A sample of the 3-*O*-methyl-D-glucose was converted to the corresponding phenylosazone which was found to melt at 180–181°, again no depression being observed on admixture with authentic material.

**Partial Hydrogenolysis of 1,2:4,6-*O*-Benzylidene-α-D-glucopyranose (III) to 1,2-*O*-Benzylidene-α-D-glucopyranose (VIII).**—A solution of 10 g. of 1,2:4,6-di-*O*-benzylidene-α-D-glucopyranose in 300 ml. of ethyl acetate was shaken with 0.5 g. of palladium black and hydrogen at room temperature until two molar equivalents of hydrogen had been absorbed (7.5 hr.). The suspended material was then removed by filtration and digested with 15 ml. of methanol. On cooling, the methanolic solution gave 0.2 g. of crude 1,2-*O*-benzylidene-α-D-glucopyranose; a second crop (0.19 g.) was obtained by concentrating the mother liquor to dryness and adding 1 ml. of water to dissolve any glucose which might be present. Cooling the original ethyl acetate filtrate provided a third (0.4 g.) crop of material.[16] Recrystallization of the combined crops from 84 ml. of ethyl acetate gave 0.7 g. of pure 1,2-*O*-benzylidene-α-D-glucopyranose melting at 173–174° and rotating $[\alpha]^{20}D$ +90.6° in methanol (*c* 0.72). The acetal was unaffected by hot Fehling solution.

*Anal.* Calcd. for $C_{13}H_{16}O_6$: C, 58.20; H, 6.01. Found: C, 57.93; H, 6.03.

**3,4,6-Tri-*O*-acetyl-1,2-*O*-benzylidene-α-D-glucopyranose (IX).**—The cyclic acetal (0.5 g.) was acetylated with acetic anhydride in pyridine solution using the usual technique to give from absolute ethanol 0.6 g. (82%) of crystalline product melting at 114–115°, a value unchanged by further recrystallization from alcohol. In chloroform (*c* 1) the pure product showed $[\alpha]^{20}D$ +47.5°.

*Anal.* Calcd. for $C_{19}H_{22}O_9$: C, 57.86; H, 5.62. Found: C, 57.96; H, 5.51.

**3,4,6-Tri-*O*-benzoyl-1,2-*O*-benzylidene-α-D-glucopyranose (X).**—1,2-*O*-Benzylidene-α-D-glucose (0.5 g.) was benzoylated with benzoyl chloride in pyridine in the usual fashion. The product (0.91 g., 84%) crystallized from alcohol; after recrystallization from the same solvent it melted at 138–139° and rotated $[\alpha]^{20}D$ −12° in chloroform (*c* 1.0).

*Anal.* Calcd. for $C_{34}H_{28}O_9$: C, 70.34; H, 4.86. Found: C, 70.45; H, 4.86.

**1,2-*O*-Benzylidene-3,4,6-tri-*O*-methyl-α-D-glucopyranose (XI).**—A stirred, boiling solution of 1.1 g. of 1,2-*O*-benzylidene-α-D-glucopyranose in a mixture of 20 ml. of methyl iodide and 10 ml. of dioxane was treated, at 0.5-hr. intervals with 1-g. batches of silver oxide until 6 g. of the latter had been added. The solution was then filtered and concentrated to a sirup which was methylated twice more in a similar fashion to give a sirup (1.2 g.) which showed no hydroxyl absorption in the infrared.

