[JOINT CONTRIBUTION FROM THE INSTITUTO DE QUIMICA DE LA UNIVERSIDAD NACIONAL AUTONOMA DE MEXICO AND THE RESEARCH LABORATORIES OF SYNTEX, S. A.]

# Steroids. LXXXVIII.[1] A New Synthesis of Desoxycorticosterone Acetate and of 16-Dehydro-desoxycorticosterone Acetate

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$\Delta^{5,16}$-Pregnadien-3$\beta$-ol-20-one acetate (Ia), the degradation product of diosgenin, has been converted to 16-dehydro-desoxycorticosterone acetate (VII) and to desoxycorticosterone acetate (IX) by the routes indicated in the flow sheet.

Recently there has been described a method for converting a $\Delta^{16}$-20-ketopregnene derivative to the corresponding $\Delta^{16}$-20-keto-21-acetoxy compound and hence by hydrogenation to a substance containing the 20-keto-21-acetoxy grouping characteristic of desoxycorticosterone acetate.[3] The route involves the conversion of the $\Delta^{16}$-20-ketone to the enol acetate (the 20-acetoxy-$\Delta^{16,20}$-diene),[4] followed by treatment with N-iodosuccinimide and replacement of the iodine in the resulting 21-iodo-$\Delta^{16}$-20-ketone with acetate by means of potassium acetate.[5] The method has not been used for the synthesis of substances with the desoxycorticosterone acetate side-chain containing also the important $\Delta^4$-3-ketone grouping present in most steroidal hormones. On the one hand, if the starting material already contains the $\Delta^4$-3-ketone, as in 16-dehydroprogesterone, enol acetylation of the 20-keto group cannot be brought about selectively.[6] On the other hand, if the reaction is carried out with a 3$\beta$-acetoxy-$\Delta^5$-compound, a 3,21-diacetate is obtained which must then be hydrolyzed and selectively re-esterified at C-21 before the $\Delta^4$-3-keto group can be introduced by Oppenauer oxidation.

It recently has been shown[7] that the $\Delta^5$-3$\beta$-ol grouping may be protected conveniently as the formate when operations are to be performed on the side-chain and that the $\Delta^5$-3$\beta$-ol formate may subsequently be oxidized directly by the Oppenauer method to the $\Delta^4$-3-one. The present paper describes a new synthesis of desoxycorticosterone acetate (IX) and of 16-dehydro-desoxycorticosterone acetate (VII) by a combination of this formate protection procedure with the N-iodosuccinimide method of introducing a 21-acetoxy group.

The starting material was $\Delta^{5,16}$-pregnadien-3$\beta$-ol-20-one acetate (Ia), a substance very readily obtained in high yield by the side chain degradation of diosgenin. Saponification of the acetate grouping has been effected conveniently by means of potassium hydroxide in aqueous *t*-butyl alcohol.[8] The resulting ketol Ib was heated with 85% formic acid and the 3-formate II thus produced was boiled with isopropenyl acetate in the presence of *p*-toluenesulfonic acid. This method of converting a $\Delta^{16}$-20-ketone to its enol acetate[4] did not affect the 3-formate grouping to any great extent, and the crystalline $\Delta^{5,16,20}$-pregnatriene-3$\beta$,20-diol 3-formate 20-acetate (III) was obtained. Treatment with N-iodosuccinimide in dioxane[3] yielded the 21-iodo-$\Delta^{16}$-20-ketone IV with its typical ultraviolet maximum at 250 m$\mu$, which with potassium acetate in acetone furnished the mixed di-ester, $\Delta^{5,16}$-pregnadiene-3$\beta$,21-diol-20-one 3-formate 21-acetate (V). This compound was now subjected to the Oppenauer oxidation in boiling xylene,[7] whereby 16-dehydrodesoxycorticosterone acetate (VII) was formed directly in one step. Alternatively, the formate grouping of the mixed di-ester V could be saponified preferentially with hydrochloric acid in dioxane and the resulting 21-monoacetate VI oxidized under the conventional Oppenauer oxidation conditions. The hormone analog VII showed physical properties in good agreement with those reported for 16-dehydrodesoxycorticosterone acetate obtained by methods[9,10] more involved than the one described in this paper.

