[CONTRIBUTION FROM THE DEPARTMENT OF THERAPEUTICS, NEW YORK UNIVERSITY COLLEGE OF MEDICINE]

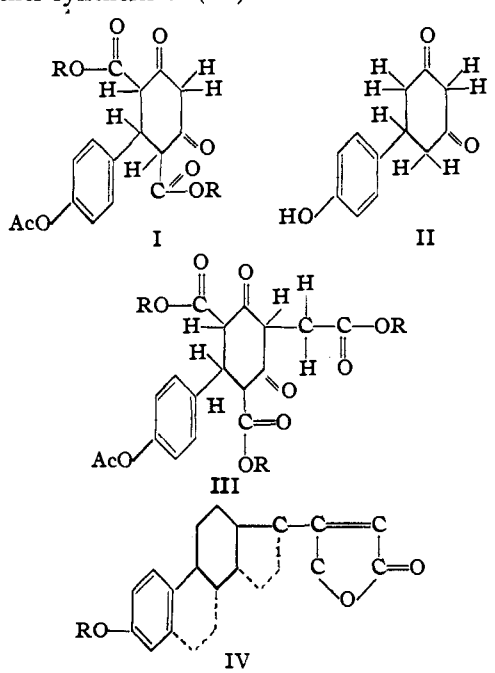
Synthesis of 1-(*p*-Acetoxyphenyl)-2,6-dicarbethoxy-cyclohexanedione-3,5 and Derivatives

BY PHILIPPOS E. PAPADAKIS

Fieser[1] and Strain[2] have brought together much of the work that has been done on the extraction, purification and therapeutic standardization of the cardiac glycosides found in the digitalis plant. They also have reported the information that has accumulated concerning the structure and the essential functional groups of these substances.

The synthesis of simpler substances having the essential functional groups of the natural glycosides has been the object of recent investigations by Elderfield[3] and others,[4] for it is hoped that some such substances may have advantages over the natural products in cardiotherapy.

In the present report the author describes the preparation of three substances, 1-(*p*-acetoxyphenyl)-2,6-dicarbethoxy-cyclohexanedione-3,5 (I), 4-hydroxyphenyl-cyclohexanedione-3,5 (II), and 1-(*p*-acetoxyphenyl)-2,6-dicarbethoxy-4-carbethoxymethyl-cyclohexanedione-3,5 (III), which should prove useful as starting materials in the further synthesis of (IV).



The synthesis of substance (IV) will furnish a compound which will have considerable similarity, in structure and in functional groups, to the cardiac glycosides. Compounds (I), (II) and (III) offer certain advantages for further synthesis, namely, the reactive hydrogen on carbon 4 and the two keto groups, meta to each other, on positions 3 and 5 of the cyclohexanedione ring.

The sequence of the syntheses involved in the present work is

p-Hydroxybenzaldehyde ⟶ *p*-Acetoxybenzaldehyde ⟶ Ethyl 4-acetoxybenzalmalonate ⟶ 1-(*p*-Acetoxyphenyl)-2,6-dicarbethoxy-cyclohexanedione-3,5 (I)

1-(*p*-Acetoxyphenyl)-2,6-dicarbethoxy-cyclohexanedione-3,5 (I) ⟶ 4-Hydroxyphenyl-cyclohexanedione-3,5 (II)

1-(*p*-Acetoxyphenyl)-2,6-dicarbethoxy-cyclohexanedione-3,5 (I) ⟶ 1-(*p*-Acetoxyphenyl)-2,6-dicarbethoxy-4-carbethoxymethyl-cyclohexanedione-3,5 (III).

Experimental

***p*-Acetoxybenzaldehyde.**—*p*-Hydroxybenzaldehyde in dry pyridine was acetylated for two hours with acetic anhydride at 0°. The reaction mixture was allowed to stand at room temperature for two days, then it was shaken with ice water in a separatory funnel. The separated oily material was washed three times with fresh portions of cold water, finally it was dried and distilled; b. p. 266–268°.

