[CONTRIBUTION FROM THE SCHOOL OF CHEMISTRY, RUTGERS UNIVERSITY]

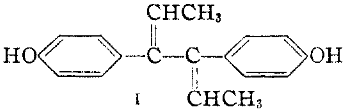
Studies on the Pinacol Rearrangement. III.[1] The Determination of Products Resulting from the Dehydration of 3,4-Bis-(*p*-acetoxyphenyl)-3,4-hexanediol

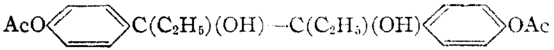
BY JOHN F. LANE AND LEONARD SPIALTER[2]

This paper presents a method for separating chromatographically on silicic acid the products of dehydration of 3,4-bis-(*p*-acetoxyphenyl)-3,4-hexanediol into four fractions: (1) diacetates of the three isomeric dienestrols and of indenestrol, (2) 4,4-bis-(*p*-acetoxyphenyl)-3-hexanone, (3) unreacted pinacol and (4) polymerized dienes.

Since two of the isomeric dienestrol diacetates (α and γ) rapidly and quantitatively absorb bromine to the extent of one mole, whereas the diacetates of the third isomer (β) and of indenestrol react sluggishly with this reagent, it has been found possible to ascertain the combined quantities of α- and γ-dienestrol in fractions (1) above to an accuracy of about 2%.

In 1939 Dodds, Goldberg, Lawson and Robinson reported[3] the synthesis of a potent new estrogen, 3,4-bis(*p*-hydroxyphenyl-2,4-hexadiene) now commonly called dienestrol, by the dehydrating action of a mixture of acetyl chloride and acetic anhydride on the pinacol 3,4-bis-(*p*-acetoxyphenyl)-3,4-hexanediol (m.p. 215–216°), followed by hydrolysis of the resulting dienestrol diacetate (m.p. 119–120°). Adler and Lundin[4] later assigned to the pinacol used in the original synthesis the *meso* configuration and isolated the *racemic* form as a monoethanolate (m.p. 83–84°).

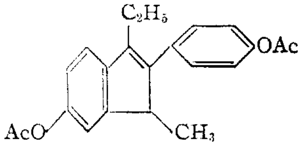

I


II

Although the dehydration of II and of related pinacols has received much attention in the recent literature[5–9] chiefly because of the physiological importance of I, no very precise information exists as to the nature and amounts of the products formed when either *meso*- or *rac*-II is treated with dehydrating agents.

It is the purpose of this paper to initiate an attack on the mysteries currently surrounding this reaction by presenting certain experimental techniques which make possible a more quantitative approach to the problem of product compositions than has hitherto been possible. Application of these techniques to the question of competition between rearrangement and dehydration as a function of reactants and conditions will then be described in Part IV[10] of this series.

The action of a dehydrating agent on II would be expected to lead, in addition to the diacetate of I, to stereoisomers[11] of this compound, polymers of the dienes, indenestrol "A" diacetate, which is known[12] to be easily produced from the diacetate of I by the action of acids, and the pinacolone, 4,4′-bis-(*p*-acetoxyphenyl)-3-hexanone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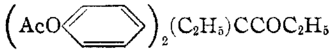
IV

As described in the Experimental part, by chromatography on silicic acid, synthetic mixtures of the above compounds can be resolved into three components: namely, a first fraction containing the three isomeric dienestrol diacetates, which is eluted by benzene containing 0.5% ethyl ether; a second fraction, consisting exclusively of IV, which is eluted by benzene containing 7.5% ether; and a third fraction, consisting of *meso*- or *rac*-II, eluted by benzene containing 16.7% ether.

Attempts to resolve, by further chromatography, the mixtures of unsaturates obtained in the first fractions were unsuccessful. But it was found possible to determine approximately the sum of the amounts of α- and γ-dienestrol present by titration of samples with bromine in acetic acid in the presence of sodium acetate. The diacetates of both α- and γ-I absorb rapidly and quantitatively one mole of bromine under these conditions. On the other hand, the diacetate of β-I and III are only slowly attacked by this

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(1) *Cf.* J. F. Lane and D. R. Walters, THIS JOURNAL, **73**, 4234 (1951).

(2) White Laboratories Fellow in Rutgers University 1947–1948. Department of Chemistry, Harvard University.

(3) E. C. Dodds, L. Goldberg, W. Lawson and R. Robinson, *Proc. Roy. Soc.* (*London*), **B127**, 148 (1939).

