room temperature for one hour gave 59% of the methylmethallyl diketone XV.

**2α,4b-Dimethyl-1-carboxymethylene-2-methallyl-7-ethylenedioxy-1,2,3,4,4aα,4b,5,6,7,8,10,10aβ-dodecahydrophenanthrene-4-one (XVIIb).**—The unsaturated ester XVIIa (4.10 g.) was saponified in 100 ml. of 50% methanol containing 10 g. of potassium carbonate and 1 g. of potassium hydroxide by boiling for 2.5 hours. The methanol was evaporated, 50 ml. of water was added to dissolve the potassium salt and the aqueous solution was extracted with ether and then acidified with sodium dihydrogen phosphate and extracted with chloroform. Evaporation of the extract and crystallization of the residue from ethyl acetate provided 3.3 g. (86%) of XVIIb, m.p. 223–225°; $\lambda_{shoulder}$ 220–230 mμ, $E_{mol}$ 5,490; $\lambda_{max}$ 5.83, 5.91, 6.18 μ.

*Anal.* Found: C, 71.80; H, 8.06.

**2α,4b-Dimethyl-1-carboxymethylene-2-methallyl-7-ethylenedioxy-1,2,3,4,4aα,4b,5,6,7,8,10,10aβ-dodecahydrophenanthrene-4α-ol (XVIII).**—To a solution of 100 mg. of XVIIb in 2 ml. of methanol and 1 ml. of tetrahydrofuran was added 100 mg. of sodium borohydride. After the gas evolution had subsided, the mixture was heated under reflux for one hour. The solvents were removed *in vacuo* and the residue was dissolved in water and acidified with excess sodium dihydrogen phosphate. The acidified mixture was thrice extracted with chloroform and the chloroform extract was washed with water and dried. Evaporation of the solvent *in vacuo* left a crystalline residue weighing 90 mg., m.p. 214–222°. The product, 2α,4b-dimethyl-1-carboxymethylene-2-methallyl-7-ethylenedioxy-1,2,3,4,4aα,4b,5,6,7,8,10,10aβ-dodecahydrophenanthrene-4α-ol (XVIII), had m.p. 220–222° after two crystallizations from ethyl acetate; $\lambda_{max}$ 2.8–4.2, 5.90, 6.08, 6.17 μ.

*Anal.* Calcd. for $C_{24}H_{34}O_5$: C, 71.61; H, 8.51. Found: C, 71.60; H, 8.36.

Acetylation in acetic anhydride-pyridine gave the 4-acetate of XVIII melting at 204–205° after recrystallization from ethyl acetate–petroleum ether; $\lambda_{max}^{CHCl_3}$ 5.81, 5.92, 6.17 μ.

*Anal.* Calcd. for $C_{26}H_{36}O_6$: C, 70.24; H, 8.16. Found: C, 70.61; H, 7.88.

**2α,4b-Dimethyl-1β-carboxymethyl-2-methallyl-7-ethylenedioxy-1,2,3,4,4aα,4b,5,6,7,8,10,10aβ-dodecahydrophenanthrene-4α-ol (XIX).**—A solution of 550 mg. of XVIII in 50 ml. of liquid ammonia was treated with 300 mg. of potassium and 10 ml. of 2-propanol by the procedure described above. The crystalline product amounted to 443 mg. (81%) melting at 225–228°. A sample twice recrystallized from ethyl acetate had m.p. 226–228°; $\lambda_{max}$ 2.93, 5.82, 6.05 μ.

*Anal.* Found: C, 70.97; H, 8.84.

**2α,4b-Dimethyl-1α-carboxymethyl-2-methallyl-7-ethylenedioxy-1,2,3,4,4aα,4b,5,6,7,8,10,10aβ-dodecahydrophenanthrene-4α-ol (XX).**—Five grams of XVIII was reduced with 550 mg. of lithium in 20 ml. of tetrahydrofuran and 180 ml. of liquid ammonia by the previously described procedure. The crude crystalline product was warmed with 50 ml. of ether and the insoluble part separated by filtration. The ether insoluble portion amounted to 3.00 g. (60%) and consisted mostly of the 1β-carboxymethyl isomer XIX. Upon evaporation of the ethereal filtrate to 5 ml., 750 mg. of crystalline material precipitated. Repeated recrystallization of this mixture from ethyl acetate gave the 1α-carboxymethyl isomer XX, m.p. 234–235°; $\lambda_{max}$ 2.82, 5.82, 6.08 μ.

