid is converted to the 3-dioxolane of dehydrocorticosterone acetate (IV) by successive iodination at C_{21} and treatment with potassium acetate. Introduction of the C_{17}-hydroxyl group is then carried out using the cyanohydrin procedure and the product is hydrolyzed with acid to give cortisone acetate. In addition, the preparation of racemic corticosterone acetate, dehydrocorticosterone and cortisone acetate is described.

In the preceding paper of this series the synthesis of *dl*-11-oxygenated progesterones from tricyclic intermediates was described.[1] With the completion of this phase there remained only the task of introducing the hydroxyl groups at C_{21} and C_{17} to complete the total synthesis of cortisone from benzoquinone and ethoxypentadiene. The present paper is concerned with the synthesis of dehydrocorticosterone and cortisone in both the racemic and natural modifications from the 3-dioxolane of *dl*-11-ketoprogesterone.

Although the introduction of halogen and thence oxygen at C_{21} into a variety of pregnane derivatives has been carried out,[2] these procedures involve direct bromination under acidic conditions. In order to retain the potential α,β-unsaturated ketone system in the 3-dioxolane of *dl*-11-ketoprogesterone (*dl*-I), a scheme which avoided acid was employed. This method involved iodination of the activated oxalyl acid at C_{21} in a mildly alkaline medium and cleavage to the 21-iodo compound.[3] In addition to furnishing a method for C_{21}-halogenation that left the cyclic ketal and unsaturation in rings AB intact, this procedure provided an intermediate carboxylic acid suitable for resolution by alkaloid salt formation.

Preparation of the required Δ^5-3-ethylenedioxypregnene-11,20-dione-21-oxalyl acid (*dl*-II) was accomplished in high yield by condensing *dl*-I with methyl oxalate in the presence of sodium methoxide followed by a mild alkaline saponification of the reaction product. From this point, the acid *dl*-II was either carried through to cortisone as racemic material or was converted to the dextrorotatory steroid *via* the strychnine salt.

The 21-oxalyl acid *dl*-II with an equimolar quantity of strychnine in acetone solution precipitated a mixture of diastereoisomeric strychnine salts in good yield. Upon treatment of this mixture with hot ethyl acetate, the *d*-steroid salt remained as the less soluble component. A single recrystallization from ethyl acetate provided the pure diastereoisomer[4] in 25% yield (theory 50%). Recovery of the optically active acid from its strychnine salt was carried out in buffered acid solution to prevent hydrolytic cleavage of the 3-dioxolane. The pure acid was not isolated under these conditions, apparently because of partial cleavage of the β-diketone function. Treatment of the crude recovered acidic and neutral material with potassium bicarbonate cleaved the remaining oxalyl acid and provided the 3-ethylenedioxy derivative of 11-ketoprogesterone (I), identical by melting point, mixed melting point, rotation and infrared spectra with a sample prepared from natural sources.[5] Acid hydrolysis gave 11-ketoprogesterone with the same melting point and infrared spectrum as an authentic specimen.

The Δ^5-3-ethylenedioxy-21-oxalylpregnene-11,20-dione (II) was prepared by condensation of I with methyl oxalate as in the racemic series. Iodination of this acid was carried out in a two-phase buffered medium; the addition of alkali effected cleavage of the intermediate (not isolated) iodo oxalyl acid. The resulting crystalline 21-iodopregnene (III) with potassium acetate in acetone gave the 3-dioxolane of dehydrocorticosterone acetate (IV), identical with an authentic sample.[5]

Introduction of the 17α-hydroxyl group was accomplished by the cyanohydrin method.[6] The 20-cyanohydrin of IV crystallized from an ethylene dichloride–ether solution of IV containing hydrogen cyanide and triethylamine.[7] Phosphorus oxychloride in pyridine was used to dehydrate the 20-cyanohydrin and provide $\Delta^{5,17}$-20-cyano-3-ethylenedioxypregnadiene-21-ol-11-one acetate (V) in good yield.

