The identity of this ester was confirmed by saponifying a small sample to the parent hydroxy lactone.

Isobisdehydroestrololactone Methyl Ether (IV).—The acetoxy lactone (193 mg.) was saponified with 10 ml. of 2% sodium hydroxide, and this solution at 50° was treated by the alternate, portionwise addition of dimethyl sulfate and sodium hydroxide solution. The warm mixture (containing some solid material) was acidified with excess hydrochloric acid, and the precipitate was collected, resaponified and again precipitated from hot solution with hydrochloric acid. The 140 mg. of product thus obtained melted at 183–185°. After recrystallization from ethanol, it melted at 189–191°.

Anal. Calcd. for $C_{19}H_{20}O_3$: C, 77.00; H, 6.80. Found: C, 77.06; H, 6.71.

A mixture of the methoxy lactone of m.p. 189–191° and the acetoxy lactone of m.p. 187–188° melted at 160–180°.

Derivatives of Isobisdehydroestrolic Acid (V).—All aqueous media in this section were prepared from distilled water. The acetoxy lactone (173 mg.) was saponified and methylated, and the initially-precipitated methoxy lactone was resaponified with 10 ml. of 2% sodium hydroxide. When this solution was concentrated to 5 ml. and cooled, the white, crystalline **sodium salt (VI)** separated. This could not be washed ion-free, as it dissolved almost immediately in water, methanol and ethanol, and no satisfactory solvent was found for recrystallization. It was collected on a filter, and repeatedly resuspended in and washed with portions of a solution prepared from 50 g. of sodium nitrate and 100 ml. of water, until the contaminating hydroxide ion was quantitatively replaced by nitrate ion. The organic sodium salt (with the adhering sodium nitrate) was dissolved in 15 ml. of warm water, and this solution was treated with dilute silver nitrate until precipitation was complete. The pale grey **silver salt (VII)** weighed 162 mg. and melted with decomposition at 176°. It is insoluble in water, organic solvents and sodium hydroxide solution, but it dissolves readily in aqueous ammonia. Analytical values indicate that it has the composition of a dihydrate.

Anal. Calcd. for $C_{19}H_{21}O_4Ag \cdot 2H_2O$: Ag, 23.59; CH_3O–, 6.79. Found: Ag, 23.68; CH_3O-, 6.73.

The silver salt (90 mg.) was covered with 10 ml. of methyl iodide and allowed to stand at 25°, with occasional shaking, for 20 hours. When the mixture was boiled gently to dryness and the residue was extracted with several portions of warm methanol, a fraction of about 48 mg. remained undissolved (calculated for silver iodide = 46.2 mg., assuming the organic silver salt to be a dihydrate). The methanol soluble fraction, after two recrystallizations from very small amounts of methanol, gave 6 mg. of a material, m.p. 107–108°, tentatively formulated as the **methyl ester (VIII)**, along with a larger amount of less pure material. This compound is soluble in ethyl acetate, moderately soluble in methanol, slightly soluble in benzene, and almost insoluble in aliphatic hydrocarbon solvents and water. Although the material melted sharply and was thought to be the pure ester, a single carbon–hydrogen determination failed to substantiate the proposed formula. Confirmation of the identity of this compound must therefore be held in abeyance.

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[CONTRIBUTION FROM THE RESEARCH LABORATORIES OF CHAS. PFIZER AND CO., INC.]

Corticosteroid Intermediates. A Selective Hydrogenation of Steroid Polyenes

BY G. D. LAUBACH AND K. J. BRUNINGS

Hydrogenation of several polyunsaturated sterols in the presence of Raney nickel catalyst at room temperature and atmospheric pressure has been shown to proceed selectively without bond isomerization or saturation of non-conjugated side-chain double bonds. The important intermediate 5-dihydroergosterol has been prepared by this technique in quantitative yield from ergosterol. The method has been applied to four of the isomers of ergosterol, and in the course of this work $\Delta^{8(14),22}$-ergostadien-3β-ol acetate has been prepared and characterized.