*Anal.* Found: C, 71.07; H, 8.74.

RAHWAY, NEW JERSEY

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[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY OF WAYNE UNIVERSITY]

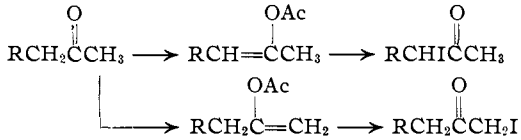
# α-Iodoketones (Part 3).[1] Synthesis of 21-Iodo-Δ[16]-20-keto Steroids by the N-Iodosuccinimide–Enol Acetate Reaction[2]

BY CARL DJERASSI AND CARL T. LENK[3]

RECEIVED DECEMBER 2, 1953

Unsaturated enol acetates such as 20-acetoxy-Δ[16,20]-dienes, readily obtainable by the reaction of Δ[16]-20-keto steroids with isopropenyl acetate, are convertible in excellent yield to the hitherto inaccessible 21-iodo-Δ[16]-20-ketosteroids by treatment with N-iodosuccinimide in dioxane solution. Replacement of the halogen atom by acetate proceeds in nearly quantitative yield, thus opening a route to the Δ[16]-20-keto-21-acetates and thence by appropriate manipulations to the cortical hormone side chains characteristic of desoxycorticosterone and cortisone. Nuclear double bonds or aromatic rings do not interfere in this reaction.

We have recently described a new synthesis[1] of α-iodo ketones by the reaction of enol acetates with N-iodosuccinimide, a readily available and stable iodine carrier. The utility of this method was illustrated with certain methyl ketones and it was demonstrated that the iodine could be introduced at either the methyl or methylene carbon depending upon the direction of enolization.




In an attempt to delineate the scope of this reaction we have turned to certain unsaturated enol acetates and the present paper is concerned with the utilization of this procedure for a novel approach to the cortical hormone side chain characteristic of desoxycorticosterone and cortisone.

In a study of the reaction of 20-keto steroids with isopropenyl acetate, Moffett and Weisblat[4] also investigated two Δ[16]-20-keto steroids and on the basis of analytical and spectral data concluded that the resulting enol acetates should be formulated as 20-acetoxy-Δ[16,20]-dienes (*e.g.*, I → II); no reactions of these unsaturated enol acetates were reported. Since the starting material, the Δ[16]-20-ketone (*e.g.*, IA), is the immediate degradation product of the steroidal sapogenin diosgenin[5] and can thus be considered to be one of the most accessible steroids, it appeared of interest to examine the course of the reaction of its enol acetate IIA with N-iodosuccinimide (NIS). The enol acetate IIA was obtained in 77% yield by a slight modification of the published procedure[4] and upon treatment with NIS in the standard manner[1]

(1) Part 2, C. Djerassi and C. T. Lenk, THIS JOURNAL, **75**, 3493 (1953).

(2) From part of the Ph.D. dissertation of Carl T. Lenk.

(3) Research Corporation Fellow, 1952–1953.

