(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

[CONTRIBUTION FROM THE WORCESTER FOUNDATION FOR EXPERIMENTAL BIOLOGY]

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

BY N. L. MCNIVEN

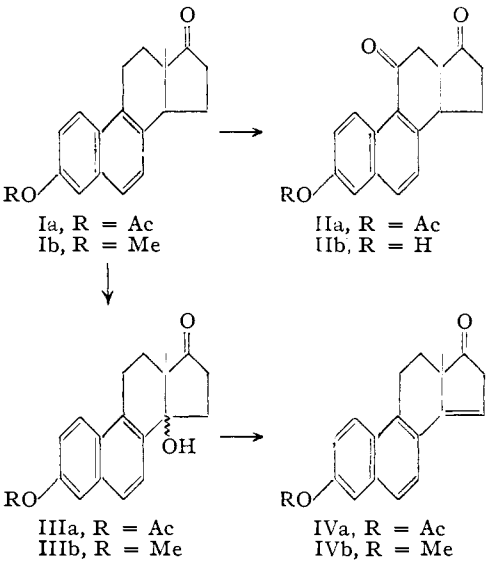
RECEIVED OCTOBER 22, 1953

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).

pound IVa whose infrared spectra lacked the characteristic band of a conjugated keto group indicating that the new double bond was in the 14,15-position. Confirmation of the structure of IIIa was obtained by treating it with dimethyl sulfate to form IVb whose infrared absorption spectrum was identical with that of synthetic (±)-14,15-dehydroequilenin methyl ether.[3] The ease with which (IIIa) becomes dehydrated is further evidence that a tertiary hydroxyl is present. Additional evidence in favor of this structure was obtained by oxidizing (±)-equilenin methyl ether (Ib) by chromic anhydride. The main component IIIb of the oxidation product was isolated and dehydrated to IVb whose infrared absorption spectrum was again identical with that of synthetic (±)-14,15-dehydroequilenin methyl ether. No depression in melting point was obtained when IVb was mixed with authentic (±)-14,15-dehydroequilenin methyl ether. Compound IIIa gave a positive Zimmerman color reaction.[4] This is in contrast to the negative reaction obtained with 3β-acetoxy-14ξ-hydroxy-5-androstene-17-one.[5]

The optical isomers of the two compounds IIa and IIIa were prepared by oxidation of (−)-equilenin acetate. The procedure of Bachmann[6] for the resolution of (±)-equilenin was followed. For the (−)-isomer it was found more convenient to prepare and resolve (±)-menthoxyacetic acid by (−)-menthol instead of resolving (±)-menthol as in Bachmann's procedure. It was also found possible to isolate (−)-equilenin (−)-menthoxyacetate from the mother liquors resulting from the isolation of (+)-equilenin (−)-menthoxyacetate. This permitted the preparation of both (+)- and (−)-equilenin by the use of (−)-menthol although the yield of (−)-equilenin was lower than by the method of Bachmann.

Table I shows the properties of the isomers.

TABLE I

Isomer oxidized	11-Oxoequilenin acetate M.p., °C.	[α]D	14ξ-Hydroxyequilenin 3-acetate M.p., °C.	[α]D
(+)-Equilenin acetate	198.5–199.5	−31°	178–179.5	+105°
(−)-Equilenin acetate	198–200	+31°	177–177.5	−104°

Discussion

The direct oxidation of a tertiary hydrogen atom to a tertiary hydroxyl group has been frequently described, especially in the earlier literature. Much of this early work was done on the oxidation by alkaline permanganate of branched chain carboxylic acids. A recent publication[7] summarizes these investigations.

When the tertiary hydrogen is adjacent to an aromatic ring system the oxidation proceeds in the same manner with the formation of a tertiary alcohol. This is illustrated by the oxidation of triphenylmethane,[8,9,10] cumic acid[11] and *m*-cymene[12] to the corresponding tertiary carbinol. It is not necessary, however, for the tertiary hydrogen to be adjacent to an aromatic ring system since Fieser[13] has shown that treatment of 2-hydroxy-3-isoalkyl-1,4-naphthoquinones with chromic anhydride in glacial acetic acid results in the oxidation of the tertiary hydrogen of the side chain to the corresponding tertiary hydroxyl compound.