Discussion

The $\Delta^{7,9(11)}$-sterol dienes[1,2] have long been considered attractive intermediates for the synthesis of 11-oxygenated steroids. A key step in the preparation of dienes of this type from readily available starting materials involves the selective hydrogenation of $\Delta^{5,7}$-sterol dienes to Δ^{7}-monounsaturated ("5-dihydro") derivatives. A typical example is the preparation of the important intermediate ergosterol-D-acetate ($\Delta^{7,9(11),22}$-ergostatrien-3β-ol acetate,[3] which involves selective hydrogenation of ergosterol (I) to 5-dihydroergosterol ($\Delta^{7,22}$-ergostadien-3β-ol) (III)[4] followed by dehydrogenation at the 9,11-position. In all sterols possessing a synthetically useful side-chain double bond, selective hydrogenation of ethylenic linkages within the sterol nucleus is rendered difficult by the reactivity of the side-chain function. Furthermore, the 7,8-double bond generated in the reduction is extremely labile and susceptible to migration to the 8,14-position under certain catalytic hydrogenation conditions.[5] Despite the extensive study devoted to the selective hydrogenation of ergosterol,[4] no method satisfactory for large-scale operation has been described. The best yields thus far reported have been of the order 30 to 35%[4a] and purification of the product (by fractional recrystallization) has been described as capricious and difficult.[4]

A series of attempts to repeat in this Laboratory the hydrogenation of ergosterol acetate over platinum in chloroform,[4a] which appeared to be the most straightforward of the published procedures, did not give consistent results, the product generally containing varying proportions of the monounsaturated rearranged sterol, $\Delta^{8(14)}$-ergosten-3β-ol acetate. This product could in fact be obtained in excellent yields by allowing the hydrogenation to proceed to completion. Incorporation of solid calcium carbonate in an attempt to maintain the neutral conditions essential for non-migration of steroid

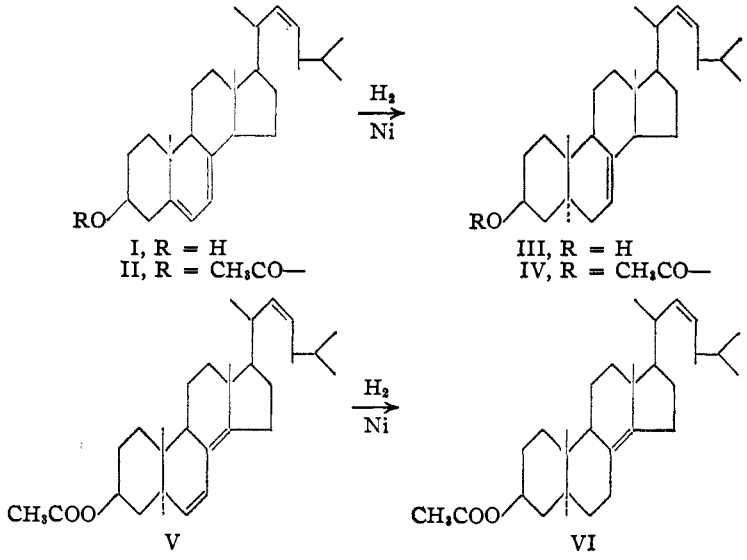
(1) W. Bergmann and J. Klacsman, *J. Org. Chem.*, **13**, 21 (1948).

(2) Subsequent to the completion of this work M. Tishler and co-workers, THIS JOURNAL, **73**, 2396 (1951), and Fieser and co-workers, *ibid.*, **73**, 2397 (1951), reported the first successful conversion of $\Delta^{7,9(11)}$-sterol dienes to 11-oxygenated corticosteroid intermediates. A second route was later announced by G. Stork, *et al.*, *ibid.*, **73**, 3546 (1951).

(3) A. Windaus and E. Auhagen, *Ann.*, **472**, 185 (1929); I. Heilbron, F. Johnstone and F. Spring, *J. Chem. Soc.*, 2248 (1929). (a) D. R. H. Barton and J. Cox, *ibid.*, 219 (1949).

(4) A. Windaus and J. Brunken, *Ann.*, **460**, 225 (1927); I. Heilbron and W. Sexton, *J. Chem. Soc.*, 921 (1929); H. Wieland and W. Benend, *Ann.*, **554** 1 (1943). (a) D. R. H. Barton and J. Cox, *J. Chem. Soc.*, 1354 (1948).

(5) A survey of bond migration on hydrogenation of steroids is given by L. F. and M. Fieser, "Natural Products Related to Phenanthrene," 3rd Edition, Reinhold Publishing Corp., New York, N. Y., 1949, p. 240. See also Wieland and Benend, ref. 4.



double bonds over platinum in the presence of hydrogen[5] did not prove consistently successful. The use of alternate media in this hydrogenation was found to be somewhat limited by the poor solubility of ergosterol and its esters in most organic solvents.