For the synthesis of desoxycorticosterone acetate (IX), it is necessary in principle only to hydrogenate the $\Delta^{16}$-double bond of the dehydro derivative VII. However, in practice it was not possible to carry out this preferential hydrogenation, which had to be performed at the previous stage. The $\Delta^{16}$-double bond in $\Delta^{5,16}$-pregnadiene-3$\beta$,21-diol-20-one 3-formate 21-acetate (V) is considerably more reactive toward hydrogen than the $\Delta^5$-bond and hydrogenation of V over palladium–charcoal in ethyl acetate solution smoothly produced $\Delta^5$-pregnene-3$\beta$,21-diol-20-one 3-formate 21-acetate (VIIIa). The structure of this compound was confirmed through partial saponification by chromatography on alkaline alumina to the known 21-monoacetate VIIIb.[11] Finally, Oppenauer oxidation of the mixed di-ester VIIIa in boiling xylene again effected the conversion of the $\Delta^5$-3$\beta$-ol formate grouping to the $\Delta^4$-3-one and led to desoxycorticosterone acetate (IX), identical with the natural hormone.

(1) Steroids LXXXVII, see F. A. Kincl, H. J. Ringold and G. Rosenkranz, *J. Org. Chem.*, **22**, in press (1957).

(2) Weizmann Institute of Science, Rehovoth, Israel.

(3) C. Djerassi and C. T. Lenk, THIS JOURNAL, **76**, 1722 (1954).

(4) R. B. Moffett and D. I. Weisblat, *ibid.*, **74**, 2183 (1952).

(5) Alternatively, in order to obtain the saturated 21-acetoxy-20-ketone, the $\Delta^{16}$-20-ketone may first be hydrogenated and the resulting saturated ketone subjected to enol acetylation and then to treatment with N-iodosuccinimide and potassium acetate (C. Djerassi and C. T. Lenk, *ibid.*, **75**, 3493 (1953)). This method, however, is inferior since the yield in the iodination step is poorer in the case of the enol acetate derived from a saturated 20-ketone than from a $\Delta^{16}$-20-ketone.

(6) A possible way of avoiding this difficulty is to prepare the dienol acetate of 16-dehydroprogesterone or of progesterone and then to carry out a preferential reaction at C-6 (*cf.* C. Djerassi, J. Grossman and G. H. Thomas, *ibid.*, 3826 (1955)).