That the tertiary hydrogen atom need not be part of a molecule containing an activating function was shown by the observation that 3-methylpentane decolorized permanganate.[14] The oxidation by benzoyl peroxide[15] or by oxygen[16] of other paraffins containing a tertiary hydrogen atom to tertiary alcohols also has been reported. Saturated polycyclic hydrocarbons containing tertiary hydrogen atoms have been oxidized to the corresponding tertiary alcohol. This is shown by the oxidation by ozone-oxygen of the decalins to the corresponding 9-hydroxy and 9,10-dihydroxy compounds and of tetradecahydrophenanthene to the corresponding 11-hydroxy and 12-hydroxy compounds.[17]

In the steroid field oxidative degradation of the cholesterol side chain involving the direct oxidation of a tertiary hydrogen atom with formation of 2-hydroxyisobutyric acid has been reported.[18] Degradation of cholesterol by chromic acid was shown[19] to give a hydroxy acid (isolated as the lactone) with the hydroxyl group at C-20. Recently it has been reported[5] that chromic acid oxidation of dehydroepiandrosterone acetate 5,6-dibromide results in the formation of the corresponding 14-hydroxy compound. In this case the 14-H is not adjacent to an activating function. A similar 14-hydroxylation has been produced by microbiological oxidation of 17α,21-dihydroxy-4-pregnene-3,20-dione.[20]

The formation of 14-hydroxyequilenin acetate by chromic acid oxidation is another case of the direct oxidation of a tertiary hydrogen of a steroid to the corresponding tertiary hydroxyl compound. In this case the tertiary hydrogen atom is adjacent to an activating function, a naphthalene ring system.

No definite conclusion for the configuration of the 14-hydroxyl of 14-hydroxyequilenin acetate can be obtained from molecular rotation differences. The M_D effect for 14-β-hydroxyl compared to 14-β-H in the compound 14β,17α-etiocholanic acid is

(3) W. S. Johnson, J. W. Petersen and C. D. Gutsche, THIS JOURNAL, **69**, 2942 (1947). Dr. Johnson kindly supplied a sample of synthetic (±)-14,15-dehydroequilenin methyl ether for comparison purposes.

(4) W. Zimmermann, "Vitamine u. Hormone," Vol. 5, Akademische Verlagsgesellschaft, m.b.H., Leipzig, 1944, p. 1.

(5) A. F. St. André, H. B. MacPhillamy, J. A. Nelson, A. C. Shabica and C. R. Scholz, THIS JOURNAL, **74**, 5506 (1952).

(6) W. E. Bachmann, W. Cole and A. L. Wilds, *ibid.*, **62**, 824 (1940).

(7) J. Kenyon and M. C. R. Symons, *J. Chem. Soc.*, 2129 (1953).

(8) W. Hemilian, *Ber.*, **7**, 1203 (1874).

(9) E. Fischer and O. Fischer, *ibid.*, **14**, 1942 (1881).

(10) O. Dimroth and R. Schweizer, *ibid.*, **56**, 1375 (1923).

(11) R. Meyer, *ibid.*, **11**, 1283 (1878).

(12) O. Wallach, *Ann.*, **275**, 145 (1893).

(13) L. F. Fieser, THIS JOURNAL, **70**, 3237 (1948).

(14) N. Zelinsky and J. Zelikow, *Ber.*, **34**, 2856 (1901).

(15) J. Böeseken, W. C. Smith and A. Gaster, *Proc. Acad. Sci. Amsterdam*, **32**, 377 (1929).

(16) W. E. Vaughan and F. F. Rust, U. S. Patent 2,403,771 (1946).

(17) J. R. Durland and H. Adkins, THIS JOURNAL, **61**, 429 (1939).

(18) A. Windaus, *Ber.*, **42**, 3770 (1909).

(19) J. R. Billeter and K. Miescher, *Helv. Chim. Acta*, **30**, 1409 (1947).

(20) H. C. Murray and D. H. Peterson, U. S. Patent, 2,602,769 (1952).