These results led to a consideration of a variety of other catalysts, with special emphasis on those not prone to attack isolated double bonds. A deactivated noble metal catalyst, palladium–lead on barium carbonate in chloroform was investigated. Under the conditions of the experiment, no hydrogen uptake was observed at ordinary conditions of temperature and pressure. Similarly, hydrogenation of ergosterol over the same catalyst in dioxane resulted in essentially no absorption of hydrogen and afforded starting material of good purity.

However, when the hydrogenation was carried out in dioxane in the presence of a Raney nickel catalyst[6] a rapid uptake of exactly one mole of hydrogen was observed, affording excellent yields of 5-dihydroergesterol (III). The product was shown to be essentially uncontaminated by products of bond migration or side-chain saturation. The rapidity of this hydrogenation when carried out at room temperature and atmospheric pressure is particularly striking, since Raney nickel has not been extensively used for saturation of carbon–carbon double bonds under these conditions.[7] The use of dioxane as solvent in this preparation was found to allow convenient operation in relatively concentrated solution, and excellent results have been attained with large runs at atmospheric or slightly elevated pressures.

In order to investigate further the scope and generality of the method as applied to other conjugated steroid dienes, several known isomers of ergosterol were prepared and subjected to hydrogenation over Raney nickel. The $\Delta^{8,14,22}$-isomer (ergosterol-B_1 acetate)[8] failed to adsorb hydrogen under the conditions adequate for rapid hydrogenation of ergosterol, a result in keeping with the reported resistance of the $\Delta^{8,14}$-dienic system to catalytic hydrogenation.[9] Ergosterol-D (the $\Delta^{7,9(11),22}$-isomer), of considerable interest because of its unsaturated center at the 11-position, similarly proved inert under the conditions of the hydrogenation, in contrast to results obtained with platinum in acidic medium.[3a] Ergosterol-B_3 acetate (the $\Delta^{7,14,22}$-isomer)[8] was found to be equally resistant to hydrogenation.

However, the $\Delta^{6,8(14),22}$-triene (ergosterol-B_2 acetate)[8] readily absorbed exactly one mole of hydrogen to afford in excellent yield an ergostadien-3β-ol acetate (VI), shown to be the $\Delta^{8(14),22}$-diene by quantitative conversion to the known $\Delta^{8(14)}$-ergosten-3β-ol acetate over platinum catalyst in neutral medium. The observed molecular rotation of the diene (M_D obsd. −117) is in fair agreement with the value calculated (M_D calcd. −99) using the side-chain rotatory contribution derived by Barton in his study of β-dihydroergosterol acetate.[10]

The reduction of dehydroergosterol acetate ($\Delta^{5,7,9(11),22}$-ergostatetraen-3β-ol acetate) seemed of potential importance because selective hydrogenation could conceivably lead directly to ergosterol-D acetate by saturation of the 5,6-double bond as in the case of ergosterol itself. However, under the conditions of the hydrogenation over Raney nickel an indefinite amount of hydrogen (approximating 1.3 moles) was absorbed to afford a complex reaction mixture suggestive of attack at more than one of the double bonds of the conjugated trienic system. The ultraviolet spectrum of the crude product indicated the presence of about 53% of ergosterol-D acetate, and suggested the presence of ergosterol acetate. The spectrum appeared to be very similar to that observed by Bergmann[1] for the crude product of the sodium–alcohol reduction of dehydroergosterol, indicating that the hydrogenation had probably taken a similar course to the sodium–alcohol reduction or platinum hydrogenation[3a] of this compound.

Experimental[11]

5-Dihydroergosterol (III) (A).—A solution of 0.793 g. (0.002 mole) of ergosterol (m.p. 156.0–158.5°, $[\alpha]^{24}D$ −117.5°, *c* 1.99, chloroform) in 14 ml. of peroxide-free dioxane was hydrogenated over about 1.2 g. of Raney nickel catalyst which had previously been saturated with hydrogen.[6] After three hours 51.0 ml. (105%) of the theoretical quantity of hydrogen had been absorbed and hydrogen uptake ceased. The reaction mixture was diluted with chloroform and the catalyst removed by filtration through a filter-aid. Concentration under reduced pressure afforded 0.749 g. (94%) of nearly pure III, m.p. 165.4–172.0°, $[\alpha]^{24}D$ −18.3° (*c* 1.97, chloroform). Recrystallization from methylene chloride–methanol afforded material m.p. 173.0–176.2°, $[\alpha]^{24}D$ −19.3° (*c* 2.06, chloroform) in 80% recovery.