**3,4,6-Tri-*O*-methyl-D-glucose (XII).**—A portion (1.1 g.) of the sirup, prepared as described above, was dissolved in 20 ml. of ethanol and reduced with palladium black (0.5 g.) at room temperature to give 0.59 g. of a sirup which, diluted with ether at −5° and seeded, crystallized: 197 mg., m.p. 83–96°. The addition of pentane to the mother liquor afforded a second crop: 30 mg., m.p. 90–98°. Combined, the two crops were recrystallized from ether and then twice from isopropyl ether to give pure 3,4,6-tri-*O*-methyl-β-D-glucopyranose (70 mg.): m.p. 98–102°, $[\alpha]^{20}D$ +40.0° (7 min.) → +77.6° (24 hr., constant) (water, *c* 0.5). Sundberg, *et al.*,[17] reported m.p. 97–98° and $[\alpha]^{25}D$ +41.1° (2.5 min.) → +78.0° (constant) ($H_2O$, *c* 1.6) for this substance. A mixed melting point with authentic material was undepressed; in both borate ionophoresis and paper chromatography the substance behaved like authentic 3,4,6-tri-*O*-methyl-D-glucose.

Cautious addition of pentane to the combined mother liquors afforded 380 mg. of material (m.p. 62–70°) which, recrystallized from ether at −5°, was obtained as beautiful needles (164 mg.): m.p. 76–78°, $[\alpha]^{20}D$ +122° (extrapolated) → +77.7° (28 hr., constant, $H_2O$, *c* 1.0). While the final value here is in agreement with recorded values for 3,4,6-tri-*O*-methyl-D-glucose, the initial value lies some 30° higher than that recorded by Sundberg, *et al.*,[17] for the α-anomer. However, this new value leads to a 2A value which is quite close to that of D-glucose (Table I) and is, therefore, not unreasonable. Borate ionophoresis of this material gave a migration rate identical with that of authentic 3,4,6-tri-*O*-methyl-D-glucose.

TABLE I

| | $[\alpha]^{20}D$ ($H_2O$) | $[M]^{20}D$ | Difference (2A) |
|---|---|---|---|
| 3,4,6-Tri-*O*-methyl-α-D-glucose | +122° | +27,100 | 17,970 |
| 3,4,6-Tri-*O*-methyl-β-D-glucose | + 41.1° | + 9,130 | |
| α-D-Glucose | +112.2° | +20,210 | 16,840 |
| β-D-Glucose | + 18.7° | + 3,370 | |

**Acknowledgment.**—Analyses were carried out in the Institutes' Microanalytical Laboratory under the direction of Dr. W. C. Alford.

(16) By selective adsorption on carbon the material remaining in the mother liquor was induced to yield a further 0.35 g. of 1,2-*O*-benzylidene-D-glucopyranose.

(17) R. L. Sundberg, C. M. McCloskey, D. E. Rees and G. H. Coleman, THIS JOURNAL, **67**, 1080 (1945).

BETHESDA 14, MD.

---

[CONTRIBUTION FROM THE FISHERIES RESEARCH BOARD OF CANADA, CHEMISTRY SECTION OF THE TECHNOLOGICAL STATION AT VANCOUVER, B. C.]

# Marine Sterols. III. The Synthesis of 24-Methylenecholesterol and 25-Dehydrocholesterol

BY D. R. IDLER AND U. H. M. FAGERLUND

RECEIVED OCTOBER 22, 1956

A new sterol, 24-methylenecholesterol, recently isolated from several molluscs, has been synthesized from 24-ketocholesterol employing triphenylphosphinemethylene. The synthesis of 25-dehydrocholesterol is also reported and discrepancies in its properties with the products previously assigned this structure are discussed. Evidence is presented to support the conclusion that the earlier preparations are not 25-dehydrocholesterol and it is suggested that they are the previously undescribed 24-dehydrocholesterol. The broader implications of the use of triphenylphosphine alkylidene compounds in syntheses in the sterol side chain are outlined.

A new sterol, 24-methylenecholesterol, has recently been isolated from several species of shellfish.[1,2] The structure was established by chemical degradation and the present study was undertaken to confirm this structure by synthesis. Further, it was suggested that the biological reduction of 24-methylenecholesterol offered a possible explanation for the origin of $C_{24}$-epimeric 28-carbon sterols in nature and by a similar route fucosterol (24-ethyl-

(1) D. R. Idler and U. H. M. Fagerlund, THIS JOURNAL, **77**, 4142 (1955).

