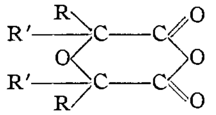
The Structure of Benzilide

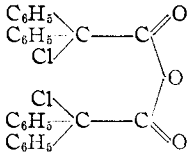
BY HARRY H. WASSERMAN AND HOWARD E. ZIMMERMAN

The pyrolysis of α-hydroxy acids which may result in polyester or lactide formation[1,2,3] has yielded products which, in certain instances, have been formulated as ether-anhydrides. For example, it has been proposed[4] that in the pyrolysis of mandelic acid and benzilic acid, the anhydrides (I) and (II), respectively, are formed. The interaction of two moles of α-hydroxy acid in this manner (head-to-head elimination of water from the two hydroxyl groups) has been ascribed[4] to the enhanced reactivity of the benzyl-type alcohol, where there is aryl substitution on the hydroxyl-bearing carbon.

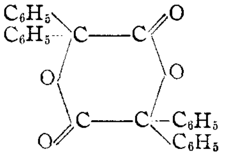


I R = H
R′ = C_6H_6
II R = R′ = C_6H_5

In the case of benzilide (derived from benzilic acid) the assignment of an ether-anhydride structure (II) to the pyrolysis product is based primarily on synthetic evidence reported by Stollé.[5] When α,α′-dichlorotetraphenylacetic anhydride (III) was heated with mercuric oxide in boiling benzene, benzilide, identical with the pyrolytic product, was isolated. In this reaction, substitution of oxygen for the two chlorine atoms would yield the anhydride (II); Stollé assumed that a lactide structure (IV) could result only by rearrangement.



III



IV

On the basis of the purely chemical evidence, such as the ready hydrolysis of benzilide to benzilic acid, the cleavage to benzophenone, diphenylketene and carbon dioxide by slow distillation, and the formation of diphenylacetic acid anilide by heating with aniline, one cannot distinguish between the two possibilities, (II) and (IV). However, infrared data, reported here, clearly indicate that benzilide has the lactide structure (IV).

Both *meso*-lactide and benzilide exhibit a single intense band in the lactone region of the infrared at 5.66–5.69 μ (Fig. 1), whereas glutaric anhydride shows the typical anhydride splitting in the carbonyl region, with absorption maxima at 5.55 and 5.68 μ. It may thus be concluded that the lack of correspondence between benzilide and the model six-membered cyclic anhydride in the infrared makes the ether-anhydride formulation extremely unlikely, whereas the good agreement between the spectra of benzilide and the related symmetrical lactide model represents convincing evidence in favor of the lactide structure (IV).

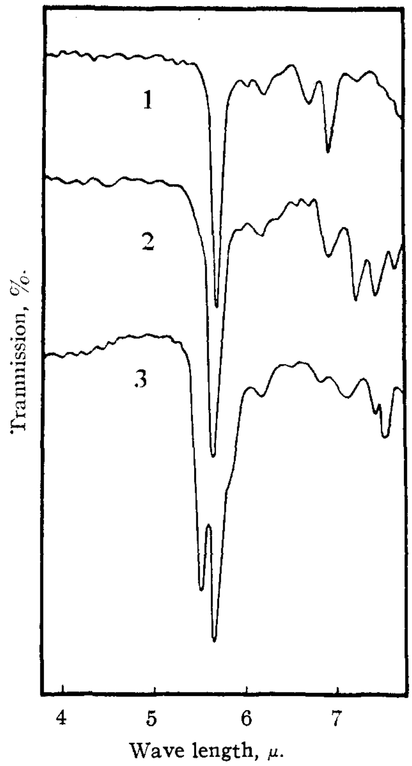


Fig. 1.—Infrared absorption spectra in chloroform: (1) benzilide; (2) meso-lactide; (3) glutaric anhydride.

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[1] Drechsel, *Ann.*, **127**, 154 (1863); Fittig and Thomson, *ibid.*, **200**, 79 (1879).

[2] Krafft and Dyes, *Ber.*, **28**, 2591 (1895).

[3] Bischoff and Walden, *Ann.*, **279**, 100 (1894).

[4] Hurd, "The Pyrolysis of Carbon Compounds," A. C. S. Monograph Series, 1929, p. 433.

[5] Stollé, *Ber.*, **43**, 2473 (1910).