-190.[21] The M_D increment of 14 hydroxyequilenin acetate over equilenin acetate (14-α-H) is $+118$. This would indicate an α-configuration for the 14-OH. However, this result must be taken with some reserve due to the possibility of vicinal effects arising from the proximity of the aromatic ring system in equilenin. For example the M_D effect of an 11-keto group in steroids is given[21] as $+79$ while in the case of 11-oxoequilenin acetate the corresponding increment is -322.

Experimental[22]

Oxidation of (+)-Equilenin Acetate.—To a solution of 4 g. of (+)-equilenin acetate (derived from natural (+)-equilenin or by resolution of synthetic (±)-equilenin) in 750 ml. of glacial acetic acid was added a solution of 2.6 g. (2.0 moles) chromic anhydride in 7.85 ml. of water and 32 ml. of glacial acetic acid. The mixture was stirred mechanically and maintained at 20° during the addition which required 3 minutes. Stirring was continued for one hour at 20°.

The solution was poured into 2 liters of water at room temperature and extracted with ten 50-ml. portions of methylene chloride. The combined extract was washed with five 135-ml. portions of a solution made up of 24 ml. of saturated aqueous sodium carbonate, 34 ml. of saturated aqueous sodium bicarbonate and 77 ml. of water. After drying over anhydrous sodium sulfate, the solvent was removed by distillation *in vacuo*. The residual gum containing the neutral oxidation products weighed 3.81 g. The alkaline washings containing the acid oxidation products were discarded.

The non-acidic material in benzene solution was chromatographed on 110 g. of silica gel (Davison grade 23, 100–200 mesh) in a 2.4 cm. diameter column. Using benzene–ethyl acetate as the eluting agent, a chromatogram with three distinct peaks was obtained with the material distributed as follows: peak 1, 10:1 benzene–ethyl acetate, 0.76 g.; peak 2, 5:1 benzene–ethyl acetate, 2.05 g.; peak 3, 2:1 benzene–ethyl acetate, 0.49 g. Material represented by peak 1 contained unchanged (+)-equilenin acetate.

(−)-11-Oxoequilenin Acetate (IIa).—The fractions making up peak 2 were divided into two lots using the summit of the peak as the point of division. The first lot representing material to the left of the peak weighed 0.67 g. and had $[\alpha]^{24}D$ +29°. Treatment with Darco in methanol solution followed by recrystallization gave 0.19 g. of acicular crystals, m.p. 198.5–199.5°, $[\alpha]^{24}D$ −31°; reported m.p. 195–197°.[2] A second crop (0.05 g.) had a m.p. 197–198° giving a yield of 6%; ultraviolet absorption maxima at 246 mμ (log ε 4.40), and 314 mμ (log ε 3.86) in methanol; infrared spectrum bands at 1511 and 1598 cm.$^{-1}$ (benzene rings), 1666 cm.$^{-1}$ (conjugated keto −) and 1742 cm.$^{-1}$ (carbonyl) (film).

Anal. Calcd. for $C_{20}H_{18}O_4$: C, 74.5; H, 5.6. Found: C, 74.1; H, 5.5.

Inactive 11-Oxoequilenin (IIb).—A 50-mg. sample of (−)-11-ketoequilenin acetate was refluxed for one hour in 3.5 ml. of 7.7% methanolic potassium hydroxide. After acidifying with hydrochloric acid and recrystallizing from methanol, 22 mg. of material was obtained having m.p. 271–273° (red melt), $[\alpha]^{24}D$ 0° in dioxane; infrared spectrum bands at 1658 cm.$^{-1}$ (conjugated keto −), 1735 cm.$^{-1}$ (carbonyl) and 3460 cm.$^{-1}$ (phenolic hydroxyl).

Anal. Calcd. for $C_{18}H_{16}O_3$: C, 77.1; H, 5.8. Found: 77.1; H, 5.8.

(+)-14ξ-Hydroxyequilenin-3-acetate (IIIa).—The second lot of material from peak 2 (1.38 g., $[\alpha]^{23}D$ +92°) was recrystallized from methanol giving 0.60 g. (14%) of a substance, m.p. 178–179.5°, $[\alpha]^{23}D$ +105°; infrared bands at 1742 cm.$^{-1}$ (carbonyl) and 3580 cm.$^{-1}$ (hydroxyl) (film).