Ethyl 4-Acetoxybenzalmalonate.—*p*-Acetoxybenzaldehyde, ethyl malonate and acetic anhydride, in equimolar concentrations, were mixed and saturated with hydrogen chloride at 0°. The reaction mixture was allowed to come to room temperature and then stand for eight days. After this, dry air was passed through the solution for six hours. Then it was distilled at temperatures up to 210° under ordinary pressure; the remainder was fractionated, under reduced pressure, into a receiver cooled with Dry Ice and acetone mixture. The distillate at 176° and 0.6 mm. (bath temperature 240°) consisted of a viscous liquid and shiny plate-like crystals. The latter were filtered off with suction, washed with ether, and recrystallized from alcohol, m. p. 67–68°.

Anal. Calcd. for $C_{16}H_{18}O_6$: C, 62.74; H, 5.87. Found: C, 62.80; H, 5.87.

1-(*p*-Acetoxyphenyl)-2,6-dicarbethoxy-cyclohexanedione-3,5 (I).—Equimolar quantities of 4-acetoxybenzalmalonic acid diethyl ester, ethyl acetoacetate and sodium ethoxide in absolute alcohol were refluxed for an hour, and then allowed to stand at room temperature for several days. A crystalline precipitate formed which was soluble in water, giving a solution alkaline to litmus. The crystalline material treated with a water solution of acetic acid gave a yellowish precipitate. The latter was dissolved in boiling ethyl acetate, bone-blacked, filtered, and cooled in a refrigerator. The crystals formed were filtered off and recrystallized from absolute alcohol, m. p. 209–210°.

Anal. Calcd. for $C_{20}H_{22}O_8$: C, 61.54; H, 5.64. Found: C, 61.95; H, 5.83.

4-Hydroxyphenyl-cyclohexanedione-3,5 (II).—1-(*p*-Acetoxyphenyl)-2,6-dicarbethoxy-cyclohexanedione-3,5 (10 g.) was treated with 300 cc. of *N* hydrochloric acid and allowed to stand for fourteen hours, then refluxed for three hours, made alkaline, and allowed to stand at room temperature for two days. The mixture was made acid with hydrochloric acid, refluxed for an hour, filtered hot and allowed to cool. The crystals formed were recrystal-

(1) Fieser, "Chemistry of Natural Products Related to Phenanthrene," Reinhold Publishing Corp., New York, N. Y., 1937, pp. 256–302.

(2) Gilman, "Organic Chemistry, an Advanced Treatise," Vol. II. John Wiley & Sons, Inc., New York, N. Y., 1943, pp. 1427–1448.

(3) Elderfield and co-workers, *J. Org. Chem.*, **6**, 260, 270, 273, 289, 566 (1941); **7**, 362, 374, 383, 444 (1942); **8**, 29 (1943).

(4) Ruzicka and co-workers, *Helv. Chim. Acta*, **24**, 76, 716 (1941).

lized from 90% alcohol and then from boiling water, m. p. 186–187°, yield, 3.5 g.

Anal. Calcd. for $C_{12}H_{12}O_3$: C, 70.58; H, 5.88. Found: C, 70.67; H, 6.38.

1-(*p*-Acetoxyphenyl)-2,6-dicarbethoxy-4-carbethoxymethyl-cyclohexanedione-3,5 (III).—Equimolar quantities of 1-(*p*-acetoxyphenyl)-2,6-dicarbethoxy-cyclohexanedione-3,5, ethyl bromoacetate and sodium ethoxide in absolute alcohol were mixed with dry ether and the mixture refluxed for two hours. After acidifying, the solvents were removed by distillation under reduced pressure. Residues were washed with cold water, filtered off and dissolved in alcohol. Solution evaporated gave crystals and a yellowish glassy material which looked like supercooled liquid. Residues recrystallized twice from boiling water gave crystals, m. p. 168°. Continued heating after melting caused a rise of the melt in the capillary at 178°.