(2) U. H. M. Fagerlund and D. R. Idler, *J. Org. Chem.*, **21**, 372 (1956).

enecholesterol), isolated from algae,[3,4] would explain the origin of $C_{24}$-epimeric 29-carbon sterols. In our planned approach to test the validity of this hypothesis it will be necessary to have a source of 24-methylenecholesterol and fucosterol labeled with $C^{14}$ in the alkylidene group.

Syntheses of side chain double bonds have been accomplished in a few instances by the use of dehydrohalogenation reactions. Thus, a compound assigned the structure 25-dehydrocholesteryl acetate has been prepared from 25-hydroxycholesteryl acetate in good yield with $POCl_3$ and pyridine, but the same reaction conditions employing 26-nor-5-cholestene-3,25-diol-3-acetate gave the 25-chloro derivative.[5-7] The conversion of cholestane-3,22-diol-3-acetate to 20(22)-cholestenyl acetate, apparently in reasonable yield, has been reported.[8]

Syntheses in the side chain have been made possible primarily by the availability of ketones such as 22- and 24-ketocholesterol and 25-ketonorcholesterol prepared from readily available intermediates.[9-11] Because of the sometimes numerous and closely related possible products from dehydrohalogenation reactions, a more direct method of introducing double bonds, but preferably still employing the ketone starting materials, was sought. The recently discovered elegant triphenylphosphine alkylidene reagent of Wittig and Schöllkopf, which permits the direct replacement of a ketone by an alkylidene group, appeared to be such a reagent.[12,13] This reagent has already been used to a limited extent, notably in the synthesis of squalene[14] and precursors to be used for the synthesis of vitamin D type compounds.[15-17]

The present paper reports the successful synthesis of 24-methylenecholesterol (II) from 24-ketocholesterol (I) and shows its identity with the natural product. In addition, 25-dehydrocholesterol has been prepared and discrepancies in properties with previously described products discussed. Other applications of the reaction to sterol syntheses are outlined briefly.

## Experimental[18]

**Methyltriphenylphosphonium Bromide.**—To 50 ml. of benzene at 0° were added 20 g. of triphenylphosphine and 10 g. of methyl bromide. After standing for one day at room temperature in a pressure bottle, the methyltriphenylphosphonium bromide was filtered off and washed with benzene (13.3 g., m.p. 227–228°).

**Triphenylphosphine Methylene Reagent.**—Methyltriphenylphosphonium bromide (2.45 g.), phenyllithium (7.5 ml. of an ether solution titrating 9.5 ml. of 0.1 *N* HCl per ml. and prepared from 1.4 g. of lithium and 15.7 g. of bromobenzene in 50 ml. of ether in the usual manner) and 19 ml. of ether, were shaken in a pressure bottle for 3 hr. at 20°.

**24-Ketocholesteryl Acetate.**—Diisopropylcadmium was treated with 3-acetoxy-5-cholenyl chloride (prepared as previously described)[19,20] according to the procedure of Riegel and Kaye.[10] (For our early experiments 3-acetoxy-5-cholenyl chloride and 24-ketocholesteryl acetate were gifts of other workers.) The product was purified by chromatography on silicic acid,[1] m.p. 128°, $[\alpha]^{22}D$ −43°, mixed m.p. 128° with the ozonolysis product from 24-methylenecholesterol.

*Anal.* Calcd. for $C_{29}H_{46}O_3$: C, 76.68; H, 10.48. Found: C, 76.59; H, 10.40.