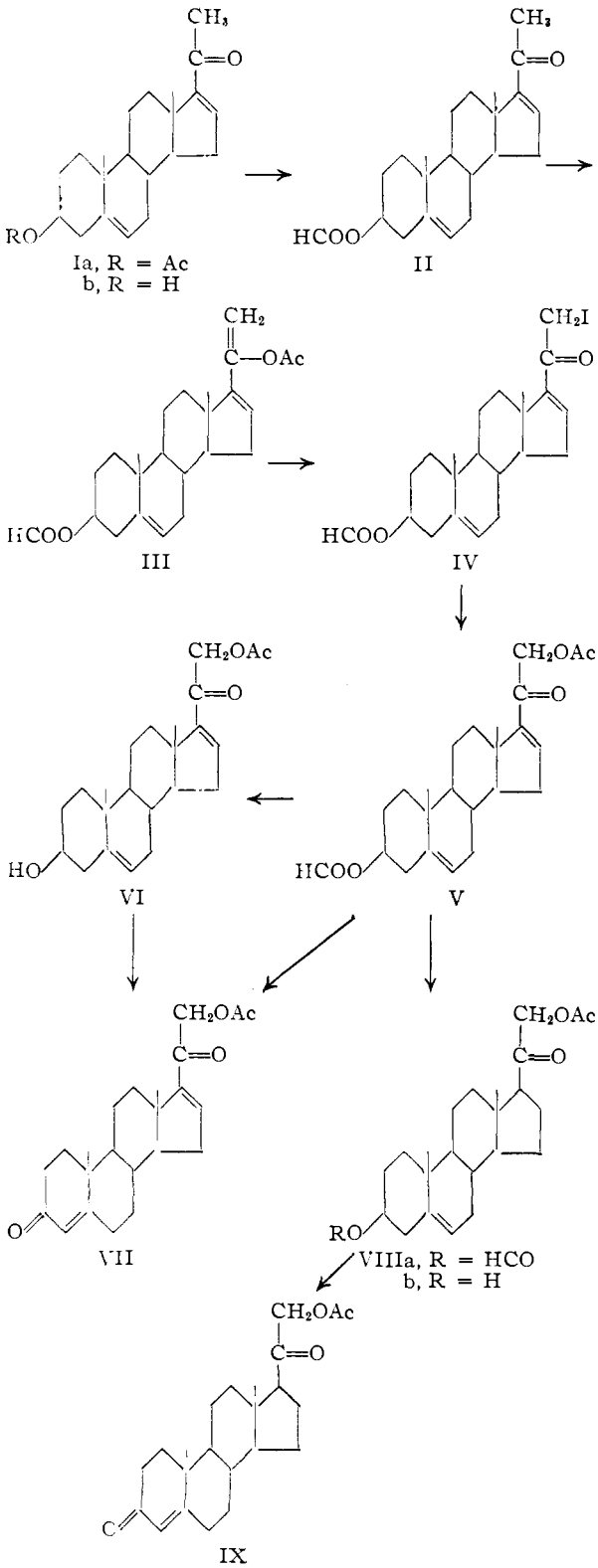
(7) H. J. Ringold, B. Löken, G. Rosenkranz and F. Sondheimer, *ibid.*, **78**, 816 (1956); H. J. Ringold, G. Rosenkranz and F. Sondheimer, *ibid.*, **78**, 820 (1956).

(8) M. E. Wall, H. E. Kenney and E. S. Rothman, *ibid.*, **77**, 5665 (1955).

(9) W. Cole and P. L. Julian, *J. Org. Chem.*, **19**, 131 (1954).

(10) W. S. Allen and S. Bernstein, THIS JOURNAL, **77**, 1028 (1955).

(11) M. Steiger and T. Reichstein, *Helv. Chim. Acta*, **20**, 1164 (1937).




## Experimental[12]

**$\Delta^{5,16}$-Pregnadien-3$\beta$-ol-20-one Formate (II).**—A mixture of 20 g. of $\Delta^{5,16}$-pregnadien-3$\beta$-ol-20-one (Ib)[9] and 250 cc. of 85% formic acid was heated to *ca.* 80° for 1 hour, with stirring. The clear violet solution was poured onto ice and the precipitate was collected and washed well with water. The dried product on crystallization from chloroform–methanol produced 15.3 g. (70%) of the formate II, m.p. 173–175°. The analytical sample showed m.p. 175–177°, $[\alpha]_D$ −40°, $\lambda_{max}$ 238 m$\mu$, log $\epsilon$ 4.05, $\nu_{max}$ 1718 and 1660 cm.$^{-1}$.

*Anal.* Calcd. for $C_{22}H_{30}O_3$: C, 77.15; H, 8.83. Found: C, 77.25; H, 9.13.

**$\Delta^{5,16,20}$-Pregnatriene-3$\beta$,20-diol 3-Formate 20-Acetate (III).**—A solution of 20 g. of the formate II and 3 g. of *p*-toluenesulfonic acid monohydrate in 400 cc. of isopropenyl acetate was distilled slowly through a 15-cm. Vigreux column for 10 hours, 200 cc. of distillate being collected during this time. The residue was diluted with ether and was then washed with sodium bicarbonate solution and water. The dried extract was evaporated, finally, under reduced pressure. Crystallization from acetone–hexane furnished 7.5 g. (33%) of the enol acetate III, m.p. 133–135°. The analytical specimen exhibited m.p. 140–142°, $[\alpha]_D$ −62°, $\lambda_{max}$ 238 m$\mu$, log $\epsilon$ 4.20, $\nu_{max}$ 1744 and 1718 cm.$^{-1}$.

