for thirty minutes. After the usual work-up, there was obtained 1.54 g. (88%) of 1-methyl-Δ^6-dehydroestradiol with m. p. 129–132°, which gave no depression on admixture with the sample prepared according to (A) and possessed the same rotation and spectrum.

Hydrogenation of 1-Methyl-Δ^6-dehydroestradiol 3,17-Diacetate to 1-Methylestradiol 3,17-Diacetate.—Hydrogenation of the Δ^6-dehydro diacetate in the usual manner in ethyl acetate solution with 10% palladium-on-charcoal catalyst (barium sulfate supported catalyst was equally satisfactory) afforded 81% of shiny, prismatic blades (from methanol) of **1-methylestradiol 3,17-diacetate** with m. p. 178–180° (Kofler), $[\alpha]^{20}D$ +111°, u. v. maximum at 268 mμ (log E 2.53) and minimum at 252 mμ (log E 2.44). The so-called 1-methylestradiol 3,17-diacetate described in the literature[5,7] had m. p. 138.5–139°.

Anal. Calcd. for $C_{23}H_{30}O_4$: C, 74.56; H, 8.16. Found: C, 74.50; H, 8.19.

1-Methylestradiol (IVa), prepared either by saponification of its diacetate or by hydrogenation of 1-methyl-Δ^6-dehydroestradiol (XIIIa), was obtained from ether–hexane as a microcrystalline powder, which shrank at 95° and melted at 110–116° (Kofler), $[\alpha]^{20}D$ +146°, u. v. maximum at 284 mμ (log E 3.28) and minimum at 250 mμ (log E 2.25). The physical constants of this alkali-soluble phenol are in complete contrast to those reported for the so-called 1-methylestradiol[5,7]: insoluble in alkali, crystallizes readily, m. p. 235.5–236.5°, $[\alpha]D$ +185° (dioxane).

Anal. Calcd. for $C_{19}H_{26}O_2$: C, 79.67; H, 9.14. Found: C, 79.87; H, 9.36.

The **3,17-dipropionate** was isolated in nearly quantitative yield on heating 1-methylestradiol (IVa) for one hour with propionic anhydride and pyridine; colorless plates from methanol, m. p. 125.5–127° (Kofler), $[\alpha]^{20}D$ +101.5°. u. v. maximum at 268 mμ (log E 2.58) and minimum at 254 mμ (log E 2.45).

Anal. Calcd. for $C_{25}H_{34}O_4$: C, 75.34; H, 8.59. Found: C, 75.16; H, 8.63.

1-Methyl-17-dihydroequilenin-17β (XIVa).—This phenol was obtained by both selenium dioxide oxidation of 1-methyl-Δ^6-dehydroestradiol 3,17-diacetate followed by saponification, or by lithium aluminum hydride reduction of 1-methylequilenin acetate exactly as described for the analog lacking the 1-methyl group.[2]

1-Methyl-17-dihydroequilenin-17β crystallized as small, prismatic needles from either aqueous methanol or hexane–acetone, m. p. 225–227° (Kofler), $[\alpha]^{20}D$ +33° (dioxane), u. v. spectrum Fig. 2.

Anal. Calcd. for $C_{19}H_{22}O_2$: C, 80.81; H, 7.85. Found: C, 80.54; H, 7.65.

The **3,17-diacetate** was obtained as colorless needles from methanol, m. p. 145–147° (Kofler), $[\alpha]^{20}D$ −16°. The u. v. spectrum was very similar to that of 1-methylequilenin acetate and is depicted in Fig. 2.

Anal. Calcd. for $C_{23}H_{28}O_4$: C, 75.38; H, 7.15. Found: C, 75.58; H, 7.12.

Summary

The dienone-phenol rearrangement of the recently described[2,10] $\Delta^{1,4,6}$-androstatrien-17-ol-3-one and the corresponding 3,17-dione (XII) produced 1-methyl-Δ^6-dehydroestradiol and 1-methyl-Δ^6-dehydroestrone (XIII). Dehydrogenation led to the corresponding 1-methylequilenin derivatives (XIV), while catalytic hydrogenation afforded 1-methylestradiol and 1-methylestrone, characterized by alkali solubility and high estrogenic potency. A consideration of the reaction mechanism and earlier work on model compounds[6,8] indicates that the present compounds are the true 1-methylestrogens in contrast to the rearrangement products of steroidal $\Delta^{1,4}$-dien-3-ones (III), previously believed to have this structure,[5] which should now be referred to as "x-methyl*hetero*phenols."