**24-Methylenecholesterol.**—24-Ketocholesteryl acetate (225 mg.) and triphenylphosphinemethylene reagent (15 ml.) were shaken in a pressure bottle for 1 hr. at room temperature followed by 5 hr. at 65°. The precipitate was filtered and washed with anhydrous ether. The filtrate was evaporated to dryness, reacetylated and taken up in 20 ml. of Skellysolve C and the steryl acetate adsorbed on a column (7.5 cm. o.d. × 8 cm.) of silicic acid–Celite 2:1.[1] The adsorbent was washed with 400 ml. of Skellysolve C and the eluate discarded. The steryl acetate broke through with 300 ml. of benzene–Skellysolve C 1:1 and a further 400 ml. completed the elution. 24-Methylenecholesterol (140 mg.), prepared by hydrolyzing the acetate, melted at 143°, $[\alpha]^{22}D$ −34.8° (26 mg. in 1 ml. of $CHCl_3$), (N.P.[21] m.p. 142°, $[\alpha]^{22}D$ −35.0°) mixed m.p. with N.P. 143°. The infrared spectrum was identical with the natural product and had the prominent absorption bands at 1637 and 885 $cm.^{-1}$ associated with a terminal methylene group[1] (Fig. 1).

A further 20 mg. of sterol, m.p. 140°, was obtained with digitonin from the supernatant. The total yield was 160 mg. (70%).

*Anal.* Calcd. for $C_{28}H_{46}O$: C, 84.35; H, 11.63. Found: C, 84.41; H, 11.60.

**Derivatives.**—The acetate crystallized from ethanol in plates, m.p. 135°, $[\alpha]^{22}D$ −44.1° (28.5 mg. in 1 ml. of $CHCl_3$), (N.P. m.p. 136°, $[\alpha]^{22}D$ −42.4°) mixed m.p. with N.P. 136°.

*Anal.* Calcd. for $C_{30}H_{48}O_2$: C, 81.76; H, 10.98. Found: C, 81.64; H, 10.88.

The benzoate was prepared in the usual manner and crystallized from acetone in plates, m.p. 148°, $[\alpha]^{22}D$ −14.0° (N.P. m.p. 148°, clear 153°), $[\alpha]^{22}D$ −14.1°, mixed m.p. with N.P. 148°.

**25-Dehydrocholesterol.**—The triphenylphosphinemethylene reagent (15 ml.) was treated with 225 mg. of 25-ketonorcholesteryl acetate and after reacetylation the steryl acetate isolated by chromatography as described above for the 24-methylene compound. Hydrolysis, followed by crystallization from methanol gave fine needles, m.p. 132.5°, $[\alpha]^{22}D$ −40.7° (20.2 mg. in 1 ml. of $CHCl_3$) (lit. 121.2–122.2°, $[\alpha]^{22.5}D$ −43.0°,[5] and 120.5–121.5°, $[\alpha]^{25}D$ −40.2°[7]). The yield was 120 mg. (53%).

*Anal.* Calcd. for $C_{27}H_{44}O$: C, 84.31; H, 11.53. Found: C, 84.23; H, 11.42.

**Derivatives.**—The acetate crystallized from methanol in plates, m.p. 112°, $[\alpha]^{22}D$ −44.4° (32 mg. in 1 ml. of $CHCl_3$) (lit. 93.5–94°, $[\alpha]^{29}D$ −43.6°,[5] and 92.5–93.5°, $[\alpha]^{22}D$ −42.8°[7]).

*Anal.* Calcd. for $C_{29}H_{46}O_2$: C, 81.63; H, 10.87. Found: C, 81.60; H, 10.72.

(3) I. M. Heilbron, R. F. Phipers and H. R. Wright, *Nature*, **133**, 419 (1934); *J. Chem. Soc.*, 1572 (1934).

(4) H. B. MacPhillamy, THIS JOURNAL, **64**, 1732 (1942).

(5) A. I. Ryer, W. H. Gebert and N. M. Murrill, *ibid.*, **72**, 4247 (1950); **75**, 491 (1953).

(6) A. I. Ryer and W. H. Gebert, U. S. Patent 2,673,206 (1954).