Anal. Calcd. for $C_{20}H_{20}O_4$: C, 74.1; H, 6.2. Found: C, 73.9; H, 6.2.

Attempted acetylation with acetic anhydride and pyridine led to recovery of starting material. This substance gave a positive Zimmermann color reaction.[23] Maximum absorption at 520 mμ with an intensity of 61% of that given by dehydroepiandrosterone, concentration, 40 μg./ml.

(±)-14ξ-Hydroxyequilenin-3-methyl Ether (IIIb).—A 0.68-g. sample of (±)-equilenin methyl ether was oxidized by the procedure used for (+)-equilenin acetate. Chromatography of the product gave three peaks. Material represented by the latter half of the second peak after crystallization from methanol gave a product, m.p. 164–165.5°; infrared bands at 1728 cm.$^{-1}$ (carbonyl) and 3450 cm.$^{-1}$ (hydroxyl) (film).

Anal. Calcd. for $C_{19}H_{20}O_3$: C, 77.0; H, 6.8. Found: C, 76.5; H, 6.9.

(±)-14,15-Dehydroequilenin Methyl Ether (IVb).—A 95-mg. portion of (±)-14-hydroxyequilenin-3-methyl ether was refluxed for 2 hours in 6 ml. of benzene containing a few crystals of iodine. After washing with sodium thiosulfate solution and drying over anhydrous sodium sulfate the product was chromatographed on 4.7 g. of silica gel (Davison grade 23, 100–200 mesh) in a 8.5-mm. diameter column. Elution with benzene–ethyl acetate (25:1) gave a chromatogram with a single peak. Fractions represented by the first part of the peak were combined and recrystallized from methanol–chloroform giving a substance, m.p. 166–167°, which did not depress the melting point of synthetic (±)-14,15-dehydroequilenin methyl ether. The infrared absorption spectra curve was identical with that of the above synthetic material.

(−)-14,15-Dehydroequilenin Acetate (IVa).—A 146-mg. s mple of (+)-14ξ-hydroxyequilenin-3-acetate was dehydrated by iodine in benzene solution. After working up the product as before, the first part of the chromatogram yielded a substance, m.p. 172–174.5°, $[\alpha]^{25}D$ −54°; infrared bands at 1746 cm.$^{-1}$ (carbonyl), no hydroxyl band (CS_2).

Anal. Calcd. for $C_{20}H_{18}O_3$: C, 78.4; H, 5.9. Found: C, 78.0; H, 5.5.

(−)-14,15-Dehydroequilenin Methyl Ether (IVb).—A solution of 80 mg. of (+)-14ξ-hydroxyequilenin-3-acetate in 4 ml. of methanol was refluxed with 5 mg. of sodium hydrosulfite and 0.85 ml. of 7.7% methanolic potassium hydroxide in nitrogen for 75 minutes. To this solution was added 0.5 ml. of dimethyl sulfate and refluxing was continued for one hour. Water was then added and the solution was extracted with ether. The ether layer was washed with water and with saturated sodium chloride solution and dried over anhydrous sodium sulfate. After distilling off the solvent, the residue was crystallized from methanol–chloroform after Darco treatment giving a product, m.p. 185–187.5°, $[\alpha]^{27}D$ −41°. The infrared absorption spectrum was identical with that of synthetic (±)-14,15-dehydroequilenin methyl ether.

(−)-Equilenin Acetate.—(±)-Menthoxyacetic acid was resolved using (−)-menthol and the resulting (+)-menthoxyacetic acid after conversion to the acid chloride was allowed to react with (±)-equilenin. Crystallization of the product gave (−)-equilenin (+)-menthoxyacetate (46% yield), m.p. 177–178°, $[\alpha]^{30}D$ −4.5° in benzene; literature value[6] m.p. 174.5–175° (vac.), $[\alpha]^{30}D$ −16° in benzene. After acid hydrolysis, the (−)-equilenin was acetylated by pyridine–acetic anhydride to (−)-equilenin acetate, m.p. 159–161°, $[\alpha]^{30}D$ −69.5°.