The best method for selective hydroxylation of the 17,20-double bond proved to be oxidation with potassium permanganate.[8] Thus the reaction of V with potassium permanganate in acetone solution followed by alkaline hydrolysis of the resulting 20-cyanohydrin (not isolated) led to the 3-dioxolane of cortisone acetate[5] (VI) in good yield. Acid hydrolysis of VI removed the 3-dioxolane which had been

(1) W. F. Johns, R. M. Lukes and L. H. Sarett, THIS JOURNAL, **76**, 5026 (1954).

(2) See for example T. H. Kritchevsky, D. L. Garmaise and T. F. Gallagher, *ibid.*, **74**, 483 (1952); P. L. Julian, E. W. Meyer, W. J. Karpel and I. R. Waller, *ibid.*, **72**, 5145 (1950); J. Pataki, G. Rosenkranz and C. Djerassi, *ibid.*, **74**, 5615 (1952).

(3) H. Ruschig, *Angew. Chem.*, **60A**, 247 (1948).

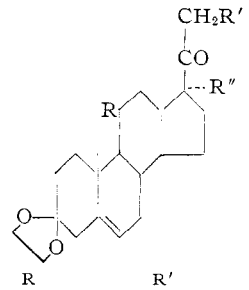
(4) The resolution was facilitated considerably by the availability of dextrorotatory Δ^5-3-ethylenedioxypregnene-11,20-dione (ref. 5) which was converted to the 21-oxalyl acid. Various alkaloids were combined with this optically active acid and nicely crystalline brucine and strychnine salts were obtained. The racemic acid was combined first with brucine which gave an inseparable salt mixture, and led to the successful use of strychnine.

(5) J. M. Constantin, A. C. Haven and L. H. Sarett, THIS JOURNAL, **75**, 1716 (1953).

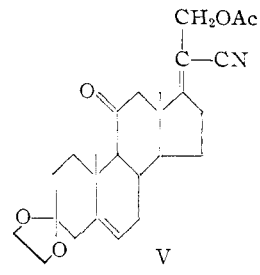
(6) L. H. Sarett, *ibid.*, **70**, 1454 (1948).

(7) Unpublished procedure of Drs. R. Tull, V. S. Frank and K. Pfister of these laboratories.

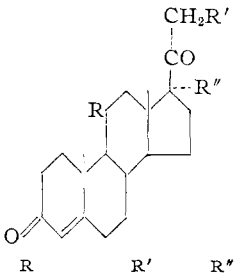
(8) U. S. Patent 2,597,190, May 20, 1952; von J. Heer and K. Miescher, *Helv. Chim. Acta*, **34**, 359 (1951). The experimental procedure is that of R. Tull, R. E. Jones, S. A. Robinson and M. Tishler, THIS JOURNAL, **76**, in press (1954).



	R	R′	R″
I, O=		H	H
II, O=		$COCO_2H$	H
III, O=		I	H
IV, O=		OAc	H
VI, O=		OAc	OH
VIII, O=		$COCO_2CH_3$	H
X, OH(β)		OAc	H



V



	R	R′	R″
VII, O=		OAc	OH
IX, O=		OH	H
XI, OH(β)		OAc	H

retained since the early tricyclic stages and afforded cortisone acetate (VII). Identity was confirmed by melting point, mixed melting point and rotation.

Preparation of the racemic steroids was carried out in essentially the same manner as described above for the optically active compounds. A variation in the procedure for the preparation of 21-iodo derivatives such as *dl*-III involved isolation of the oxalyl ester *dl*-VIII which was iodinated and cleaved in cold methanolic sodium methoxide.[9] Racemic dehydrocorticosterone acetate 3-dioxolane obtained from *dl*-III by potassium acetate treatment had the same infrared solution spectrum as IV. Acid hydrolysis of *dl*-IV yielded *dl*-dehydrocorticosterone acetate and saponification of the latter gave racemic dehydrocorticosterone (*dl*-IX).