(7) W. G. Danben and H. Leon Bradlow, THIS JOURNAL, **72**, 4248 (1950).

(8) L. F. Fieser and Wei-Yuan Huang, *ibid.*, **75**, 5356 (1953).

(9) L. Ruzicka and W. H. Fischer, *Helv. Chim. Acta*, **20**, 1291 (1937).

(10) B. Riegel and I. A. Kaye, THIS JOURNAL, **66**, 723 (1944).

(11) W. Cole and P. L. Julian, *ibid.*, **67**, 1369 (1945).

(12) G. Wittig and U. Schöllkopf, *Chem. Ber.*, **87**, 1318 (1954).

(13) The selection of this reaction resulted from discussions of D.R.I. with Dr. G. Tener and Dr. J. G. Moffatt of the British Columbia Research Council.

(14) S. Trippett, *Chemistry & Industry*, 80 (1956).

(15) N. A. Milas, Li-chin Chiang, C. P. Priesing, A. A. Hyatt and J. Peters, THIS JOURNAL, **77**, 4180 (1955).

(16) I. T. Harrison, B. Lythgoe and S. Trippett, *Chemistry & Industry*, 507 (1955).

(17) H. H. Inhoffen, K. Bruckner, G. F. Domagk and H. M. Erdmann, *Chem. Ber.*, **88**, 1415 (1955).

(18) Melting points are uncorrected except for 25-dehydrocholesterol and derivatives. Optical rotations were measured by means of a Rudolph precision polarimeter with a photoelectric attachment. Rotations also were checked visually. Infrared spectra were recorded with a Perkin–Elmer recording infrared spectrophotometer.

(19) E. S. Wallis and E. Fernholz, THIS JOURNAL, **57**, 1511 (1935).

(20) S. Kuwada and M. Yogo, *J. Pharm. Soc. (Japan)*, **57**, 963 (1937).

(21) The natural product (N.P.) obtained from molluscs.[1,2]

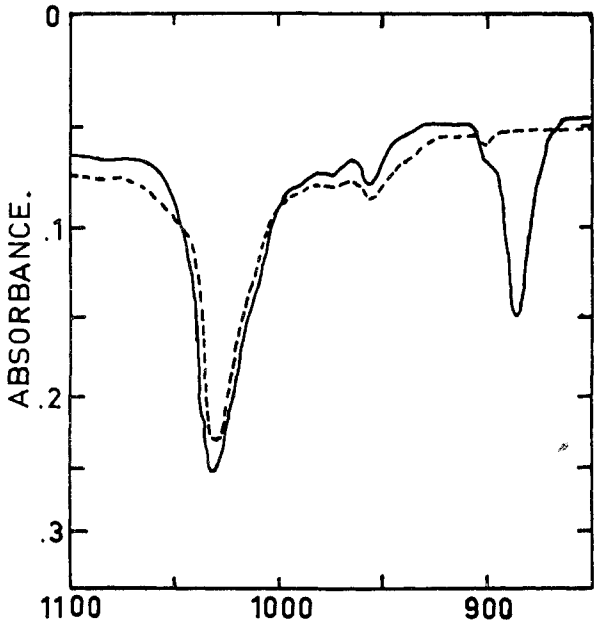



Fig. 1.—Infrared spectra of 25-dehydrocholesteryl acetate — and an earlier preparation[5] - - -. Spectra were determined in carbon tetrachloride.

The benzoate was prepared by dissolving 35 mg. of the sterol in 1 ml. of pyridine and 0.2 ml. of benzoyl chloride, followed by incubation at 37° overnight. The steryl benzoate was precipitated with 90% ethanol and crystallized twice from aqueous acetone in clusters of fine needles, m.p. 126°, $[\alpha]^{22}D$ −16.7° (21 mg. in 1 ml. of $CHCl_3$); molecular rotational differences: 25-dehydrocholesterol, $\Delta^{Ac}$ −24, $\Delta^{Bz}$ +84; cholesterol, $\Delta^{Ac}$ −51, $\Delta^{Bz}$ +84.