(−)-Equilenin acetate also was prepared as follows: (±)-equilenin was allowed to react with the acid chloride of (−)-menthoxyacetic acid. Crystallization of the product gave (+)-equilenin (−)-menthoxyacetate, m.p. 178–179°, $[\alpha]^{28}D$ +7° in benzene. Fractional crystallization of the mother liquors afforded (−)-equilenin (−)-menthoxyacetate, m.p. 155–159°, $[\alpha]^{23}D$ −100°.

Anal. Calcd. for $C_{30}H_{38}O_4$: C, 77.9; H, 8.3. Found: C, 77.6; H, 8.1.

Hydrolysis gave (−)-equilenin (6%), m.p. 247–249°, $[\alpha]^{25}D$ −87° in dioxane.

Oxidation of (−)-Equilenin Acetate.—A 1.33-g. sample of (−)-equilenin acetate was oxidized and the product worked up by the procedure used for (+)-equilenin acetate.

(21) D. H. R. Barton and W. Klyne, *Chemistry and Industry*, 755 (1948).

(22) All melting points were made using a Kofler microscope hot stage and hence are corrected. Except where noted, all rotations were determined in chloroform solution. We are indebted to Dr. R. T. Dillon and his associates of G. D. Searle and Company for some of the microanalyses. The remaining microanalyses are by Drs. Weiler and Strauss, Oxford.

(23) The author is indebted to Dr. B. Rubin and her group for carrying out this determination.

Material represented by the first peak of the chromatogram contained unchanged (−)-equilenin acetate.

(+)-11-Oxoequilenin Acetate.—The fractions represented by the first half of the second peak were combined and recrystallized from methanol giving 0.078 g. (6% yield) of acicular crystals, m.p. 198–200°, $[\alpha]^{24}D$ +31°.

(−)-14ξ-Hydroxyequilenin-3-acetate.—The second lot of material from the second peak was recrystallized from methanol giving 0.11 g. (8% yield) of white crystals, m.p. 177–177.5°, $[\alpha]^{25}D$ −104°.

Acknowledgment.—The receipt of a generous gift of (±)-equilenin methyl ether from Professor W. S. Johnson through the Research Committee of the Graduate School of the University of Wisconsin is gratefully acknowledged. The author is indebted to Dr. R. P. Jacobsen for valuable suggestions during the course of this work and to Dr. Harris Rosenkrantz for interpreting the infrared data.

SHREWSBURY, MASS.

[CONTRIBUTION FROM THE CHEMICAL LABORATORY OF HARVARD UNIVERSITY]

Cholesterol and Companions. IX. Oxidation of Δ^5-Cholestene-3-one with Lead Tetraacetate

BY LOUIS F. FIESER AND ROBERT STEVENSON[1]

RECEIVED OCTOBER 27, 1953

Oxidation of Δ^5-cholestene-3-one with lead tetraacetate at 15–25° gives Δ^5-cholestene-4α-ol-3-one acetate (VI) as the major crystalline product. The structure and configuration were established by reduction to Δ^5-cholestene-3β,4α-diol (VII) and cholestane-3β,4α-diol (XI), oxidation of these diols to Diels acid and dihydro-Diels acid, respectively, and characterization of VII as a digitonin-precipitated *trans* diol isomeric with the 3α,4β-diol. Δ^5-Cholestene-4α-ol-3-one acetate (VI) on contact with alumina undergoes acyl migration to the known Δ^5-cholestene-3β-ol-4-one acetate (XIII); on acid hydrolysis VI yields the known Δ^4-cholestene-4-ol-3-one (XV). The carbonyl group of VI is unusually reactive since the substance can be converted under mild conditions to a dimethyl ketal and a dimethylene ketal; the former derivative was converted by saponification, oxidation and acid hydrolysis to diosterol-I(IV). Condensation of VI with phenylhydrazines affords derivatives of $\Delta^{4,6}$-cholestadiene-3-one; condensation with ethanedithiol gives the bis-ethylenethioketal of cholestane-3,6-dione.