(B).—An efficient large-scale hydrogenation was carried out using an apparatus constructed from a standard Parr hydrogenator tank by attaching a magnetically stirred 2-

(6) R. Mozingo, *Org. Syntheses*, **20**, 15 (1941).

(7) In a preliminary communication received subsequent to the completion of this work, Fieser and co-workers, ref. 2, have reported a similar case in the hydrogenation of 7-dehydrocholesterol to Δ^7-cholesten-3β-ol. This work does not point up the specificity of the catalyst in non-attack of reactive side-chain double bonds.

(8) A. Windaus, K. Dithmar, H. Murke and F. Suckfull, *Ann.*, **488**, 91 (1931).

(9) D. R. H. Barton and J. Cox, *J. Chem. Soc.*, 214 (1949).

(10) D. R. H. Barton, J. Cox and W. Holness, *ibid.*, 1771 (1949).

(11) All melting points corrected.

liter filter flask suitable for the large quantity of solvent required. In this apparatus a solution of 39.7 g. (0.1 mole) of ergosterol in 800 ml. of dioxane containing 50 g. of Raney nickel caused a pressure drop of 7.0 lb. (110% of the theory) of hydrogen when stirred for two hours under 10-15 lb. pressure at room temperature. At this time all hydrogen uptake ceased. From the filtered solution was isolated directly 40.1 g. (100%) of quite pure III, m.p. 170.8–172.4°.

5-Dihydroergosterol Acetate (IV).—A solution of 0.199 g. (0.0005 mole) of 5-dihydroergosterol (III) in 5 ml. of acetic anhydride containing one drop of pyridine was refluxed for 20 minutes. On cooling, 0.182 g. (82.5%) of the acetate IV separated as large plates, m.p. 174.6–177.4°, $[\alpha]^{24}D$ −21.2° (*c* 2.00, chloroform). The melting point on admixture with an authentic sample prepared by the method of Barton,[4a] m.p. 176.0–180.6°, was not depressed.

$\Delta^{8(14),22}$-Ergostadien-3β-ol Acetate (VI).—$\Delta^{5,8(14),22}$-Ergostatrien-3β-ol acetate, m.p. 119.0–120.6°, $[\alpha]^{25}D$ −94.0° (*c* 1.03, chloroform) was prepared essentially as described by Windaus[8] who reported the physical constants as m.p. 100°, $[\alpha]D$ −80.4°.[12]

A solution of 0.700 g. (0.0016 mole) of the acetate (V) in 20 ml. of dioxane was hydrogenated over about 1.5 g. of Raney nickel catalyst as described in the preparation of III (A). After three hours nearly the theoretical quantity of hydrogen had been absorbed and hydrogen uptake ceased. The filtered reaction mixture on concentration to dryness under reduced pressure afforded 0.690 g. of crystalline product as small colorless platelets, m.p. 111.8–114.0° (98%). Recrystallization from ethyl acetate–methanol afforded an 82% recovery of pure $\Delta^{8(14),22}$-ergostadien-3β-ol acetate (VI), m.p. 122.6–124.0°, $[\alpha]^{26}D$ −26.5° (*c* 1.12, chloroform). The physical constants were not altered by further recrystallization.

Anal. Calcd. for $C_{30}H_{48}O_2$: C, 81.76; H, 10.98. Found: C, 81.96; H, 10.89.

Hydrogenation of $\Delta^{8(14),22}$-Ergostadien-3β-ol Acetate (VI).—A solution of 0.220 g. (0.0005 mole) of VI in 10 ml. of anhydrous peroxide-free dioxane was hydrogenated over 0.050 g. of prereduced platinum oxide catalyst. After 69 minutes, 12.4 ml. (100%) of the theoretical quantity of hydrogen required for saturation of one double bond had been absorbed. The filtered reaction mixture on concentration afforded quantitatively nearly pure $\Delta^{8(14)}$-ergosten-3β-ol acetate, m.p. 101.5–110.0°. Recrystallization from ethyl acetate afforded pure acetate as large glistening plates, m.p. 109.0–110.5°, $[\alpha]D$ +2.7° (*c* 1.11, chloroform). The melting point on admixture with an authentic sample, m.p. 109.0–110.5°, $[\alpha]D$ +4.0 (*c* 1.01, chloroform), prepared by hydrogenation of ergosterol acetate over platinum in chloroform, was not depressed.