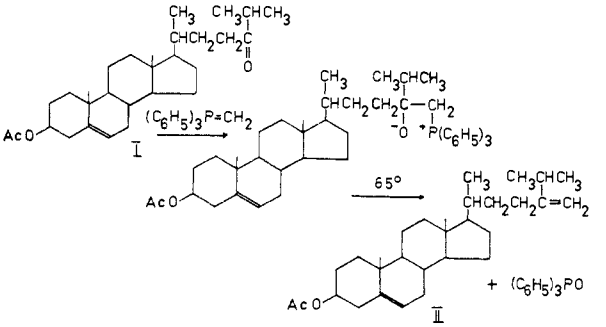
It is thus apparent that the contribution to molecular rotation differences of the 25-double bond is significant for the acetate but not for the benzoate.

**Periodate Oxidation.**—Formaldehyde was determined by the periodic acid–permanganate procedure of Bricker and Roberts slightly modified to allow for the limited solubility of steryl acetates in aqueous ethanol.[22] The modification simply involved the use of 6 ml. of alcohol in place of 3 ml. as described in the original procedure. Employing 24-methylenecholesteryl acetate as a standard our preparation of 25-dehydrocholesteryl acetate gave 98% of the theoretical weight of formaldehyde. By comparison the earlier preparations[5,6] gave 99 and 100%, respectively. Hence, within the limits of the method all preparations gave the yield of formaldehyde expected from one terminal methylene group.

The cleavage also was carried out by the same procedure except that basic $KMnO_4$ was added first followed by periodic acid. Acetone was then determined by both the nitroprusside reaction and conversion to indigo with O-nitrobenzaldehyde.[23] Both earlier preparations of 25-dehydrocholesteryl acetate gave positive tests for acetone.

## Discussion

Syntheses of the type described in this paper provide a route to steroids $C^{14}$-labeled in specific positions in the side chain from readily available intermediates. Conditions found suitable for obtaining an adequate yield of 24-methylenecholesterol were used without modification for the preparation of 25-dehydrocholesterol. A Grignard reaction previously has been employed to synthesize 7-methylenecholesterol from 7-ketocholesterol.[24] In our hands 7-ketocholesterol acetate was converted to 7-methylenecholesteryl acetate with triphenylphosphinemethylene as described above for 24-methylenecholesterol but the yield was not investigated. It is obvious that this reaction suggests a route to many interesting sterols, including the still undescribed 17(20)- and 20(21)-unsaturated derivatives in the cholesterol series. For example, 5,17(20)-cholestadiene-3β-ol would be prepared from dehydroandrosterone and 2-bromo-6-methylheptane, both fairly readily available. Interest in these compounds is also centered around determining the contribution of the remaining isolated side chain double bonds to infrared spectra, optical rotation and the color reactions of sterols. We hope to make some of these syntheses the subject of a future report.




A sterol assigned the 25-dehydrocholesterol structure previously has been synthesized concurrently in two laboratories by a dehydrohalogenation reaction, and the properties of the sterol and its derivatives differ significantly from those reported here (Table I).[5-6] The dehydrohalogenation of 25-chlorocholesterol would have to proceed nearly quantitatively in the unexpected manner in order to obtain pure 25-dehydrocholesterol, and for this reason we first believed that the products were contaminated with the 24-unsaturated isomer.