Application of this 21-acetoxylation sequence to the 3-ethylenedioxy derivative of *dl*-11β-hydroxyprogesterone[1] provided *dl*-corticosterone acetate 3-dioxolane (*dl*-X) which was converted to racemic corticosterone acetate (*dl*-XI) by acid hydrolysis. The infrared spectrum of *dl*-corticosterone acetate in chloroform was identical with that of natural corticosterone acetate.

Introduction of the 17-hydroxyl group into the 3-dioxolane of *dl*-dehydrocorticosterone acetate by the cyanohydrin route was carried out smoothly in high yield. In general the racemic materials were somewhat less soluble than the corresponding optically active compounds, a property which facilitated isolation. The 3-ethylenedioxy derivative of *dl*-cortisone acetate (*dl*-VI) had the same infrared spectrum[10] as a sample prepared from cortisone acetate.[5] Racemic cortisone acetate, from the hydrolysis of *dl*-VI, proved to be considerably less soluble than the natural material. Due to this insolubility it was not possible to obtain a suitable solution spectrum for comparison with natural cortisone acetate. Spectra of specially prepared amorphous samples of the two materials were obtained for a satisfactory confirmation of identity.

It was of interest to test the biological activity of *dl*-cortisone acetate. In its ability to produce glycogen deposition in the rat liver, racemic cortisone acetate proved to be about one-half as active as the natural hormone.[11] The optically inactive cortisone acetate was also examined for granuloma-inhibiting properties by a modification of the cotton pellet technique of Meier, *et al.*[12] When applied locally to the pellet, it had an appreciably greater inhibiting effect on granuloma formation than did cortisone acetate.[13] In general, the more insoluble esters of cortisone show the highest degree of activity in this test; the marked insolubility of *dl*-cortisone acetate may account for its high activity.

Experimental[14]

***dl*-Δ⁵-3-Ethylenedioxypregnene-11,20-dione-21-oxalyl Acid (*dl*-II).**—Three grams of the 3-ethylenedioxy derivative of *dl*-11-ketoprogesterone (*dl*-I) was added to a mixture of 3.6 g. of methyl oxalate, 1.5 g. of dry sodium methoxide (prepared by evaporating methanolic sodium methoxide to dryness and heating the solid residue at 100° under vacuum) and 25 ml. of benzene. The resulting homogeneous solution was allowed to stand at room temperature overnight and poured into a mixture of ice and 15 ml. of 2 *M* phosphoric acid overlayered with ether. After thorough mixing, the organic layer was separated, the aqueous phase was extracted with ether and the combined ether solution was extracted with 100 ml. of 1 *N* aqueous potassium hydroxide. The resulting emulsion slowly clarified as a solid phase dissolved (1.5 hours). The alkaline extract was cooled with ice, acidified with phosphoric acid and extracted three times with ether. Evaporation of the ether left a crystalline residue of 3.47 g.; recrystallization from ether afforded 3.20 g. (89%) of *dl*-II. The analytical sample melted at 174–177° (dec.) after recrystallization from dilute alcohol and ether.

Anal. Calcd. for $C_{25}H_{32}O_7$: C, 67.55; H, 7.26. Found: C, 67.36; H, 7.08.

Resolution of *dl*-II.—A mixture of 445 mg. of *dl*-Δ⁵-3-ethylenedioxypregnene-11,20-dione-21-oxalyl acid (*dl*-II) and 334 mg. of strychnine was dissolved in 15 ml. of boiling acetone. As the solution cooled a mixture of strychnine salts, 641 mg., dec. 168–175°, precipitated. Part of the acetone was evaporated from the mother liquor providing second and third crops of the salt mixture; total yield 742 mg., 96%. The salt mixture, 742 mg., was suspended in 9 ml. of ethyl acetate and heated to boiling. All of the solid dissolved and on continued boiling, the very insoluble strychnine salt of Δ⁵-3-ethylenedioxypregnene-11,20-dione-21-oxalyl acid, 205 mg., dec. 205–210° (darkens 190°) separated. Recrystallization of the 205–210° material from ethyl acetate resulted in a sample dec. 215–221°, $[\alpha]^{28}D$ 0 ± 2° (*c* 1, tetrahydrofuran) identical with the strychnine salt prepared from Δ⁵-3-ethylenedioxypregnene-11,20-dione-21-oxalyl acid.