Hydrogenation of $\Delta^{8,14,22}$-Ergostatrien-3β-ol Acetate.—A solution of 0.397 g. (0.001 mole) of $\Delta^{8,14,22}$-ergostatrien-3β-ol acetate (ergosterol-B_1 acetate),[8] m.p. 139.8–142.0°, $[\alpha]D$ −57.9° (*c* 1.04, chloroform) in 11 ml. of dioxane was stirred over prereduced Raney nickel catalyst (0.58 g.) in an atmosphere of hydrogen for several hours. No hydrogen absorption was observed, and the product isolated on filtration and concentration proved to be unchanged ergosterol-B_1 acetate, m.p. 139.0–144.4°, not depressed on admixture with starting material.

Hydrogenation of $\Delta^{7,9(11),22}$-Ergostatrien-3β-ol Acetate.—$\Delta^{7,9(11),22}$-Ergostatrien-3β-ol acetate (ergosterol-D acetate) was prepared by the method of Barton,[3a] m.p. 165.8–169.0°. Hydrogenation of a 0.175-g. portion over 0.43 g. of Raney nickel in 10 ml. of dioxane by the usual procedure resulted in no hydrogen uptake and quantitative recovery of starting material, m.p. 162.0–168.9°, $[\alpha]D$ +26.7° (*c* 0.98, chloroform), not depressed on admixture with an authentic sample.

Hydrogenation of $\Delta^{5,7,9(11),22}$-Ergostatetraen-3β-ol Acetate.—$\Delta^{5,7,9(11),22}$-Ergostatetraen-3β-ol acetate (dehydroergosterol acetate) was prepared by mercuric acetate dehydrogenation of ergosterol acetate as described by Bergmann and Stevens,[13] m.p. 146.2–151.0°, $[\alpha]D$ +157° (*c* 2.03, chloroform).

A solution of 0.437 g. (0.001 mole) of the tetraene acetate in 12 ml. of dioxane was hydrogenated over 0.63 g. of Raney nickel catalyst. Hydrogen uptake showed a sharp inflection after 1.33 moles had been absorbed, and only a slight further uptake was observed. Filtration and concentration *in vacuo* afforded a quantitative recovery of crystalline product as tiny platelets, m.p. 149.8–156.4°, $[\alpha]^{25}D$ +21.8° (*c* 1.97, chloroform). An ultraviolet spectrum measured in ether solution showed strong bands at 235 and 242.5 mμ (log ϵ 3.82), indicating the presence of about 53% $\Delta^{7,9(11),22}$-ergostatrienol acetate.

Acknowledgments.—We wish to express our appreciation to Mr. Robert Richter for technical assistance. We are indebted to Dr. John Means and his associates of these laboratories for the microanalyses.

(12) An alternate preparation of this triene will be the subject of a later communication.

(13) W. Bergmann and P. G. Stevens, *J. Org. Chem.*, **13**, 10 (1948).

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[CONTRIBUTION FROM THE EASTERN REGIONAL RESEARCH LABORATORY[1]]

Diesters of Lactic Acid. Esterification of Lactates with Dibasic Acids

BY C. E. REHBERG AND MARION B. DIXON

Twenty-six esters made by the esterification of lactate esters with dibasic acids are described. Boiling points, refractive indices, densities and viscosities of the esters at different temperatures are given. Potential usefulness of these compounds as plasticizers is suggested.

In the previous paper of this series,[2] the adipates of a number of esters of lactic acid were described, and their potential usefulness as plasticizers was suggested.

The present paper reports work of the same general nature in which instead of adipic acid, various other dibasic acids were used to esterify the hydroxyl group of esters of lactic acid. These products may be represented by the formula

$$X[-OCH(CH_3)COOR]_2$$

where X is the divalent acyl radical of a dibasic acid and R is the alcohol radical of the lactic ester. The dibasic acids used were phthalic, maleic, succinic, sebacic, carbonic and benzenephosphonic. Most attention was devoted to phthalic esters because of their importance in the plasticizer industry.

The products obtained by the esterification of dicarboxylic acids with allyl lactate contain two allyl groups in the molecule and are polymerizable. Several such esters have been reported. Thus, allyl lactate has been treated with acid chlorides to produce the carbonate, succinate, fumarate, adipate, sebacate and phthalate.[3] The maleates of allyl[4]

(1) One of the laboratories of the Bureau of Agricultural and Industrial Chemistry, Agricultural Research Administration, U. S. Department of Agriculture. Article not copyrighted.

(2) Rehberg and Dixon, THIS JOURNAL, **72**, 5757 (1950).

(3) Howald and Jones, U. S. Patent 2,462,042, Feb. 15, 1949.

(4) Jones, U. S. Patent 2,443,915, June 22, 1948.