TABLE I

PROPERTIES OF 25-DEHYDROCHOLESTEROL AND EARLIER PREPARATIONS

| | Idler and Fagerlund | | Ryer, *et al.*[5] | | Dauben, *et al.*[7] | |
|---|---|---|---|---|---|---|
| | M.p., °C. | $\alpha_D$ | M.p., °C. | $\alpha_D$ | M.p., °C. | $\alpha_D$ |
| Sterol | 133 | −40.7° | 121.2–122.2 | −43.0° | 120.5–121.5 | −40.2° |
| Acetate | 112 | −44.4 | 93.5–94 | −43.6 | 92.5–93.5 | −42.8 |
| Benzoate | 126 | −16.7 | ..... | | ..... | |
| Yield of $CH_2O$, % | 98 | | 99 | | 100 | |
| Infrared adsorption at 885 and 1637 cm.⁻¹ | Yes | | No | | No | |

The results of periodate oxidation indicate that the earlier preparations do yield the theoretical amount of formaldehyde as compared with the product prepared from triphenylphosphinemethylene (Table I). However, mixture melting points of our 25-dehydrocholesteryl acetate (m.p. 118°) in both cases depressed the melting point (92.5–93.5° and 92.5–94°[6,7]) of the earlier preparations. This contradicted the conclusion that the previous preparations were 25-dehydrocholesteryl acetate

(22) C. E. Bricker and K. H. Roberts, *Anal. Chem.*, **21**, 1297 (1949).

(23) F. Feigl, "Qualitative Analysis by Spot Tests," Elsevier Publ. Co., Inc., New York, N. Y., 1947, p. 351.

(24) B. Bann, I. M. Heilbron and F. S. Spring, *J. Chem. Soc.*, 1274 (1936).

contaminated with 24-dehydrocholesteryl acetate, for if this were the case the further addition of 25-dehydrocholesteryl acetate should have raised the melting point. Infrared spectra were run on all three preparations and there was no evidence for any significant absorption at 885 cm.$^{-1}$ characteristic of terminal unsaturation in the earlier preparations. The absorption at 1637 cm.$^{-1}$ for terminal unsaturation found in our preparation of 25-dehydrocholesterol (Fig. 1) and 24-methylenecholesterol was also absent.[1,25,26] We must conclude that the earlier products are not 25-dehydrocholesterol but are predominately the previously undescribed 24-dehydrocholesterol arising by dehydrohalogenation proceeding in the expected manner. The incorrect assignment of structure by the earlier workers may be explained by the apparent non-specificity of the formaldehyde determination when applied to sterols of this type; bond migration under the acid conditions of the periodate oxidation might offer an explanation. The formation of acetone when basic permanganate was used lends support to this hypothesis.

(25) R. B. Barnes, R. C. Gore, R. W. Stafford and V. Z. Williams, *Anal. Chem.*, **20**, 402 (1948).

(26) H. W. Thompson and D. H. Whiffen, *J. Chem. Soc.*, 1412 (1948).

**Acknowledgment.**—We are indebted to Dr. Byron Riegel, G. D. Searle and Co., Chicago, Ill., for a sample of synthetic 24-ketocholesterol; to Drs. Eugene P. Oliveto and W. Gebert, Schering Corp., Bloomfield, N. J., for synthetic 25-ketonorcholesterol and 25-dehydrocholesterol; to Dr. H. B. MacPhillamy, Ciba Pharmaceutical Products, Inc., Summit, N. J., for 3-acetoxy-5-cholenic acid; and to Dr. W. G. Dauben, University of California, for 25-dehydrocholesterol. Dr. R. H. Wright, British Columbia Research Council, kindly recorded infrared spectra. Mr. A. P. Ronald of our instrumentation section obtained many of the analytical data.

VANCOUVER 2, B. C.