The present work, coupled with the results of Woodward and Singh,[8] demonstrates that the dienone-phenol rearrangement in the steroid series proceeds in different directions depending on the presence or absence of an additional, conjugated double bond.

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The Structures of β-Diacetone-D-fructose and β-Monoacetone-D-fructose

BY M. L. WOLFROM, WILBUR L. SHILLING[1] AND W. W. BINKLEY[1]

Fischer[2] obtained two crystalline products on treating D-fructose with acetone in the presence of acid and these have come to be designated α-diacetonefructose and β-diacetonefructose wherein the prefixes were assigned in accordance with the order of isolation and bear no anomeric significance. The structure of the former can be considered to be adequately established as 1,2:4,5-diisopropylidene-D-fructopyranose[3,4] while that of the latter cannot.

It is known that C_1 is open in the β-isomer since on oxidation with alkaline permanganate an acid was obtained without acetone removal and this acid on hydrolysis yielded 1-C-carboxy-D-arabinose (2-keto-D-gluconic acid).[5] The main difficulties preventing a solution of this problem have been those encountered in preparing the mono-isopropylidene derivative, essential to the structure determination. Both isopropylidene residues hydrolyze at nearly the same rate and on partial hydrolysis there is obtained a difficultly separable mixture of starting material, D-fructose and a relatively small amount of the sirupy mono-isopropylidene-D-fructose. In the work herein reported the mono derivative has been separated by chroma-

(1) Sugar Research Foundation Fellow (W. L. S.) and Research Associate (W. W. B.) of The Ohio State University Research Foundation (Project 190).

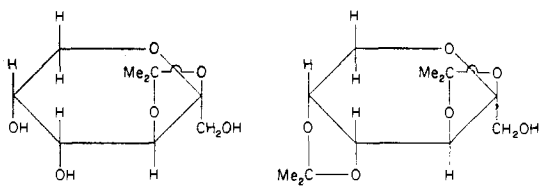
(2) E. Fischer, *Ber.*, **28**, 1164 (1895); *cf.* H. Ohle and Ilse Koller, *ibid.*, **57**, 1566 (1924).

(3) H. Ohle, *ibid.*, **60**, 1168 (1927).

(4) C. G. Anderson, W. Charlton, W. N. Haworth and V. S. Nicholson, *J. Chem. Soc.*, 1337 (1929).

(5) H. Ohle, *Ber.*, **58**, 2577 (1925); H. Ohle and Gertrud Berend, *ibid.*, **60**, 1159 (1927).

tography on clay and characterized as a crystalline triacetate. Deacetylation of this non-reducing compound yielded a product consuming one mole of periodate per mole of substance. Only two possible non-reducing monoisopropylidene derivatives of D-fructose are compatible with this analysis: 1,2-isopropylidene-D-fructofuranose and 2,3-isopropylidene-D-fructopyranose. The former is eliminated by the evidence cited above. The structure of β-monoacetone-D-fructose is thus rigorously proven to be 2,3-isopropylidene-D-fructopyranose (I) and since hydrolysis by aqueous acid will not shift the position of an attached isopropylidene group, the structure of β-diacetone-D-fructose is likewise established as 2,3:4,5-diisopropylidene-D-fructopyranose (II).



I* II*

* Anomeric configurations arbitrary.

The prefixes α and β are then no longer required to distinguish the known isopropylidene derivatives of D-fructose and the definitive rational names should replace the older trivial terms. It is interesting that in the formation of both of these diisopropylidene derivatives of D-fructose, this ketose has reacted under acid conditions in the pyranoid ring conformation. The properties of the three crystalline isomeric monoisopropylidene-D-fructose triacetates are compared in Table I.

TABLE I

PROPERTIES OF THE ISOMERIC MONOISOPROPYLIDENE-D-FRUCTOSE TRIACETATES

Substance	M. p., °C.	$[\alpha]^{22-27}D$ $c < 10$, ethanol	Ref.
1,2-Isopropylidene-D-fructopyranose triacetate	99–101 (cor.)	−135.5°	6
2,3-Isopropylidene-D-fructopyranose triacetate	55.5–56 (cor.)	+18	This work
2,3-Isopropylidene-D-fructofuranose triacetate	55	− 8	7