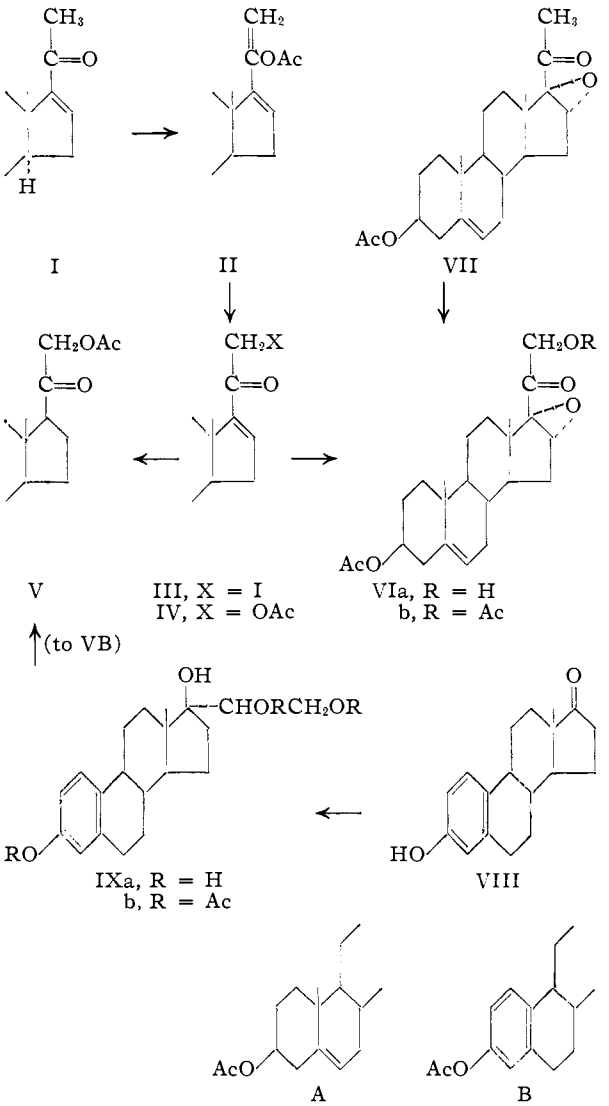
(4) R. B. Moffett and D. I. Weisblat, THIS JOURNAL, **74**, 2183 (1952).

(5) *Inter al.*, R. E. Marker, *ibid.*, **62**, 3350 (1940).

furnished in 94% yield an unsaturated iodo ketone, which was shown by analytical data and further chemical reactions to be 21-iodo-$\Delta^{5,16}$-pregnadien-3$\beta$-ol-20-one acetate (IIIA).[6] Although the enol acetate contained an isolated double bond and a conjugated diene system, iodination occurred exclusively on the enol acetate function thereby exhibiting a very fortuitous specificity of reaction. In a model experiment, the parent ketone IA was subjected to treatment with NIS in the standard manner. Under conditions which produced a high yield of the iodo ketones from the enol acetates, the ketone IA was recovered in quantitative yield. Treatment of the iodo ketone with potassium acetate in acetone solution led in 98% yield to the previously unknown $\Delta^{5,16}$-pregnadiene-3$\beta$,21-diol-20-one diacetate (IVA) with the expected spectral properties and catalytic hydrogenation of this unsaturated ketone IVA yielded the known[7] $\Delta^{5}$-pregnene-3$\beta$,21-diol-20-one diacetate (VA). This reaction sequence (I → V), therefore, represents a four-step conversion of a $\Delta^{16}$-20-keto steroid to the ketol acetate side chain, characteristic of desoxycorticosterone, and appears to be of general applicability. The only two other feasible procedures for accomplishing this aim proceed *via* the saturated 20-keto steroid and involve either lead tetraacetate oxidation[7] or condensation with ethyl oxalate followed by iodination, ketonic cleavage and acetoxylation.[8]