---

[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY OF THE UNIVERSITY OF WISCONSIN]

# The Action of Lead Tetraacetate on an Enol Acetate. The Epimeric 16-Acetoxy Derivatives of Epiandrosterone Acetate, their Interconversion and Rearrangement

BY WILLIAM S. JOHNSON, BERNARD GASTAMBIDE[1] AND RAPHAEL PAPPO[2]

RECEIVED OCTOBER 12, 1956

Lead tetraacetate has been found to react stereoselectively with the enol acetate I of epiandrosterone acetate to produce the 16$\beta$-acetoxy compound IV. Evidence for the mechanism of the rearrangement of the epoxy acetate III to the 16$\alpha$-acetoxy ketone II has been advanced. A previous postulate that the 16$\beta$-isomer IV serves as an intermediate has been invalidated. It now appears that rearrangement of such epoxyacetates involves two competing reactions, one proceeding by retention and the other by inversion of the configuration of the carbon accepting the acetoxy group. Treatment with dilute sulfuric acid followed by reacetylation converted IV into the 17$\beta$-acetoxy-16-keto compound V but did not effect rearrangement of II. Theoretical implications of this difference are discussed. The two epimeric acetates II and IV were unaffected by heating at 190° or by treatment with silica gel but could be equilibrated with potassium acetate in acetic acid as demonstrated by infrared spectroscopy. By the aid of ultraviolet spectroscopy and polarimetry the position of this equilibrium was shown to lie between 44 and 56% of the $\beta$-form.

In connection with another investigation we had occasion to treat the enol acetate I of 3$\beta$-acetoxyandrostane-17-one with lead tetraacetate and discovered that the reagent was consumed after a few hours at room temperature. The major product, produced stereoselectively and isolated in 57% yield, corresponded in composition and spectral properties to a diacetoxy ketone which we presumed to be a 3$\beta$,16-diacetoxyandrostane-17-one formed by attack of acetoxy free radicals or cations at the nucleophilic 16-position of the enol acetate I. Our product existed in two polymorphic forms, m.p. 139° and 159°, and was clearly different from the 16$\alpha$-acetoxy ketone II, m.p. 185°, of known configuration obtained by Leeds, Fukushima and Gallagher[3] by rearrangement of the epoxy acetate III. The inference that our isomer was the 16$\beta$-epimer IV was since confirmed by a recent disclosure of Fajkos[4] who prepared the 16$\beta$-acetoxy ketone IV from 16$\alpha$,17$\alpha$-epoxyandrostane-3$\beta$-ol acetate by cleavage of the epoxide group with acetic acid, followed by chromic acid oxidation. The reported properties of Fajkos' material are in good agreement with those of our compound.[5]

With the 16$\beta$-acetoxy ketone IV in hand we found ourselves in a position to shed some light on the mechanism of the rearrangement of the epoxy acetate III, which has been effected by chromatography on silica gel, or by heat alone.[3] One of two mechanisms previously proposed[3] involved the postulation of the 16$\beta$-acetoxy ketone IV as an intermediate which was assumed to be unstable, readily undergoing epimerization (*via* the enol) to the 16$\alpha$-isomer (see chart B of reference 3). When we submitted the 16$\beta$-acetoxy ketone IV to these

(1) On leave from the Centre National de la Recherche Scientifique, Paris, on funds provided by the International Coöperation Administration, Washington, D. C.

(2) Lecturer in Chemistry supported by the Research Committee of the Graduate School on funds provided by the Wisconsin Alumni Research Foundation, 1954–1955. On leave from the Weizmann Institute of Science.

(3) N. S. Leeds, D. K. Fukushima and T. F. Gallagher, THIS JOURNAL, **76**, 2943 (1954).

(4) J. Fajkos, *Coll. Czechoslovak. Communs.*, **20**, 1478 (1955).

(5) The action of lead tetraacetate on enol acetates is receiving further attention. In preliminary work we have found that the enol acetates of coprostanone and cholestanone react only slowly. The bis-enol acetate from pregnane-3,20-dione (isopropenyl acetate method) afforded the 21-acetoxy derivative. The reaction is similar to the reaction of lead tetraacetate with enols (see R. Criegee, "Newer Methods of Preparative Organic Chemistry," Interscience Publishers, Inc., New York, N. Y., 1948, p. 8) or with their ethers (see, for example, H. O. L. Fischer, *et al.*, *Ber.*, **63**, 1732 (1930); **65**, 345 (1932)).