Experimental

Preparation of 2,3-Isopropylidene-D-fructopyranose (β-Monoacetone-D-fructose).—This substance was prepared essentially according to the procedure of Ohle and Koller[2] but was purified by chromatographic technics. An amount of 32.4 g. of finely powdered β-diacetone-D-fructose[8] was hydrolyzed for thirteen hours (approximately the point of smallest levorotation; $[\alpha]D$ −20°, basis starting material) at 22° in 1100 ml. of *N* sulfuric acid. At this point an equal quantity of crushed ice was added and the resultant solution was passed over a 680 × 74 mm. (diam.) column of Duolite A-4[9] anion acceptor resin precooled to *ca.* 5° with ice water. The effluent and washings were concentrated under reduced pressure to a mixture of sirup and crystals. This residue was dissolved in 1 liter of 98% 2-propanol (sp. g. 0.786/23°) and chromatographed on 3 kg. of Florex XXX[10]–Celite[10] (5:1 by wt.) in an 8 l. pharmaceutical percolator. Development was effected with 3.5 l. of 98% 2-propanol, the course of the development being followed by applying the Molisch reaction to the effluent. This removed the diisopropylidene derivative (17.5 g.), isolable on solvent removal. Development with 98% 2-propanol was continued and the succeeding 8 l. of effluent was concentrated under reduced pressure, treated with decolorizing charcoal and concentrated to a colorless sirup; yield 5.7 g. of monoisopropylidene derivative, $[\alpha]^{24}D$ +17.5° (*c* 2.3, water), $[\alpha]^{24}D$ +28.2° (*c* 2.9, ethanol), after purification through the crystalline triacetate described below. Ohle and Koller[2] record the value $[\alpha]^{22}D$ + 27.6° (*c* 1.5, ethanol). The D-fructose fraction remained on the top of the column and was isolable by elution with 2 liters of 80/20 (by vol.) ethanol/water with subsequent solvent removal; yield 3.2 g. of sirup.

2,3-Isopropylidene-D-fructopyranose Triacetate.—An amount of 7.8 g. of the above sirupy 2,3-isopropylidene-D-fructopyranose (β-monoacetone-D-fructose) was acetylated for five hours at 75° with acetic anhydride (40 ml.) and anhydrous sodium acetate (1 g.). The cooled reaction mixture was poured into 250 g. of ice and water and adjusted, with stirring, to *p*H 6 with sodium bicarbonate (60 g.). The dried chloroform extract was concentrated to a sirup under reduced pressure and acetic acid was removed by co-distillation with toluene under reduced pressure. The product was crystallized from ether–petroleum ether (b. p. 30–60°); 10.6 g. (two crops, 93%), m. p. 55.5–56° (cor.) unchanged on further recrystallization, $[\alpha]^{27}D$ +18° (*c* 5, abs. ethanol), $[\alpha]^{27}D$ +7° (*c* 5, chloroform). The substance crystallized as thick prisms or thin plates. It was readily soluble in the common solvents except water and petroleum ether.

Anal. Calcd. for $C_6H_7O_3\cdot(CH_3)_2C\cdot(COCH_3)_3$: C, 52.02; H, 6.40; CH_3CO, 9.9 ml. 0.1 *N* NaOH per 100 mg.; CH_3-C, 4 moles/mole. Found: C, 51.92; H, 6.41; CH_3CO, 9.5 ml.; CH_3-C, 3.7 moles.

Periodate Assay on 2,3-Isopropylidene-D-fructopyranose (β-Monoacetone-D-fructose) Purified through its Crystalline Triacetate.—To 0.1745 g. of the above crystalline 1,4,5-triacetyl-2,3-isopropylidene-D-fructopyranose dissolved in 10 ml. of dry methanol was added a solution of 7.5 mg. of sodium in 1.5 ml. of dry methanol. After standing overnight at 10°, the solution was made up to 100 ml. with 20 ml. of 0.046 *M* sodium metaperiodate, 1.6 ml. of 0.1 *N* hydrochloric acid, and water. The solution was maintained at 20° and aliquots showed the following periodate consumption in moles of oxidant per mole of substance: 0.95 at 1.5 hr.; 0.96 at 4.5 hr.; 1.0 at 11.8 hr.

Summary

Chromatographically purified β-monoacetone-D-fructose, characterized as its crystalline triacetate, consumes one mole of periodate per mole of substance. This, together with previously known facts, establishes this substance as 2,3-isopropylidene-D-fructopyranose and demonstrates that β-diacetone-D-fructose is 2,3:4,5-diisopropylidene-D-fructopyranose.

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