Anal. Calcd. for $C_{46}H_{54}N_2O_9$: C, 70.93; H, 6.99; N, 3.60. Found: C, 71.45; H, 6.84; N, 3.21.

Three hundred milligrams of the strychnine salt of II prepared from *dl*-II was suspended in 25 ml. of water containing 2.0 g. of sodium dihydrogen phosphate and 0.1 ml. of 5 *N* sulfuric acid. This mixture was extracted with five 25-

(9) H. Ruschig, U. S. Patent 2,609,379, Sept. 2, 1952.

(10) In this case, the spectra of the crystalline solids were the same. The racemic material was considerably more soluble than the optically active steroid indicating that *dl*-VI is most probably a racemic mixture. The other *dl*-steroids described in this paper would seem to be racemic compounds from the solubility characteristics and from the fact that only the infrared *solution* spectra were identical.

(11) Tests were carried out by Drs. R. H. Silber and C. C. Porter of the Merck Institute for Therapeutic Research.

(12) R. Meier, W. Schuler and P. Desaulles, *Experientia*, **6**, 469 (1950).

(13) Test performed by Dr. C. A. Winter of the Merck Institute for Therapeutic Research.

(14) All melting points were determined on a Kofler micro hotstage. Ultraviolet spectra were measured in methanol solution and infrared spectra are of the crystalline solids in Nujol.

ml. portions of ether over a half-hour period, each ether extract being washed with water until neutral. The combined ether extracts were dried and evaporated to dryness *in vacuo*. The crude product, 167 mg., $[\alpha]^{25}D$ +46 ± 2° (*c* 1, tetrahydrofuran) failed to crystallize readily and was subjected to alkaline cleavage without purification.

A suspension of this alkaloid-free residue in 10 ml. of 10% aqueous potassium bicarbonate was heated at 100° for one-half hour. The crystalline precipitate which formed was extracted into ether. Evaporation of the ether left 74 mg. of a crystalline residue which was adsorbed on 2 g. of acid-washed alumina. Elution with 1:1 ether–petroleum ether provided Δ^5-3-ethylenedioxypregnene-11,20-dione, m.p. and mixed m.p. 175–176.5°, $[\alpha]^{25}D$ +53 ± 2° (*c* 1, $CHCl_3$) after recrystallization from benzene–petroleum ether.

Anal. Calcd. for $C_{23}H_{32}O_4$: C, 74.16; H, 8.66. Found: C, 74.37; H, 8.45.

A 40-mg. sample of this Δ^5-3-ethylenedioxypregnene-11,20-dione and 10 mg. of *p*-toluenesulfonic acid hydrate in 4 ml. of acetone was heated under reflux for 45 minutes. Most of the acetone was removed *in vacuo*. Water was added and the product was extracted into chloroform. The extract was washed once with water, dried over sodium sulfate, and the solvent evaporated. The residue was crystallized from ether–petroleum ether, m.p. and mixed m.p. 177–178°, $[\alpha]^{23}D$ 231° ± 2° (*c* 0.50, $CHCl_3$). The infrared spectrum of this product was identical with that of authentic 11-ketoprogesterone.

Anal. Calcd. for $C_{21}H_{28}O_3$: C, 76.76; H, 8.59. Found: C, 77.21; H, 8.76.

Δ^5-3-Ethylenedioxypregnene-11,20-dione-21-oxalyl Acid (II).—The procedure described above for the preparation of *dl*-II was used to convert 2.50 g. of Δ^5-3-ethylenedioxypregnene-11,20-dione to the corresponding 21-oxalyl acid; 2.92 g. (100%), dec. 176–185° from ether. A sample recrystallized from tetrahydrofuran–ether had melting point 183–185° (dec.), $[\alpha]^{25}D$ +61° ± 2° (*c* 0.87, $CHCl_3$).