*Anal.* Calcd. for $C_{24}H_{32}O_4$: C, 74.96; H, 8.39. Found: C, 75.23; H, 8.37.

**21-Iodo-$\Delta^{5,16}$-pregnadien-3$\beta$-ol-20-one Formate (IV).**—A mixture of 10 g. of the enol acetate III and 7 g. of N-iodosuccinimide in 35 cc. of dioxane was heated under nitrogen at 80° for 1 hour. The solution was then poured onto ice and water containing 3 g. of sodium bisulfite. The precipitate was collected, washed well with water, dried and crystallized from chloroform–methanol. This procedure yielded 10.2 g. (84%) of the iodo-ketone IV, m.p. 140–142° dec., $[\alpha]_D$ −53°, $\lambda_{max}$ 250 m$\mu$, log $\epsilon$ 3.96, $\nu_{max}$ 1718 and 1660 cm.$^{-1}$.

*Anal.* Calcd. for $C_{22}H_{29}IO_3$: C, 56.41; H, 6.24. Found: C, 56.53; H, 6.09.

**$\Delta^{5,16}$-Pregnadiene-3$\beta$,21-diol-20-one 3-Formate 21-Acetate (V).**—A mixture of 20 g. of potassium bicarbonate and 14 cc. of acetic acid was ground in a mortar and was then refluxed with 10 g. of the iodoketone IV in 300 cc. of acetone for 10 hours. Cold water was added and the precipitate was collected, washed well with water and dried. Crystallization from chloroform–methanol yielded 7.5 g. (88%) of the 21-acetate V, m.p. 158–160°. Further crystallization from acetone–methanol led to the analytical sample, m.p. 163–165°, $[\alpha]_D$ −35°, $\lambda_{max}$ 240 m$\mu$, log $\epsilon$ 4.10; $\nu_{max}$ 1740, 1718 and 1672 cm.$^{-1}$.

*Anal.* Calcd. for $C_{24}H_{32}O_5$: C, 71.97; H, 8.05. Found: C, 72.24; H, 8.26.

**$\Delta^{5,16}$-Pregnadiene-3$\beta$,21-diol-20-one 21-Acetate (VI).**—A solution containing 6.5 g. of the formate V, 30 cc. of distilled water, 10 cc. of concentrated hydrochloric acid and 200 cc. of dioxane was allowed to stand at room temperature for 14 hours. Water was added and the product was extracted with ethyl acetate. The dried extract was evaporated to a small volume and methanol was added. The diol monoacetate VI which crystallized weighed 5.0 g. (83%) and showed m.p. 168–170°. Crystallization from acetone–methanol produced the analytical sample, m.p. 174–176°, $[\alpha]_D$ −47°, $\lambda_{max}$ 240 m$\mu$, log $\epsilon$ 4.11; $\nu_{max}$ 1740, 1666 cm.$^{-1}$ and free hydroxyl band.

*Anal.* Calcd. for $C_{23}H_{32}O_4$: C, 74.16; H, 8.66. Found: C, 73.95; H, 8.85.

**$\Delta^{4,16}$-Pregnadien-21-ol-3,20-dione Acetate (16-Dehydrodesoxycorticosterone Acetate) (VII). (a) By Direct Oppenauer Oxidation of V.**—A solution of 7 g. of the mixed diester V in 300 cc. of xylene and 120 cc. of cyclohexanone was distilled until 20 cc. of distillate had been collected, in order to remove moisture. A solution of 6 g. of aluminum isopropoxide in 30 cc. of xylene was then added and the mixture was refluxed for 2 hours with exclusion of moisture. Ice and dilute hydrochloric acid were added, the organic layer was separated, washed with water and then distilled in steam until no more organic material passed over. The residue was diluted with ether and the resulting solution was washed with water, dried and evaporated. The resi-