Another important feature of the present reaction sequence is that it constitutes by far the simplest synthesis of the $\Delta^{16}$-20-keto-21-acetate moiety (IV). Such unsaturated ketols had not been prepared until 1946 when Plattner and co-workers[9] obtained $\Delta^{16}$-allopregnene-3$\beta$,21-diol-20-one diacetate in poor to fair yields by way of the corresponding $\Delta^{16}$-20-keto-21-bromo derivative[10] or 17-bromo-20-keto-21-acetate. An interesting synthesis of an unsaturated ketol starting with the 20-keto-21-acetate has been reported by Colton, *et al.*,[11] in the 11-keto steroid series, where it was observed that polybromination under special conditions affords a 15,21-dibromo-$\Delta^{16}$-20-keto-21-acetate, which can then be dehalogenated to the requisite unsaturated ketol. As illustrated by these investigators, the importance of such an unsaturated $\Delta^{16}$-20-keto-21-acetate lies in the fact that it can be epoxidized to the corresponding 16$\alpha$,17$\alpha$-oxido derivative, which upon opening *via* the bromohydrin and debromination affords the dihydroxyacetone side chain characteristic of cortisone. Hence, as further proof of structure, the presently described $\Delta^{5,16}$-pregnadiene-3$\beta$,21-diol-20-one diacetate (IVA) was converted with alkaline hydrogen peroxide to the crystalline 16$\alpha$,17$\alpha$-oxido-$\Delta^{5}$-pregnene-3$\beta$,21-diol-20-one 3-monoacetate (VIa) and thence by acetylation to the known[12] oxido diacetate VIb. Recently, it has been reported[13] that chromous chloride reduction of 16$\alpha$,17$\alpha$-oxido-20-keto-21-acetates leads to $\Delta^{16}$-20-keto-21-acetates, thus representing a further approach to such unsaturated ketols, but this method does not permit their utilization for the synthesis of 17$\alpha$,21-dihydroxy-20-ketones.

The inertness of both isolated double bonds and double bonds in conjugation with the enol acetate function toward NIS having been established, it appeared of interest to examine an enol acetate which also possessed a phenolic ring. For instance, it is known[14] that estradiol in alcohol solution is readily dibrominated with N-bromoacetamide to furnish 2,4-dibromoestradiol. The example chosen




(6) It is interesting to note that the ultraviolet absorption maximum of the iodo ketone IIIA was found to be at 249 m$\mu$ as compared to *ca.* 240 m$\mu$ for the parent compound.

(7) T. Reichstein and C. Montigel, *Helv. Chim. Acta*, **22**, 1212 (1939).

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

(9) P. A. Plattner, H. Heusser and E. Angeliker, *Helv. Chim. Acta*, **29**, 468 (1946).

(10) These substances, in turn, are obtained by selective dehydrobromination of 17,21-dibromo-20-ketones (*inter al.*, R. E. Marker, H. M. Crooks and R. B. Wagner, THIS JOURNAL, **64**, 213 (1942); P. L. Julian and W. J. Karpel, *ibid.*, **72**, 362 (1950)).

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

(12) P. L. Julian, E. W. Meyer, W. J. Karpel and I. R. Waller, THIS JOURNAL, **72**, 5145 (1950), prepared the diacetate VIb by the introduction of the 21-acetoxy substituent from 16$\alpha$,17$\alpha$-oxido-$\Delta^{5}$-pregnen-3$\beta$-ol-20-one acetate (VII).

(13) W. Cole and P. L. Julian, Abstracts, p. 28-O, A.C.S. Meeting, Chicago, Illinois, September, 1953.

(14) R. B. Woodward, THIS JOURNAL, **62**, 1625 (1940).

was 3-hydroxy-17-acetyl-$\Delta^{1,3,5(10),16}$-estratetraene (IB)[15] since the final products of the NIS-enol acetate method would be of interest for certain Birch reduction experiments. The unsaturated enol acetate IIB was obtained in 78% yield and could be converted in 88% yield to the unsaturated iodo derivative IIIB without effecting iodination of the aromatic ring. Replacement of the iodine atom by means of potassium acetate proceeded smoothly to give the unsaturated aromatic ketol acetate IVB. The spectral properties of IIIB and IVB were in full accord with the assigned structures; chemical proof was furnished by catalytical hydrogenation of IVB to 3-acetoxy-17$\beta$-(acetoxyacetyl)-$\Delta^{1,3,5(10)}$-estratriene (VB), the aromatic analog of desoxycorticosterone acetate, and independent synthesis by Serini reaction of the 3,20,21-triacetate of 19-nor-$\Delta^{1,3,5(10)}$-pregnatriene-3,17$\beta$,20,21-tetrol (IXb).[16] Such a method had been used earlier[17] in the preparation of the corresponding 3-methyl ether of VB.

**Acknowledgment.**—We are indebted to the Research Corporation of New York for financial support in the form of a fellowship, to Syntex, S. A., Mexico City, for a generous gift of various steroid intermediates, to the Glidden Company, Chicago, Ill., for a comparison sample of 16$\alpha$,17$\alpha$-oxido-$\Delta^5$-pregnene-3$\beta$,21-diol-20-one diacetate and to Arapahoe Chemicals, Boulder, Col., for the N-iodosuccinimide.