Anal. Found: C, 67.71; H, 7.17.

The brucine salt was prepared in acetone and after two recrystallizations from acetone melted at 175–180° (dec.), $[\alpha]^{25}D$ 0 ± 1° (*c* 1.00, tetrahydrofuran)

The strychnine salt recrystallized twice from ethyl acetate had m.p. 215–216° (dec.), $[\alpha]^{25}D$ −2 ± 1° (*c* 1.00, tetrahydrofuran).

Δ^5-3-Ethylenedioxypregnene-21-ol-11,20-dione Acetate (IV).—A solution of 1.80 g. of II in 450 ml. of water containing 20 g. of disodium hydrogen phosphate was overlayered with ether and treated dropwise with stirring with a solution of 1.05 g. of iodine in 100 ml. of ether. After the addition of the iodine solution was completed (45 minutes), a solution of 1 g. of potassium hydroxide in 30 ml. of water was added and the reaction mixture was stored in the refrigerator overnight. The ether layer was separated and the aqueous phase was extracted twice with ether. After washing and drying, the combined ethereal extract was concentrated to a small volume and the resulting crystalline 21-iodo derivative III was collected; 910 mg., dec. 75–90°.

The unstable iodo compound (910 mg.) was combined in 70 ml. of acetone with moist potassium acetate freshly prepared from 6 g. of potassium bicarbonate and 3.5 ml. of acetic acid. The reaction mixture was boiled for one hour and then concentrated *in vacuo* to low volume. Treatment of the residue with methanol–water gave 720 mg. of a crude crystalline precipitate, m.p. 183–191°. The entire product was chromatographed over 20 g. of acid-washed alumina. With benzene there were first eluted mixtures containing I, followed by 668 mg. (40% from II) of Δ^5-3-ethylenedioxypregnene-21-ol-11,20-dione acetate, m.p. 191–193°. Recrystallization from acetone–petroleum ether afforded material with m.p. 193.5–194°, $[\alpha]^{25}D$ +52° (*c* 1.39, $CHCl_3$); $\lambda_{max.}$ 5.71, 5.77, 5.86 μ.

Anal. Calcd. for $C_{25}H_{34}O_6$: C, 69.74; H, 7.96. Found: C, 70.02; H, 7.65.

The melting point was not depressed on admixture with authentic IV.[5]

20-Cyanohydrin of Δ^5-3-Ethylenedioxypregnene-21-ol-11,20-dione Acetate.—One milliliter of liquid hydrogen cyanide was added to a solution of 1.30 g. of the 3-dioxolane of 11-dehydrocorticosterone acetate (IV) in 8 ml. of chloroform followed by 0.2 ml. of triethylamine and 5 ml. of ether. After four hours, an additional 10 ml. of ether was added and the crystalline cyanohydrin was collected on a filter and washed with ether; 1.12 g. (80%), dec. 205–215°. Recrystallization from chloroform–ether afforded a sample which decomposed at 220–224°.

Anal. Calcd. for $C_{26}H_{35}O_6N$: C, 68.24; H, 7.72; N, 3.06. Found: C, 68.17; H, 7.63; N, 3.33.

$\Delta^{5,17}$-20-Cyano-3-ethylenedioxypregnadiene-21-ol-11-one Acetate (V).—A solution of 1.10 g. of the 20-cyanohydrin of IV in 6 ml. of pyridine was treated with 0.6 ml. of phosphorus oxychloride and allowed to stand at room temperature overnight. The reaction mixture was quenched with ice and water and the resulting crystalline precipitate was collected, washed with water and dried; 1.05 g. Recrystallization from aqueous pyridine afforded 877 mg. (83%) of V, m.p. 197–200°. The analytical sample melted at 202–203° after recrystallization from ethanol and ethyl acetate; $[\alpha]^{25}D$ −42 ± 2° (*c* 1.14, $CHCl_3$).