(4) E. Adler and M. Lundin, *Arkiv Kemi Mineral., Geol.*, **19A**, No. 24, 1 (1945); *cf. C. A.*, **41**, 2028 (1947).

(5) N. R. Campbell and F. W. Chattaway, *Proc. Roy. Soc.* (*London*), **B130**, 435 (1942).

(6) G. I. Hobday and W. F. Short, *J. Chem. Soc.*, 609 (1943); British Patent 566,581 (Jan. 4, 1945).

(7) Hoffman-LaRoche and Co., British Patent 598,798 (Feb. 26, 1948); U. S. Patent 2,465,505 (Mar. 29, 1949).

(8) J. B. Niederl, *et al.*, THIS JOURNAL, **70**, 619, 2894 (1948); *J. Org. Chem.*, **14**, 10 (1949).

(9) C. F. H. Allen, C. G. Eliot and A. Bell, *Can. J. Research*, **17B**, 75 (1939).

(10) J. F. Lane and L. Spialter, THIS JOURNAL, **73**, 4411 (1951).

(11) Three geometrical isomers of (I) are theoretically possible. The isolation of one of these, an "isodienestrol" (m.p. 184–185°), distinct from Dodds' compound, has been reported by Hobday and Short (ref. 6, *cf.* also H. v. Euler and, E. Adler, *The Svedberg* (Mem. Vol.) 246 (1944); *C. A.*, **39**, 1638 (1945). Recently (1948) Dr. Phillip Breivogel of the White Laboratories, Newark, N. J. (private communication) isolated the third isomer (m.p. 121–122°; diacetate, m.p. 104.5–105°) which he characterized by hydrogenation to *meso*-hexestrol and by isomerization in ethanolic hydrogen chloride to indenestrol "A." In this and succeeding papers dealing with these compounds we shall refer to Dodds' compound as "α-dienestrol" (α-I), Hobday's compound as "β-dienestrol" (β-I) and Breivogel's compound as "γ-dienestrol" (γ-I). The relative estrogenic potencies as determined by Breivogel by tests on ovariectomized rats are: α,1; β,0.003; γ,0.03.

(12) E. Adler and B. Hagglund, *Arkiv Kemi, Mineral, Geol.*, **19A**, No. 23, 1 (1945); *C. A.*, **41**, 2030 (1947). *Cf.* W. Hausman and A. E. Wilder-Smith, *Nature*, **161**, 892 (1948); *J. Chem. Soc.*, 1030 (1949).