## Experimental[18]

**$\Delta^{5,16,20}$-Pregnatriene-3$\beta$,20-diol Diacetate** (IIA).—A solution of 64 g. of $\Delta^{5,16}$-pregnadien-3$\beta$-ol-20-one acetate (IA) and 8.0 g. of *p*-toluenesulfonic acid monohydrate in 800 cc. of isopropenyl acetate was heated under a 15-cm. Vigreux column equipped with a fractionating head. After removal of an initial fraction of acetone, the temperature was raised to the boiling point of the solvent and 600 cc. of distillate was collected over a period of 14 hours. The residue, which solidified on cooling, was taken up in ether, neutralized with 60 g. of sodium bicarbonate, washed with water, dried and evaporated. Crystallization of the resulting brown solid from 1.75 l. of methanol and decolorization with Norit yielded 50 g. (70%) of colorless enol acetate II with m.p. 144–146°, $[\alpha]^{22}D$ −57°, $\lambda_{max.}^{CS_2}$ 5.74, 5.79 and 6.12 $\mu$; reported,[4] m.p. 144–146, $[\alpha]^{25}D$ −57.7°.

Dilution of the filtrate with a large volume of water gave a gummy precipitate which was extracted with ether and subsequently crystallized first from aqueous ethanol and then methanol to furnish an additional 4.8 g. of enol acetate IIA with m.p. 140–143°, raising the total yield to 77%.

**21-Iodo-$\Delta^{5,16}$-pregnadien-3$\beta$-ol-20-one Acetate** (IIIA).—A mixture of 29.85 g. (0.075 mole) of the enol acetate IIA and 18.0 g. (0.08 mole) of N-iodosuccinimide[1] (Arapahoe Chemicals, Boulder, Col.) in 50 cc. of dioxane was heated in a stoppered flask in an atmosphere of nitrogen at 80–85° for 1 hour. To the hot solution was added with stirring 100 cc. of methanol followed by a large excess of aqueous potassium iodide solution and the color was discharged by the addition of sodium thiosulfate. The colorless solid (m.p. 151–154°) was collected and recrystallized from 1 l. of methanol and 40 cc. of acetone yielding 31.9 g. (88%) of the unsaturated iodo ketone with m.p. 152–154°.[19] The filtrate was heated to boiling, 0.7 l. of hot water was added; chilling in ice and filtration furnished an additional 2.4 g. (7%) of iodo ketone with m.p. 148–151°. The analytical sample exhibited m.p. 158–159°, $[\alpha]^{24}D$ −57°, $\lambda_{max.}^{EtOH}$ 249.5 m$\mu$, log $\epsilon$ 3.92, $\lambda_{max.}^{CS_2}$ 5.79 and 6.02 $\mu$.

*Anal.* Calcd. for $C_{23}H_{31}IO_3$: C, 57.39; H, 6.48. Found: C, 57.59; H, 6.56.

**$\Delta^{5,16}$-Pregnadiene-3$\beta$,21-diol-20-one Diacetate** (IVA). (a) **From the 21-Iodo Ketone IIIA.**—A mixture[20] of 30 g. of potassium bicarbonate and 19 cc. of acetic acid was ground in a mortar and was then refluxed for 18 hours with 15.0 g. of the iodo ketone III in 150 cc. of pure acetone. Dilution with a large volume of water and recrystallization of the precipitate from methanol yielded 11.35 g. (90%) of the unsaturated ketol diacetate IVA with m.p. 152–153°. An additional 1.1 g. (8%) with m.p. 142–146° was obtained from the filtrate. The analytical sample exhibited m.p. 155–156°, $[\alpha]^{24}D$ −33.5°, $\lambda_{max.}^{EtOH}$ 241 m$\mu$, log $\epsilon$ 4.08, $\lambda_{max.}^{CHCl_3}$ 5.76, 5.81 and 5.97 $\mu$.