Anal. Calcd. for $C_{26}H_{33}O_5N$: C, 71.05; H, 7.57; N, 3.08. Found: C, 71.67; H, 7.81; N, 3.63.

3-Ethylenedioxy Derivative of Cortisone Acetate (VI).—Powdered potassium permanganate (94 mg.) was added to an ice-cold, stirred solution of 102 mg. of the unsaturated nitrile V in 3.5 ml. of acetone containing 0.11 ml. of piperidine. The reaction mixture was stirred at 0° for 1.5 hours, allowed to warm to room temperature (30 minutes) and then was treated with 0.02 ml. of acetic acid in 0.2 ml. of acetone. After stirring at room temperature for an additional 1.5 hours the mixture was treated with chloroform, aqueous sodium bisulfite and sufficient 1 *N* sulfuric acid to reduce all of the manganese dioxide. The separated aqueous layer was extracted with chloroform and the combined chloroform solution was washed with water and evaporated to a volume of 10 ml. *in vacuo*. Ten milliliters of 5% aqueous potassium carbonate was added and the mixture was stirred one hour at room temperature. The chloroform was distilled under reduced pressure and the resulting crystalline product was filtered, washed with water and methanol and dried; 82 mg. (79%), m.p. 248–260° dec. Recrystallization from pyridine–methanol gave a sample melting at 262–267° (dec.) The melting point was not lowered by mixture with an authentic sample[5] of VI and the infrared spectra proved to be identical.

Cortisone Acetate (VII).—Fifty milligrams of cortisone acetate-3-dioxolane (VI) in 3 ml. of acetone containing 30 mg. of *p*-toluenesulfonic acid hydrate was boiled for 15 minutes. Upon cooling the solution and diluting with water, crystalline cortisone acetate separated; 43 mg., m.p. 238–244°. Recrystallization from ethanol afforded a sample melting at 239–244°, $[\alpha]D$ +210 ± 2° (*c*, 1.00, $CHCl_3$). The melting point was not depressed on admixture with authentic cortisone acetate.

Anal. Calcd. for $C_{23}H_{30}O_6$: C, 68.63; H, 7.51. Found: C, 68.79; H, 7.28.

***dl*-Δ^5-3-Ethylenedioxy-21-iodopregnene-11,20-dione (*dl*-III).**—This compound was prepared from the oxalyl acid (*dl*-II) by iodination in disodium hydrogen phosphate solution followed by cleavage with sodium hydroxide as described above for III. From 2.36 g. of *dl*-II there was obtained 1.40 g. (53%) of crystalline *dl*-III, dec. 85–100°.

An alternate procedure involving the oxalyl ester was also employed. A solution of 3.04 g. of racemic 11-ketoprogesterone-3-dioxolane (*dl*-I), 3.60 g. of methyl oxalate and 1.33 g. of dry sodium methoxide (prepared as described under *dl*-II) in 50 ml. of benzene was kept at room temperature overnight. A mixture of 50 ml. of chloroform and 50 ml. of water containing 10 g. of sodium dihydrogen phosphate was added with mixing, the organic phase was withdrawn and the aqueous part was extracted with chloroform. The combined extracts were dried and evaporated to dryness *in vacuo*. The crystalline residue was warmed under high vacuum until no more methyl oxalate sublimed and was then slurried with cold ether and collected on a filter affording 3.64 g. (98%) of the methyl ester of *dl*-Δ^5-3-ethylenedioxypregnene-11,20-dione-21-oxalyl acid (*dl*-VIII), m.p. 153–156°.