Micro Syntheses with Tracer Elements. IV. The Synthesis of Hexestrol Labeled with Tritium[1]

BY D. LLOYD WILLIAMS AND ANTHONY R. RONZIO

Information was desired regarding the stability of organic compounds containing the isotope tritium in place of hydrogen. Since a higher concentration of radioactivity can be imparted to an organic compound by means of tritium than with almost any other element, this method of labeling should prove to be ideal for those chemical entities which produce profound biologic changes in the living system when present in exceedingly small concentrations.

A group of compounds having such an effect are the sex hormones. Minute amounts of these chemical entities can bring about deep seated

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[1] This document is based on work performed under U. S. Government Contract No. W-7405-Eng-36 with the Los Alamos Scientific Laboratory of the University of California.

physiological changes in both the male and female.

One of the female sex hormones, "hexestrol," is synthetic in the sense that it does not occur naturally in living organisms but it is a very powerful estrogen. This compound may be easily labeled with tritium and was accordingly chosen for study.

Hydrogenation of the unsaturated linkages of either "Stilbestrol" (4,4'-dihydroxy-α,β-diethylstilbene) or of "dienestrol" (3,4-di-(4-hydroxyphenyl)-2,4-hexadiene) should afford an efficient means of labeling "hexestrol" (3,4-di-(4-hydroxyphenyl)-hexane) with tritium.

The *d*-, *l*-, *meso*- and racemic forms of hexestrol are possible since the compound contains two asymmetric carbon atoms. Dodds, *et al.*,[2] who first isolated hexestrol from the demethylation productions obtained from anethole also isolated an isomer melting at 128° (hexestrol, m. p. 184–185°) which was a much less potent estrogen. This latter isomeric compound was named "isohexestrol" by Wessely and Welleba[3] who succeeded in resolving the compound into the *d*- and *l*-forms. An equimolar mixture of the *d*- and *l*- forms melted at 129°, confirming the accuracy of their separation. These investigators accordingly assigned the *meso*-structure to hexestrol.

Stilbestrol does not seem desirable as a starting material since it is known to give a mixture of hexestrol and isohexestrol; the proportion of the two compounds depending upon the catalyst used and the conditions of hydrogenation.[3–6] Dodds, *et al.*,[2] reported the successful synthesis of dienestrol and the hydrogenation of the compound to hexestrol with palladium catalyst and acetone as solvent. While a quantitative yield was reported, the exact nature of the catalyst and the conditions for the hydrogenation were not given, nor was the presence of isohexestrol in the product mentioned.

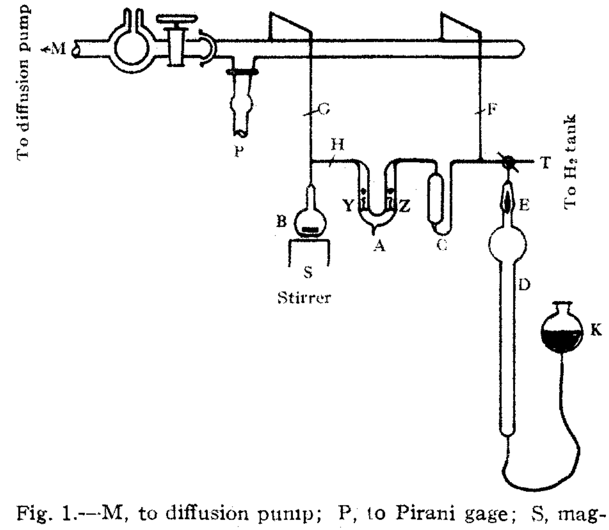

Fig. 1.—M, to diffusion pump; P, to Pirani gage; S, magnetic stirrer; T, to hydrogen tank.

Reduction of this compound using 10% palladium catalyst with hydrogen at atmospheric pressure required about 8 hours for complete hydrogenation. The dried product in every case weighed in excess of 100% due to solvent of crystallization.

A 72–77% yield of hexestrol was obtained when the product was recrystallized from benzene. A large part (27%) of the fraction remaining in the benzene was found to be isohexestrol, a by-product not reported by Dodds.[2] Recrystallization from benzene is an excellent method for the separation of hexestrol from isohexestrol.

Experimental

Labeling of Hexestrol with Tritium (H^3).—Since the health hazards involved in work with tritium are as yet uncertain, and since tritium is strongly adsorbed on glass surfaces, the system shown in Fig. 1 was designed and used in the hydrogenation. All contact of tritium with grease was eliminated and the system was so arranged that the contaminated portion could be isolated.