*Anal.* Calcd. for $C_{25}H_{34}O_5$: C, 72.43; H, 8.27. Found: C, 72.80; H, 8.12.

(b) **Without Isolation of Intermediates.**—The enol acetate IIA (2.0 g.) was iodinated as described above to yield 2.39 g. (99%) of crude iodo ketone with m.p. 150–153° which was treated directly in acetone solution with 12.5 g. of potassium bicarbonate and 7.5 cc. of acetic acid. The crude product (2.03 g., m.p. 141–148°) upon recrystallization from methanol gave 1.72 g. (85% over-all yield) of the diacetate IVA with m.p. 152–153°.

A sample (0.6 g.) of the unsaturated ketol diacetate IVA in ethyl acetate solution was hydrogenated with 0.2 g. of 5% palladium-on-barium sulfate catalyst for 1.5 hours at room temperature and atmospheric pressure. Filtration of the catalyst, evaporation of the filtrate to dryness and recrystallization from methanol afforded over 80% of $\Delta^5$-**pregnene-3$\beta$,21-diol-20-one diacetate** (V) with m.p. 160–162°; identity was established with an authentic sample[1,7] by a mixture melting point determination and comparison of the infrared spectra.

**16$\alpha$,17$\alpha$-Oxido-$\Delta^5$-pregnene-3$\beta$,21-diol-20-one 3-Monoacetate** (IVa).—In view of unfavorable solubility factors, the epoxidation procedure of Colton, *et al.*,[11] could not be applied exactly to the present case and was, therefore, modified. Nitrogen was bubbled for 2 hours through a mixture of 120 cc. of ethanol, 60 cc. of distilled water, 10 cc. of a 5% solution of sodium carbonate and 2.5 cc. of 1 *N* sodium hydroxide solution and then there was added 1.0 g. of the unsaturated ketol diacetate IVA in 15 cc. of C.P. chloroform and 10 cc. of 30% hydrogen peroxide. After thorough mixing, the clear solution was left at 0–5° for 3 hours and was then shaken at intervals for 1 hour permitting it to warm to room temperature. After the addition of saturated sodium chloride solution, the product was extracted with chloroform, the latter was dried with sodium sulfate, and evaporated to dryness *in vacuo*. Recrystallization of the colorless residue (m.p. 140–148°) from methanol furnished in two crops a total of 0.47 g. (50%) of the oxido 3-monoacetate (VIa) with m.p. 166–170°. The analytical sample was recrystallized twice from methanol and dried at 100° and 0.2 mm. for 24 hours; m.p. 180–183°, $[\alpha]^{24}D$ −20°, $\lambda_{max.}^{CHCl_3}$ 2.90, 5.82 and 8.01 $\mu$.

*Anal.* Calcd. for $C_{23}H_{32}O_5$: C, 71.10; H, 8.30. Found: C, 71.35; H, 8.48.

Acetylation of 0.2 g. of the above monoacetate (m.p. 166–170°) with acetic anhydride–pyridine followed by two recrystallizations from methanol led to 0.18 g. of 16$\alpha$,17$\alpha$-**oxido-$\Delta^5$-pregnene-3$\beta$,21-diol-20-one diacetate** (VIb) with m.p. 175–177°, undepressed upon admixture[21] with an authentic sample,[12] $[\alpha]^{22}D$ +6°; identity with the authentic specimen[12] was also established by infrared comparison ($\lambda_{max.}^{CHCl_3}$ 5.76, 5.81 and 8.0 $\mu$).

**3-Acetoxy-17-($\alpha$-acetoxyvinyl)-$\Delta^{1,3,5(10),16}$-estratetraene** (IIB).—3-Hydroxy-17-acetyl-$\Delta^{1,3,5(10),16}$-estratetraene (IB)[15]

(15) C. Djerassi, G. Rosenkranz, J. Iriarte, J. Berlin and J. Romo, THIS JOURNAL, **73**, 1523 (1951); L. Velluz and G. Muller, *Bull. soc. chim., France*, 166 (1950).

(16) H. H. Inhoffen, W. Logemann, H. Hohlweg and A. Serini, *Ber.*, **71**, 1024 (1938).