(12) Melting points are uncorrected. Rotations were determined at 20° in chloroform and ultraviolet absorption spectra in 95% ethanol solution. We are indebted to Miss M. T. Cardenas for these measurements as well as for the infrared spectra, which were determined in chlororform solution with a Perkin-Elmer model 12 C single beam spectrophotometer with sodium chloride prism. We would also like to thank Mrs. A. Gonzalez for the microanalyses and Mr. I. Lerner for his skillful technical assistance.

due was chromatographed on 200 g. of neutral alumina, and the fractions eluted with benzene–hexane (3:1) and with benzene were crystallized from acetone–hexane. The resulting diketone VII weighed 3.3 g. (51%) and showed m.p. 145–148°. The analytical specimen exhibited m.p. 152–154°, $[\alpha]_D$ +146°, $\lambda_{max}$ 240 mμ, log ε 4.40, $\nu_{max}$ 1744 and 1664 cm.$^{-1}$ (Cole and Julian[9] reported m.p. 152°, $[\alpha]_D$ +148°, $\lambda_{max}$ 241 mμ, log ε 4.40; Allen and Bernstein[10] reported m.p. 153–154°, $[\alpha]_D$ +142°, $\lambda_{max}$ 238–241 mμ, log ε 4.38).

*Anal.* Calcd. for $C_{23}H_{30}O_4$: C, 74.56; H, 8.16. Found: C, 74.66; H, 8.45.

(b) **By Oppenauer Oxidation of VI.**—A solution of 4 g. of VI in 130 cc. of toluene and 50 cc. of cyclohexanone was distilled until 30 cc. had been removed, 1.5 g. of aluminum isopropoxide in 15 cc. of toluene was added and the mixture was refluxed for 45 minutes. Isolation as above followed by chromatography on neutral alumina and crystallization from acetone–hexane yielded 2.16 g. (54%) of the diketone VII, m.p. 146–149°, $\nu_{max}$ 240 mμ, log ε 4.39. Identity with the material obtained by the first route was established through non-depression in m.p. on admixture and by infrared comparison.

**$\Delta^5$-Pregnene-3β,21-diol-20-one 3-Formate 21-Acetate (VIIIa).**—A solution of 1.5 g. of the diene V in 70 cc. of ethyl acetate was shaken in hydrogen over 200 mg. of a 10% palladium–charcoal catalyst at 22° and 592 mm. After 1 hour *ca.* 1 molar equivalent of hydrogen had been taken up and absorption had almost stopped. The catalyst was removed, the solvent was evaporated and the residue was crystallized from acetone–hexane. The resulting diester VIIIa (1.24 g., 82%) showed m.p. 172–173°, $[\alpha]_D$ +32°, no high-intensity absorption in the ultraviolet, $\nu_{max}$ 1740 and 1718 cm.$^{-1}$.

*Anal.* Calcd. for $C_{24}H_{34}O_5$: C, 71.61; H, 8.51. Found: C, 71.66; H, 8.83.

**$\Delta^5$-Pregnene-3β,21-diol-20-one 21-Acetate (VIIIb).**—The mono-unsaturated diester VIIIa (200 mg.) dissolved in 30 cc. of benzene was passed five times through a column of 10 g. of alkaline alumina. Evaporation of the solvent and crystallization from acetone–hexane furnished 140 mg. (75%) of the diol monoacetate VIIIb, m.p. 183–185°; $\nu_{max}$ 1740, 1718 cm.$^{-1}$ and free hydroxyl band (Steiger and Reichstein[11] give m.p. 184–185°). The m.p. was undepressed on admixture with an authentic sample and the infrared spectra were identical.