The isotope labeling of dienestrol was carried out according to the following procedure. Tritium diluted with hydrogen was sealed in U tube A which contained 2 breakoffsky sections Y and Z. The reaction chamber B was a 25-ml. flat bottomed, thick-walled flask containing catalyst, solvent, dienestrol and a short glass-enclosed section of iron rod which served as a magnetic stirrer. A U tube C, having a 25-ml. capacity was connected to gasometer D, the outlet of which contained a ground glass valve E. This valve was used to prevent the accidental flow of mercury out of D and into the system. Constrictions in the glass tubing were made at points F, G and H.

Tube A containing 500 mc. of tritium mixed with hydrogen (total volume about 5 ml.) and reaction chamber B containing a mixture of 503 mg. of dienestrol, 54 mg. of 10% Pd-on-carbon, 5 ml. of acetone and the magnetic stirrer was sealed to the apparatus. The contents of B were frozen in liquid nitrogen and the entire apparatus evacuated to a pressure of 3–5 microns. After testing for leakage, the manifold was isolated from the remainder of the system by sealing off at F and G.

When the solvent in B had melted completely, the breakoffsky at Y was broken and the H^3_2–H_2 was allowed to react for 45 min. with the well stirred reaction mixture. In the meanwhile the gas buret D was filled with hydrogen. With the stirrer at rest and with leveling bulb K raised to

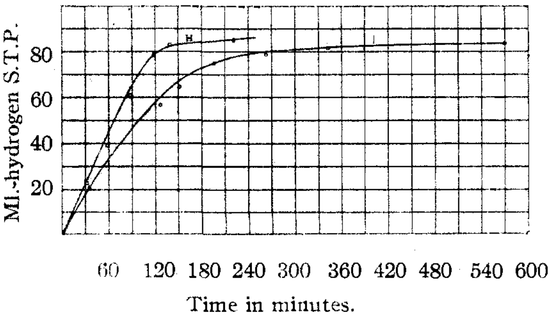

Fig. 2.—Rates of hydrogenation of dienestrol: □, expt. using $H^3{}_2$–H_2, 500 mc. of H^3; ○, expt. using H_2.

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[2] Campbell, Dodds and Lawson, *Nature*, **142**, 1121 (1938).

[3] Wessely and Welleba, *Ber.*, **74**, 777 (1941).

[4] Docker and Spielman, THIS JOURNAL, **62**, 2163 (1940).

[5] Campbell, Dodds and Lawson, *Proc. Roy. Soc.* (*London*), **B128**, 253 (1939–1940).

[6] Dodds, Goldberg, Lawson and Robinson, *ibid.*, **B127**, 140 (1939).

maintain a positive pressure in the system, the breakoffsky Z was broken. At this point the initial reading of the volume of hydrogen was taken. When stirring was again resumed, the stream of hydrogen served to carry over into the reaction chamber any tritium gas remaining in U tube A. In this, as well as in the pilot runs, the progress of the reaction was followed by the decrease in the volume of hydrogen.

After hydrogenation was complete, the bulb K was lowered and tube C and bulb D were both cooled with liquid nitrogen. When all the solvent in A had distilled off, the system was sealed at H and the reaction flask B was removed. The product was isolated by redissolving in dry acetone and filtering through a thin bed of diatomaceous earth and decolorizing carbon. The flask and filtering medium were washed thoroughly with acetone (total volume about 20 ml.). Evaporation of the filtrate and washings in a low vacuum gave a yield of 594.6 mg. of crude product (116.2%). In all the reduction experiments made, the yield was in excess of 100%. Drying in a vacuum caused no loss in weight, while heating at 100° caused sublimation and loss of product.

When absolute ethanol was used as solvent, the excess weight was 23%. The yields of crude product obtained in pilot runs with acetone as solvent were 113.1, 119.0, 118.3, 119.5, 119.5%; with alcohol as solvent the yields were 123.5, 105.5, 123.5, 123.8%. A weighed amount of catalyst used in these experiments did not lose weight when extracted with either acetone or alcohol. The excess weight with either solvent corresponds closely to one mole of solvent.

The rates of hydrogen uptake in experiments with tritium and with hydrogen are shown in Fig. 2. Under identical experimental conditions there was an apparent increase in the rate of hydrogenation when tritium was present. Since this experiment could not be repeated due to the scarcity of tritium, this catalytic effect invites further investigation. The only explanation that we can offer for the increased rate of hydrogen uptake when tritium is present is that the high concn. of radioactivity, 500 mc., brings about an activation of reactants or some related phenomena. Alpha rays are known to bring about a dissociation of hydrogen (see Munde, *et al.*, *Bull. soc. chim. Belg.*, **56**, 386 (1947); Munde, *et al.*, *ibid.*, **57**, 88 (1948)).