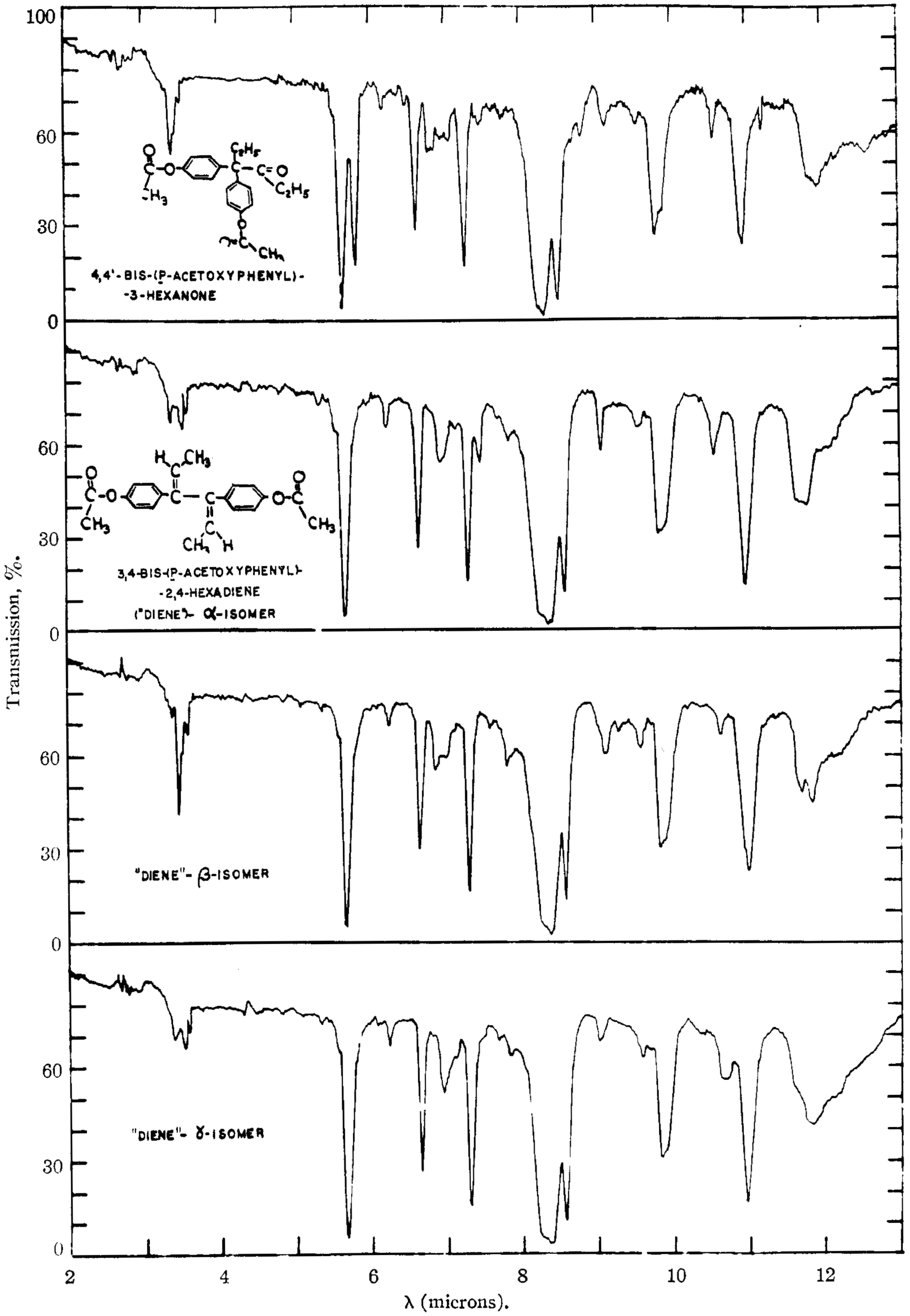

Fig. 1.—Infrared absorption spectra.

reagent. In general, the results obtained by titrating mixtures of all four compounds gave values for the combined amounts of α- and γ-I which were slightly high (*ca.* 2%), presumably because of interference at the end-point by the diacetate of β-I and III.

Experimental

***meso* and *rac*-II.**—To 100 g. of commercial (non-acetylated) II[13] was added 300 ml. of acetic anhydride. Warming the mixture gave a solution which was refluxed for 30 minutes and then filtered through a sintered glass funnel. On cooling crystals separated which were removed by filtration and washed with ether. Recrystallization from dioxane–toluene gave 48 g. (37%) of pure *meso*-II, m.p. 217–218°

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(13) This material was supplied as needed by the White Laboratories Inc., Newark, N. J. Prepared by the pinacolic reduction of *p*-hydroxypropiophenone, it consisted of a mixture of approximately equal amounts of the *meso*- and *rac*-forms.

(reported[4] 215–216°).[14] From the combined filtrates the solvent was removed *in vacuo*, and the residual reddish oil was taken up in 100 ml. of warm methanol. The solution was chilled in ice, whereupon white crystals began slowly to separate. After one hour the mixture was filtered. Recrystallization of the crude material from methanol gave 49 g. (43.5%) of *rac*-II methanolate, m.p. 91–92° (softening at 85°).

Anal. Calcd. for $C_{22}H_{26}O_6\cdot CH_3OH$: CH_3O, 7.42. Found: CH_3O (Zeisel), 7.28, 7.13.

Diacetates of the α,β,γ-Isomers of I.—These substances were supplied to us in highly purified condition by the White Laboratories, Inc., where they had been isolated from mixtures resulting from the action of acetyl chloride and acetic anhydride on mixtures of *meso* and *rac*-II. Their melting points were, respectively: α, 123.2–123.5°; β, 147–148°; γ, 104.5–105.0° (ligroin).

Recrystallization of the γ-isomer from cyclohexane gave a substance melting at 73.5–74.5°. When, however, the melt was allowed to cool, it crystallized to give a substance melting at 103–104°. To check whether this behavior was due to change in crystalline modification or to solvent of crystallization 200 mg. of the high-melting substance was dissolved in 5 ml. of warm cyclohexane in a tared flask. Removal of the solvent *in vacuo* gave 200 mg. of a crystalline residue, m.p. 70–72°. On cooling the melt crystallized, and redetermination of the m.p. gave 100–102°. The low-melting substance is evidently a solid-phase modification of the high-melting form.

Indenestrol "A" Diacetate (III).—This substance, also supplied by the White Laboratories, Inc., melted at 117–118°.

The pinacolone (IV), m.p. 90–91° (reported[6] 91–92°), was prepared by the action of sulfuric acid in acetic acid on commercial (non-acetylated) II, followed by acetylation (acetic anhydride–pyridine) of the resulting crude pinacol.