(17) C. Djerassi and C. R. Scholz, THIS JOURNAL, **71**, 3962 (1949).

(18) Melting points are uncorrected. All rotations were determined in chloroform solution. The infrared spectra were measured on a Baird Associates double beam recording spectrophotometer with sodium chloride cells of 0.1 cm. thickness.

(19) The iodo ketone was surprisingly stable. Decomposition occurred only when the melt was heated to 175°.

(20) *Cf.* G. Rosenkranz, J. Pataki, S. Kaufmann, J. Berlin and C. Djerassi, THIS JOURNAL, **72**, 4084 (1950).

(21) We are grateful to Dr. Wayne Cole of the Glidden Company for this information.

(3.98 g.) upon treatment with 100 cc. of isopropenyl acetate and 0.6 g. of *p*-toluenesulfonic acid monohydrate in the above described manner yielded 78% of the enol acetate IIB with m.p. 157–160°. Further recrystallization from methanol gave colorless needles with m.p. 158–160°, $[\alpha]^{24}D$ +59.5°, $\lambda_{max.}^{EtOH}$ 238 mμ, log ε 4.15 (shoulder at 265 mμ), $\lambda_{max.}^{CHCl_3}$ 5.70 (inflection), 5.73 and 6.10 μ.

*Anal.* Calcd. for $C_{24}H_{28}O_4$: C, 75.76; H, 7.42. Found: C, 75.77; H, 7.42.

**3-Acetoxy-17-(iodoacetyl)-$\Delta^{1,3,5(10),16}$-estratetraene (IIIB).**—The above enol acetate (3.58 g.) was treated with 2.22 g. of N-iodosuccinimide in 5 cc. of dioxane as described before. The quantitatively precipitated product (m.p. 150–154°) upon recrystallization from methanol led to 3.83 g. (88%) of the iodo ketone IIIB with m.p. 159–162°, $[\alpha]^{24}D$ +47°, $\lambda_{max.}^{EtOH}$ 249 mμ, log ε 3.91, $\lambda_{max.}^{CHCl_3}$ 5.70 and 6.03 μ.

*Anal.* Calcd. for $C_{22}H_{25}IO_3$: I, 27.3. Found: I, 26.5.

**3-Acetoxy-17-(acetoxyacetyl)-$\Delta^{1,3,5(10),16}$-estratetraene (IVB).**—Acetoxylation of 3.37 g. of the iodo ketone IIIB was carried out in the standard manner with 10 g. of potassium bicarbonate, 6 cc. of acetic acid and 80 cc. of acetone; yield, 2.48 g., m.p. 141–142° (from methanol), $[\alpha]^{24}D$ +80°, $\lambda_{max.}^{EtOH}$ 238 mμ, log ε 4.03 (shoulder at 274 mμ), $\lambda_{max.}^{CHCl_3}$ 5.71, 5.74, and 5.94 μ.

*Anal.* Calcd. for $C_{24}H_{28}O_5$: C, 72.70; H, 7.12. Found: C, 73.00; H, 7.01.

**3-Acetoxy-17β-(acetoxyacetyl)-$\Delta^{1,3,5(10)}$-estratriene (VB).**

**(a) By Catalytic Hydrogenation of IVB.**—The catalytic hydrogenation of the unsaturated ketol acetate IVB (0.25 g.) was carried out in ethyl acetate solution with 0.075 g. of 5% palladium-on-barium sulfate catalyst and furnished after recrystallization from methanol 0.2 g. of colorless needles with m.p. 121–122.5°. Further recrystallization raised the m.p. to 124–125°, $[\alpha]^{23}D$ +142°, $\lambda_{max.}^{EtOH}$ 267 and 274 mμ, log ε 2.93, 2.91, $\lambda_{min.}^{EtOH}$ 251, 272 mμ, log ε 2.52, 2.82, $\lambda_{max.}^{CHCl_3}$ 5.70 and 5.77 μ.

*Anal.* Calcd. for $C_{24}H_{30}O_5$: C, 72.33; H, 7.59. Found: C, 72.01; H, 7.42.