Separation of Hexestrol and Isohexestrol.—The solubility data for pure hexestrol in benzene[7] in the temperature range 15–16° indicated that a ratio of 5 ml. of benzene per 100 mg. of hexestrol should give a 90% yield of product after recrystallization. The crude product was dissolved in 30 ml. of hot benzene. Crystals were allowed to form at room temperature and then at 6–8° (2 hr.). The mother liquor was filtered and transferred into a tared 40-ml. cone with a filter stick. The colorless crystals, dried in a vacuum, weighed 386.4 mg. (73.8%) and melted at 184–185°.

Evaporation of the mother liquor to dryness left 220.8 mg. of colorless residue which, recrystallized from 5 ml. of benzene and treated as above, gave 34.9 mg. (6.8%) of product melting at 160–164°. This is apparently a mixture of hexestrol and isohexestrol.

The second mother liquor was evaporated to a volume of 1.5 ml. and cooled to 6° for one hour. The mother liquor was removed as before and the colorless needles, washed with 0.5 ml. of benzene and dried, weighed 142.8 mg. (28%) and melted at 126–127°. The mother liquor from these crystals upon evaporation to dryness gave 30.2 mg. of crystals melting at 124–125°. These last two fractions correspond to isohexestrol.

Anal. Calcd. for $C_{18}H_{22}O_2$; C, 79.96; H, 8.20. Found: C, 80.00, 80.00; H, 8.12, 8.05.

The above method of separation gave, in five separate experiments: 72–77% yields of product melting at 183–185°; 5–7% of product melting at 175–180°; 26–27% of product melting at 126–128°; about 7% of product melting at 123–125°.

Other solvents tried (dioxane, dioxane–water, carbon tetrachloride) did not give as sharp a separation of hexestrol from isohexestrol.

Acknowledgment.—We wish to thank Dr. C. W. Sondern and the White Laboratories, Inc., for the dienestrol used in this investigation.

Summary.—1. The estrogen "hexestrol" (*meso*-3,4-di-(4-hydroxyphenyl)-hexane) has been prepared labeled with tritium.

2. Both *meso* and racemic hexestrol are obtained by the hydrogenation of "dienestrol" (3,4-di-(4-hydroxyphenyl)-2,4-hexadiene) with palladium-on-carbon catalyst.

3. The presence of 500 mc. of tritium exerted a significant influence upon the rate of uptake of hydrogen.

4. The hexestrol labeled with tritium contained approximately 1 mc. of radioactivity per milligram.

LOS ALAMOS, NEW MEXICO RECEIVED MAY 5, 1950

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[7] Cheymol and Carayon-Gentil, *Bull. Soc. Chim. Biol.*, **28**, 136 (1946) (*C. A.*, **41**, 3518e (1947)).

The Magnetic Susceptibility of Iodine Dioxide

BY W. K. WILMARTH AND S. S. DHARMATTI

The "dioxides" of chlorine, bromine and iodine have all been known for many years but only in the case of chlorine is the degree of polymerization known, and even here only dilute solutions have been studied.[1] Iodine dioxide, the more easily prepared of the latter two members, is a non-hygroscopic relatively stable compound at room temperature. It either reacts with or is insoluble in all common solvents, so measurements can only be made on the pure solid. Magnetic susceptibility measurements, described below, show that the compound is diamagnetic and hence the molecule must contain an even number of IO_2 units. It would appear that transition in bond type must occur either in solid chlorine dioxide or at bromine dioxide. We are at present engaged in preparing bromine dioxide in quantities sufficient for both magnetic susceptibility measurements and clarification of its general chemistry.

Experimental

Iodine dioxide was prepared as described by M. M. P. Muir.[2] The initial yellow solid was decomposed by exposure to moist air and the iodine dioxide separated from iodine by washing with water, alcohol and ether. The analysis, after several such washings, was obtained by adding excess iodide to a known quantity of iodine dioxide and titrating with standard thiosulfate. *Anal.* Found: I, 79.86; calcd.: I, 78.8.

Magnetic Susceptibility of $(IO_2)_x$.—A specimen was carefully packed in the conventional glass tube and measured in the solid state using the Gouy technique. A gram susceptibility of -0.239×10^{-6} was obtained, corresponding to a molal susceptibility of -76.0×10^{-6} using

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[1] N. W. Taylor, THIS JOURNAL, **48**, 854 (1926).

[2] M. M. P. Muir, *J. Chem. Soc.*, **95**, 656 (1909).