Since oxidation of cholesterol with sodium dichromate in benzene–acetic acid has been shown to afford Δ^5-cholestene-3-one as the major primary product,[2] a study of the action on this substance of the milder agent lead tetraacetate was undertaken in the hope of clarifying the further oxidation of Δ^5-cholestene-3-one by dichromate to Δ^4-cholestene-6β-ol-3-one. In contrast to the behavior of Δ^4-cholestene-3-one,[3] which reacts with lead tetraacetate in acetic acid–acetic anhydride at 70° to give the 2α-acetoxy derivative[3,4] in 13% yield, the non-conjugated ketone is oxidized at a lower temperature (15–20°) and gives a crystalline product in higher yield (30–40%).

The easily isolated product has the composition of a monoacetoxy derivative of the starting ketone V, the infrared spectrum is that of a non-conjugated ketone acetate, the substance is unsaturated to tetranitromethane and is levorotatory, as expected for a Δ^5-ene; these observations suggest that the substance is the product of acetoxylation at the doubly activated 4-position. Confirmatory evidence of structure is afforded by transformations, discussed below, to three different substances known to have oxygen functions at C_3 and C_4, but another proof of structure that also affords evidence that the acetoxyl group is α-oriented (VI) was obtained by characterization of a cholestenediol (VII) that resulted in high yield on lithium aluminum hydride reduction of the oxidation product; the diacetate of VII also resulted on hydrogenation of VI with Raney nickel in benzene and acetylation. Cleavage of the diol with periodic acid, followed by oxidation with hydrogen peroxide in acetic acid, gave the Diels acid (VIII), and hence the two hydroxyl groups are located at positions 3 and 4. The unsaturated diol differs from the well-characterized Δ^5-cholestene-3β,4β-diol[5,6] (m.p. 177°, αD −96°) but, like this substance, is precipitated by digitonin. The inference that the hydroxyl groups are in the 3β,4α-orientation is supported by the following independent evidence. Unlike Δ^5-cholestene-3β,4β-diol, which readily loses water and affords Δ^4-cholestene-3-one,[5] the new diol is stable to mineral acid in boiling methanol and hence is a *trans* diol, 3β,4α- or 3α,4β-. On hydrogenation it yields a saturated diol that on oxidative cleavage as above gives dihydro-Diels acid (XII) and therefore belongs to the cholestanol series; since it differs from the known cholestane-3α,4β-diol[7] (m.p. 236°, αD +16°; diacetate, m.p. 133°, αD −10°), it must be the alternative *trans*-glycol cholestane-3β,4α-diol.

Ruzicka, Plattner and Furrer,[8] on hydrogenating material later characterized[4] as a mixture of the acetates of cholestane-2α-ol-3-one and cholestane-4α-ol-3-one and acetylating the product, isolated a substance that corresponds well in properties (m.p. 162°, αD +33°) with our cholestane-3β,4α-diol diacetate (see chart). Thus in this instance as well as in the reduction of Δ^5-cholestene-4α-ol-3-one acetate (VI) opening of the 3-keto group proceeds by attack from the rear with production of the more stable, equatorially oriented 3β-alcohol. Brown[9] has described two substances that he suggests may be "the unknown Δ^5-cholestene-3,4-diols," but neither substance resembles Δ^5-cholestene-3β,4α-diol (VII).

(1) Merck International Fellow, 1952–1953.

(2) L. F. Fieser, THIS JOURNAL, **75**, 4377 (1953).

(3) E. Seebeck and T. Reichstein, *Helv. Chim. Acta*, **27**, 948 (1944).

(4) L. F. Fieser and M. A. Romero, THIS JOURNAL, **75**, 4716 (1953).

(5) O. Rosenheim and W. W. Starling, *J. Chem. Soc.*, 377 (1937).

(6) A. Butenandt and E. Hausmann, *Ber.*, **70**, 1154 (1937).

(7) P. A. Plattner, H. Heusser and A. B. Kulkarni, *Helv. Chim. Acta*, **31**, 1822 (1948).

(8) L. Ruzicka, P. A. Plattner and M. Furrer, *ibid.*, **27**, 727 (1944).

(9) B. R. Brown, *J. Chem. Soc.*, 2756 (1952).