A suspension of 3.53 g. of the oxalyl ester *dl*-VIII in 60 ml. of absolute methanol was cooled to 0° and with rapid stirring treated in succession with 4.00 ml. of 1.90 *N* methanolic sodium methoxide and a solution of 1.93 g. of iodine in 50 ml. of absolute methanol. The resulting yellow solution was stirred at 0° for ten minutes and then treated

dropwise with 4.08 ml. of 1.90 *N* methanolic sodium methoxide whereupon the color was discharged and crystals began to separate. After 0.5 hour at 0°, about half the methanol was distilled under vacuum and the product was collected on a filter, washed with methanol and dried; 2.62 g. (68%) of *dl*-III, dec. 85–100°.

dl-**Δ⁵-3-Ethylenedioxypregnene-21-ol-11,20-dione Acetate** (*dl*-**IV**).—Reaction of 1.40 g. of *dl*-III in acetone with potassium acetate, freshly prepared from 9 g. of potassium bicarbonate and 5.4 ml. of acetic acid, provided 990 mg. of crude crystalline product which was chromatographed over 70 g. of acid-washed alumina. The benzene–ether fractions gave crystalline mixtures of *dl*-I and *dl*-IV followed by 700 mg. (58%) of pure *dl*-IV, m.p. 192–194°; $\lambda_{max.}$ 5.75, 5.80, 5.90 μ; infrared solution spectrum ($CHCl_3$) identical with that of IV.

Anal. Found: C, 69.87; H, 7.68.

dl-**Dehydrocorticosterone** (*dl*-**IX**).—Fifty milligrams of *dl*-IV was dissolved in 2 ml. of tetrahydrofuran and 1 ml. of 3 *M* perchloric acid and the solution was allowed to stand for three hours. It was diluted with 5 ml. of water and extracted three times with ether. The combined extracts were evaporated and the residue was taken up in 3 ml. of methanol. Two milliliters of 1 *M* potassium bicarbonate was added, the mixture was boiled for ten minutes and then was diluted with 5 ml. of water. Extraction with ether, concentration of the extract and crystallization from ether afforded 25 mg. of *dl*-dehydrocorticosterone (*dl*-IX), m.p. 173–179°; $\lambda_{max.}$ 238 mμ, ϵ_{mol} 14,700; $\lambda_{max.}^{CHCl_3}$ 2.90, 5.85, 6.01, 6.17 μ.

Anal. Calcd. for $C_{21}H_{28}O_4$: C, 73.23; H, 8.19. Found: C, 72.97; H, 8.11.

dl-**Δ⁵-3-Ethylenedioxypregnene-11β,21-diol-20-one 21-Acetate** (*dl*-**X**).—A mixture of 0.14 g. of dry sodium methoxide, 50 ml. of benzene, 1.80 g. of methyl oxalate and 1.50 g. of *dl*-11β-hydroxyprogesterone 3-dioxolane[1] was left at room temperature overnight and then treated with aqueous sodium dihydrogen phosphate and chloroform as described for the preparation of *dl*-VIII. The resulting non-crystalline oxalyl ester was iodinated with 0.75 g. of iodine in 75 ml. of methanol containing 4 mmoles of methanolic sodium methoxide and cleaved with 8 mmoles of methanolic sodium methoxide as described in the procedure for the preparation of *dl*-III. In this case the reaction mixture was diluted with water and stored at 0° overnight. The crystalline material which precipitated was collected and was then boiled for 1.5 hours in 100 ml. of acetone with potassium acetate freshly prepared from 9 g. of potassium bicarbonate and 5.4 ml. of acetic acid. The mixture was diluted with 200 ml. of water, extracted with ether and chloroform and the combined extracts were evaporated to dryness under vacuum. Chromatography of the resulting 700 mg. of residue over 60 g. of acid-washed alumina afforded 100 mg. of *dl*-X from the ether eluates; m.p. 205–209°; $\lambda_{max.}$ 2.85, 5.75, 5.85 μ.