**$\Delta^5$-Pregnen-21-ol-3,20-dione Acetate (Desoxycorticosterone Acetate) (IX).**—The Oppenauer oxidation of 800 mg. of the mono-unsaturated diester VIIIa in xylene was carried out exactly as described above for the corresponding diene V. Chromatography on alumina and crystallization from acetone–hexane yielded 380 mg. (51%) of desoxycorticosterone acetate, m.p. 155–157°, $\lambda_{max}$ 240 mμ, log ε 4.19, $\nu_{max}$ 1744, 1718 and 1660 cm.$^{-1}$. The material was identified with an authentic sample (m.p. 156–158°) in the usual way.

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[CONTRIBUTION FROM THE NEW YORK STATE AGRICULTURAL EXPERIMENT STATION, CORNELL UNIVERSITY]

# The Isolation and Identification of 3-Methyl-6-methoxy-8-hydroxy-3,4-dihydroisocoumarin from Carrots[1]

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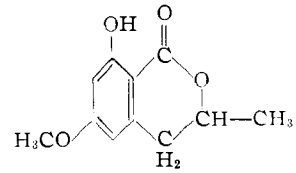
Extraction of bitter carrots with hexane yielded a colorless, optically active, crystalline substance, $C_{11}H_{12}O_4$, (I). The substance is a lactone with one phenolic, one methoxyl and one C-methyl group. Infrared absorption data indicated an 8-hydroxy-3,4-dihydroisocoumarin derivative. The methyl ether of I gives a positive iodoform test and is oxidized by alkaline permanganate to 3,5-dimethoxyphthalic acid. Potassium hydroxide fusion of I yields a phenolic monocarboxylic acid, $C_{11}H_{12}O_4$, which on hydrogenation gives 2-hydroxy-4-methoxy-6-propylbenzoic acid, a previously described compound. From these and other data it is concluded that I is 3-methyl-6-methoxy-8-hydroxy-3,4-dihydroisocoumarin.

Carrots that have been held in cold storage after harvest frequently acquire a bitter off-flavor.[3] The hydrocarbon extracts from such carrots exhibit ultraviolet absorption characteristics which can be correlated with the flavor score.[4] A crystalline compound with the ultraviolet absorption found in the hydrocarbon extracts has been isolated from bitter carrots and was designated compound A(I).[5] Evidence has been presented that lends support to the belief that the bitter off-flavor of carrots is caused by the presence of several substances and that compound I is one of these.[5a] Data leading to the identification of I as 3-methyl-6-methoxy-8-hydroxy-3,4-dihydroisocoumarin are reported here.

Except for the lack of reactivity toward diazomethane, I gives the reactions expected of a typical monohydric phenol. The methyl ether of I can be obtained though with dimethyl sulfate in the presence of alkali. Quantitative bromination showed a




I

minimum of two unsubstituted positions on the benzene ring, and coupling of I with diazotized sulfanilic acid indicated a free position *para* to the phenolic hydroxyl.[6] No carboxyl or carbonyl groups were detected, but saponification showed the presence of a lactone. I is optically active and has an absorption band at 6.02 μ. Methylation of I shifts this band to 5.85 μ, a normal value for a con-

(1) Journal Paper No. 1071, New York State Agricultural Experiment Station. Part IV in the series "Bitter Flavor in Carrots." For Part III see ref. 5a.

(2) Department of Chemistry, State University College of Forestry at Syracuse University, Syracuse 10, N. Y.

(3) J. D. Atkin, Bulletin No. 774, New York State Agricultural Experiment Station, Geneva, N. Y., March, 1956.

(4) E. Sondheimer, W. P. Phillips and J. D. Atkin, *Food Research*, **20**, 659 (1955).

(5) (a) E. Sondheimer, *Food Research*, **22**, 296 (1957); (b) A. Dodson, H. N. Fukui, C. D. Ball, R. L. Caroius and H. M. Sell, *Science*, **124**, 984 (1956), isolated a compound from bitter carrots, melting 77°, which is probably identical with I.

(6) Chang Wen-Hau, paper partition chromatography of monohydric phenols and its application to the model-lignin degradation reaction, Univ. of Minnesota Master's Thesis, 1951.