Anal. Calcd. for $C_{24}H_{28}O_{10}$: C, 60.53; H, 5.88. Found: C, 60.65; H, 5.65.

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Summary

Crystalline 4-acetoxybenzalmalonic diethyl ester, m. p. 67–68°, was prepared from acetoxybenzaldehyde and diethyl malonate in acetic anhydride, using dry hydrogen chloride as condensing agent.

The preparation of 1-(*p*-acetoxyphenyl)-2,6-dicarbethoxy-cyclohexanedione-3,5, of 4-acetoxyphenyl-cyclohexanedione-3,5 and of 1-(*p*-acetoxyphenyl)-2,6-dicarbethoxy-4-carbethoxymethyl-cyclohexanedione-3,5 is described. These are used as starting materials for further synthesis of substitutes for digitalis glycosides.

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1,3:2,5-Dimethylene-L-rhamnitol and Some of its Derivatives

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According to the recently published relationship[1] between the configurations of the polyhydric alcohols and the structures of the methylene and benzylidene cyclic acetals derived from them, it would be expected that L-rhamnitol, which is 6-desoxy-L-mannitol, would form a methylene cyclic acetal comparable in structure with that formed from L-mannitol. Since formaldehyde has been shown[2] to condense with the D-form of the hexitol to yield 1,3:2,5:4,6-trimethylene-D-mannitol it is to be expected that L-rhamnitol will form a 1,3:2,5-dimethylene-L-rhamnitol, the 4,6-acetal linkage being incapable of formation because of the presence of the 6-desoxy group in the rhamnitol. Weber and Tollens[3] condensed formaldehyde with L-rhamnitol and obtained a crystalline dimethylene-L-rhamnitol; from it a crystalline monobenzoate was prepared. Nothing has been known in the past regarding the structure of the diacetal. In the present communication we supply definitive proof that it is indeed 1,3:2,5-dimethylene-L-rhamnitol (I), the structure that is to be expected. The compound was prepared essentially by the procedure of Weber and Tollens; improvements in the method of isolation and purification of the product resulted in yields of about 75%, whereas these authors reported that only a "few grams" of dimethylene-L-rhamnitol were obtained from thirty grams of L-rhamnitol. Upon treatment with a sulfuric acid acetolyzing solution, the dimethylene-L-rhamnitol was transformed to a diacetyl-acetoxymethyl-monomethylene-L-rhamnitol (II). In the light of previous experience, the result indicated that the ruptured acetal linkage was formed through the primary hydroxyl group at position one of the L-rhamnitol. The diacetyl-acetoxymethyl-monomethylene-L-rhamnitol was saponified by methyl alcoholic barium methylate and yielded a monomethylene-L-rhamnitol that melted at 124–125° and rotated $[\alpha]^{20}D$ +62.1° in water. This monoacetal, as will be seen in the continuation, was shown to be 2,5-methylene-L-rhamnitol (III). The 2,5-structure of the monoacetal limited the position of the second methylene group in the diacetal to the 1,3-, the 1,4-, or the 3,4-position. The previous evidence obtained from the action of the acetolyzing solution on the diacetal, which indicated the presence of an acetal linkage at position 1, permitted a provisional elimination of the 3,4-type of acetal linkage. This was confirmed later by a rigorous proof that the 1,3-acetal linkage is present.

A conclusive proof of the structure of 2,5-methylene-L-rhamnitol (III) was obtained by correlating its structure with that of 2,5-methylene-D-mannitol.[2] The 2,5-methylene-D-mannitol was converted to the monotosyl derivative (IV) by treatment with one molecular equivalent of *p*-toluenesulfonyl chloride in pyridine solution. Because of the symmetry of the mannitol molecule it is immaterial whether the primary hydroxyl group at the one or the six position reacts with

(1) Hann and Hudson, THIS JOURNAL, **66**, 1909 (1944).
(2) Ness, Hann and Hudson, *ibid.*, **65**, 2215 (1943).
(3) Weber and Tollens, *Ann.*, **299**, 321 (1898).