Anal. Calcd. for $C_{25}H_{36}O_6$: C, 69.42; H, 8.39. Found: C, 69.75; H, 8.22.

dl-**Corticosterone 21-Acetate** (*dl*-**XI**),—Sixty milligrams of *dl*-X and 15 mg. of *p*-toluenesulfonic acid in 2 ml. of acetone was boiled for 15 minutes. Dilution with water precipitated 49 mg. of *dl*-corticosterone 21-acetate (*dl*-XI), m.p. 210–215°; $\lambda_{max.}$ 241 mμ, ϵ_{mol} 15,700; $\lambda_{max.}$ 3.0, 5.76, 5.80, 6.09, 6.21 μ; infrared solution spectrum ($CHCl_3$) identical with that of authentic corticosterone acetate.

Anal. Calcd. for $C_{23}H_{32}O_5$: C, 71.10; H, 8.30. Found: C, 71.18; H, 7.95.

20-Cyanohydrin of *dl*-**Δ⁵-3-Ethylenedioxypregnene-21-ol-11,20-dione Acetate.**—Within one minute after the addition of 3 drops of triethylamine and 0.4 ml. of hydrogen cyanide to a solution of 496 mg. of *dl*-IV in 4 ml. of ethylene dichloride and 4 ml. of ether, crystals of *dl*-IV-20-cyanohydrin began to separate. After 15 minutes 5 ml. of ether was added and at the end of 2.5 hours the solution was diluted to 50 ml. with ether. The product was collected and washed with ether; 498 mg. (94%), dec. 218–222°. A sample recrystallized from chloroform–ether decomposed at 220–224°.

Anal. Found: C, 68.51; H, 8.00; N, 3.53.

dl-**Δ⁵,¹⁷-20-Cyano-3-Ethylenedioxypregnadiene-21-ol-11-one Acetate** (*dl*-**V**).—A slurry of the 20-cyanohydrin of *dl*-IV (484 mg.) in 2.6 ml. of pyridine containing 0.26 ml. of phosphorus oxychloride slowly became homogeneous and deposited pyridine hydrochloride. After 20 hours at room temperature, the mixture was diluted with ice-water and extracted with chloroform. Concentration of the washed extract and crystallization from ether afforded 450 mg. (97%) of *dl*-V, m.p. 173–178°. Recrystallization from methanol raised the melting point to 180–183°.

Anal. Found: C, 71.49; H, 7.30.

3-Ethylenedioxy Derivative of *dl*-**Cortisone Acetate** (*dl*-**VI**).—A solution of 357 mg. of *dl*-V in 12 ml. of acetone containing 0.39 ml. of piperidine was treated with 329 mg. of potassium permanganate and then 0.07 ml. of acetic acid as described for V. The work-up cyanohydrin reversal and isolation of product followed the same procedure as for VI. There was obtained 322 mg. (89%) of *dl*-VI melting at 245–250°. For analysis a sample was recrystallized from ethanol, ethyl acetate and acetone; m.p. 250–256°; infrared spectrum of crystalline solid identical with that of cortisone acetate 3-dioxolane.

Anal. Calcd. for $C_{25}H_{34}O_7$: C, 67.25; H, 7.68. Found: C, 67.66; H, 7.20.

dl-**Cortisone Acetate** (*dl*-**VII**).—To 10 ml. of acetone was added 225 mg. of *dl*-VI and 70 mg. of *p*-toluenesulfonic acid. The resulting suspension was heated under reflux and after ten minutes all of the starting compound had dissolved. After 20 minutes, the solution was cooled and diluted with water, whereupon 196 mg. (96.5%) of *dl*-cortisone acetate separated as glistening platelets, m.p. 225–231°. Recrystallization from ethanol, chloroform and acetone gave m.p. 240–245°; $\lambda_{max.}$ 238 mμ, ϵ_{mol} 15,500; $\lambda_{max.}$ 2.9–2.95, 3.05, 5.76, 5.80, 5.89, 6.07, 6.20 μ.

Anal. Found: C, 68.89; H, 7.47.

A sample of *dl*-cortisone acetate under high vacuum was heated above its melting point and the melt was cooled rapidly. The resulting glass was powdered and its infrared spectrum was determined. This spectrum proved to be essentially the same as that obtained from a sample of authentic cortisone acetate which had been treated in a similar fashion.

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