(b) From **Estrone (VIII).**—One gram of 19-nor-$\Delta^{1,3,5(10)}$-pregnatriene-3,17β,20,21-tetrol (IXa) (m.p. 211–213°) obtained from estrone (VIII) by the published procedure,[16] was acetylated by warming with acetic anhydride–pyridine for 5 hours. The oily acetate IXb could not be crystallized and was, therefore, subjected directly to the Serini reaction by refluxing for 50 hours with 18 g. of zinc dust and 180 cc. of toluene. After filtering the zinc, the solvent was removed *in vacuo* and the residue was chromatographed on 14 g. of ethyl acetate-washed alumina. The crystalline fractions eluted with petroleum ether–benzene were pooled and recrystallized from methanol yielding 0.48 g. of colorless needles with m.p. 123–125°, undepressed upon admixture with a sample prepared according to (a); the infrared spectra were identical.

DETROIT, MICHIGAN

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[CONTRIBUTION FROM THE WORCESTER FOUNDATION FOR EXPERIMENTAL BIOLOGY]

# Alteration Products of Equilenin. I. The Oxidation of Equilenin Acetate[1]

BY N. L. MCNIVEN

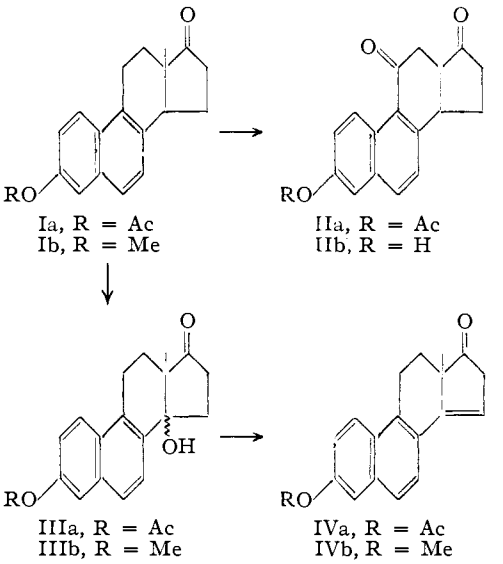
RECEIVED OCTOBER 22, 1953

Equilenin acetate on oxidation by chromic anhydride in aqueous acetic acid gave a product from which two crystalline substances were isolated and identified. One was found to be the known 11-oxoequilenin acetate and the second was identified as 14ξ-hydroxyequilenin acetate. Each of these substances was prepared in its two enantiomeric forms by using (+)- and (−)-equilenin acetate as the starting material.

In an attempt to prepare equilenin derivatives containing an 11-oxygen function, the oxidation of equilenin acetate by chromic anhydride was studied. Marker and Rohrmann[2] have already reported the preparation of 11-oxoequilenin acetate in low but unspecified yield by the treatment of (+)-equilenin acetate with chromic anhydride in aqueous acetic acid solution.

Dextro-equilenin acetate (Ia) was oxidized by chromic anhydride in aqueous acetic acid under somewhat milder conditions than those used by Marker and Rohrmann. Chromatography of the neutral product led to the isolation of two compounds. The first of these had the empirical formula $C_{20}H_{18}O_4$ indicating conversion of a methylene group to a keto group. Infrared absorption spectra measurements showed the presence of a conjugated keto group. Hydrolysis gave the compound $C_{18}H_{16}O_3$ (IIb). From these results and the similarity in the melting points of the acetate it is concluded that this compound is identical with that reported by Marker and Rohrmann and must be (−)-11-oxoequilenin acetate (IIa).

The second compound which was the main component of the oxidation product had the empirical formula $C_{20}H_{20}O_4$ indicating that it contained one additional oxygen atom. The infrared absorption spectra contained the characteristic band of a free hydroxyl group. The compound was resistant to acetylation indicating that the hydroxyl probably occupied the tertiary 14-position. This was supported by mild dehydration of IIIa to a com-




(1) The work described in this paper was supported by a grant from G. D. Searle & Company.

(2) R. E. Marker and E. Rohrmann, THIS JOURNAL, **61**, 3314 (1939).