Infrared Spectra.—The infrared spectra[15] of the pinacolone IV and the three isomeric diene diacetates (I), are shown in Fig. 1. They are fairly similar as might be expected for large molecules with so many identical strongly absorbing groups. The ketone curve differs most strikingly from those for the dienes in that it alone possesses, as expected, a carbonyl band at 5.83 microns. There are also some small band-shifts apparent. The absence of any hydroxyl vibration appears to rule out the presence of significant amounts of the enol tautomer of IV, at least in carbon tetrachloride as the solvent.

The only differences between the diene traces seem to be the small ones which one might expect to find among *cis-trans* isomers.

Chromatographic Studies.—The columns used in these studies were glass tubes 22 cm. × 1.0 cm. (i.d.) with glass stopcocks fused to the bottoms. Adsorbent beds were constructed on a layer 1 cm. thick of purified sea sand, supported on a mat of glass wool, by pouring a slurry of silicic acid (Eimer and Amend Co. C.P. grade) in benzene into the column, previously half-filled with benzene. In general a weight of silicic acid was taken equal to 40 times that of the sample to be analyzed. It was found that every gram of adsorbent retained 2 ml. of eluting solvent; this minimum volume of displacing solvent, in the succeeding text, is referred to as the "elution unit" (E.U.).

Weighed samples of materials to be analyzed were dissolved in the minimum quantity of benzene (C.P., distilled over sodium) and transferred quantitatively to the freshly prepared column. Elution with 12 E.U. of benzene containing 0.5% ethyl ether (Mallinckrodt anhydrous, distilled over sodium) sufficed completely to remove the isomeric dienestrol diacetates and indenestrol diacetate. The eluting solution was then changed to benzene containing 7.5% ethyl ether. Elution with 9 E.U. of this solvent sufficed to remove the pinacolone diacetate (IV). The composition of the eluting solvent was next changed to benzene containing 16.7% ethyl ether. Elution with 7 E.U. of this solvent removed the pinacol diacetates.

Mixtures obtained[10] from the action of dehydrating agents on the pinacols often contain small amounts of polymeric dienes. These are not eluted by the above treatment, but are quantitatively removed from the column by 5 E.U. of pure ethyl ether.

TABLE I

TITRATION OF THE DIACETATES OF α-I AND γ-I AND OF MIXTURES CONTAINING THEM WITH BROMINE IN ACETIC ACID

Composition taken, mg.					Bromine absorbed		Weight (mg.) of α-I and γ-1 diacetates	
α-I	β-I	γ-I	III	IV	Normality	Volume, ml.	Calcd.	Obsd.
50.0					0.149	0.985	50.0	51.5
		50.0			.149	0.994	50.0	51.7
100.2		101.7		99.6	.149	3.920	203	208
63.9	35.6	138.0			.149	3.992	202	208
72.3	25.2	119.6		94.7	.149	3.782	192	198
112.2	30.1	102.7			.140	4.467	215	219
69.7		125.3	24.8		.140	4.061	195	199
80.9	22.1	130.2	25.0	50.3	.140	4.412	211	216

Typical data on the analysis of synthetic mixtures in terms of (1) total monomeric unsaturated (I and III), (2) pinacolone (IV) and (3) pinacols (II) follow:

	Taken (mg.)					Found (mg.)		
Expt.	α-I	γ-I	III	IV	II	(1)	(2)	(3)
1		50.2		32.2		51.0	32.0	..
2			20.7	10.6		21.0	10.7	..
3				31.6	20.8(*r*)	..	31.4	21.3
4	15.5	10.3		45.3	13.1(*m*)	24.7	46.8	11.1

Titrations with Bromine.—In general, a sample containing up to 0.65 mmole of bromine-absorbing diene was dissolved in 25 ml. of 1.76 potassium acetate in glacial acetic acid. The solution was then titrated with 0.14*M* bromine in acetic acid (standardized against sodium arsenite in the presence of excess potassium iodide) with rapid dropwise addition and constant swirling of the flask until the bromine absorption began to slacken. The bromine solution was then added at the rate of one drop (0.01 ml.) every 10 seconds until a faint yellow end-point appeared which was stable for at least 10 seconds. Results of analyses so performed on the diacetates of α-I, γ-I and mixtures of these with other substances are given in Table I.

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[14] All melting points reported in this paper were determined on the Kofler micro hot-stage.

[15] Determined, through the courtesy of the Department of Chemistry, Harvard University, with their Baird Associates infrared spectrograph.