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STUDIES ON LACTONES RELATED TO THE CARDIAC AGLYCONES. IV. PREPARATION OF β-PHENYL-$\Delta^{\alpha,\beta}$-BUTENOLIDE FROM PHENYLGLYOXAL AND FROM ETHYL β-METHYLCINNAMATE

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In the preceding papers (1) successful syntheses for representative β-substituted $\Delta^{\alpha,\beta}$-butenolides have been described and evidence has been presented (2) which suggests that the natural cardiac aglycones are best represented by such a structure rather than by that of a $\Delta^{\beta,\gamma}$-butenolide. Concurrently with these investigations we have studied other possible methods by which the $\Delta^{\beta,\gamma}$-butenolides might be prepared. These projected syntheses involved, for the most part, the preparation of β-substituted-β-aldehydopropionic acids and subsequent ring closure through the enolic form. It now seems probable as a result of our own observations (2), as well as earlier ones of others (3, 4, 5), that ring closure of such an aldehydo acid to a $\Delta^{\beta,\gamma}$-unsaturated lactone is at best exceedingly difficult if not impossible. Although the desired β-aldehydopropionic acids are now readily available (1, 2) we wish to present the results of the exploration of a number of suggested syntheses of these substances.

The most direct route to such aldehydo acids appeared to be based on the work of Perkin and Sprankling (6) who prepared β-aldehydopropionic acid by condensation of bromoacetal with sodio malonic ester and decarboxylation of the product. The logical extension of this synthesis would involve a similar condensation of the acetal of any appropriate α-bromoaldehyde. In an exploratory investigation we have attempted the condensation of α-bromoheptaldehyde diethyl acetal with sodio malonic ester. The condensation could not be made to proceed as desired under a variety of experimental conditions, and either the original materials were recovered, or extensive resin formation took place under more drastic conditions. We therefore conclude that the condensation of bromoacetal with sodio malonic ester represents a special case and that the reaction is not a general one for α-bromoaldehyde acetals. Along the same line, condensation of the cyclohexyl or cyclopentyl derivative of malonic ester with bromoacetal, or of cyclohexyl bromide with acetal malonic ester, gave only mixtures of undesired by-products or cleavage products.

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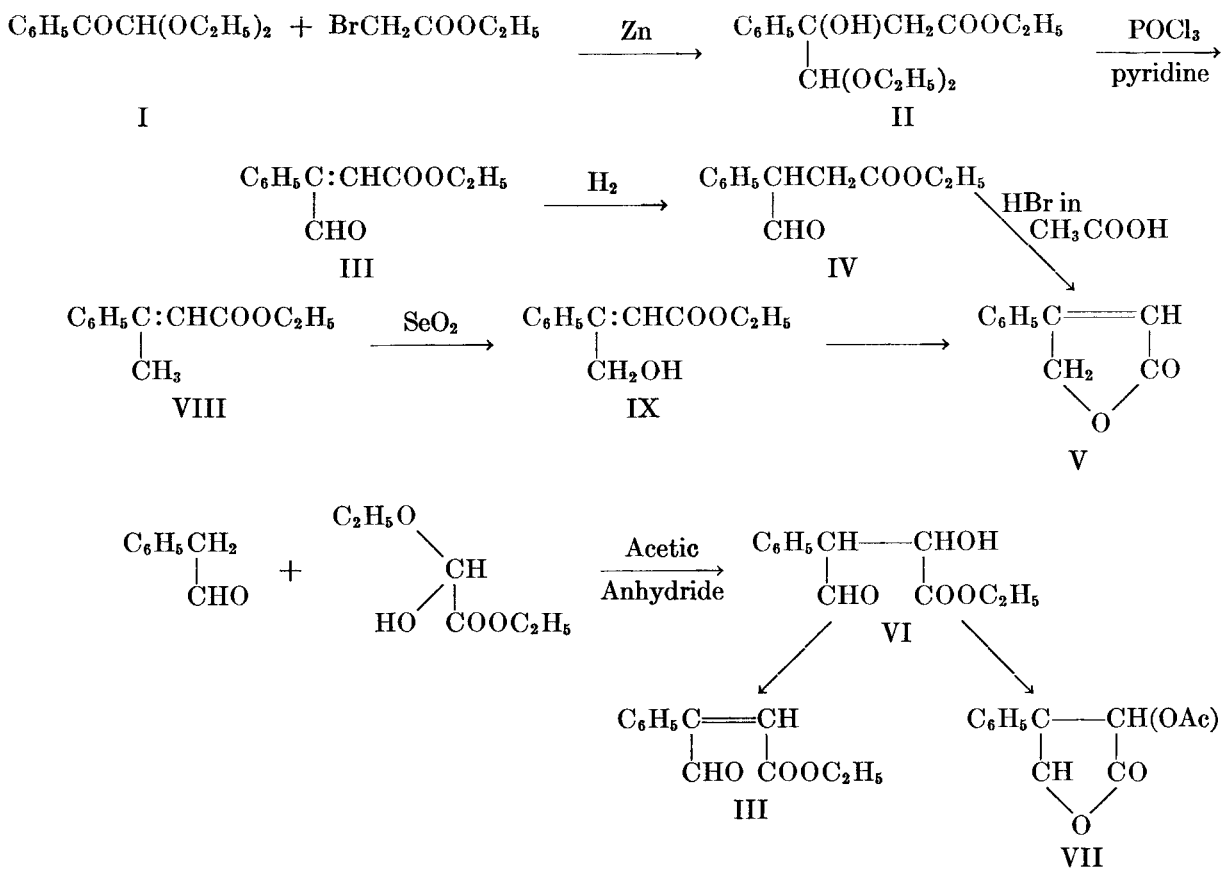
Other attempted avenues of approach to β-aldehydopropionic acids involved use of the Darzens glycid rearrangement and reduction of β-cyano esters (or acids) by the Stephen method. As a model the preparation of β-phenyl-β-formylpropionic acid was chosen because of the accessibility of the starting material. In the attempted application of both of these methods, serious difficulties were encountered at one stage or another, as a result of which these syntheses do not appear to be practical.

Better success attended the application of the Reformatzky reaction to the acetal of phenylglyoxal, although in comparison with the methods presented in earlier papers (1, 2) this scheme possesses serious disadvantages. Nevertheless, it seems of interest to present at this time our experiences dealing with phenylglyoxal and its derivatives, in view of the experiments along the same line recently reported by Shemyakin and Red'kin (7). The diethyl acetal of phenylglyoxal (I) readily undergoes the Reformatzky reaction with ethyl bromoacetate to yield ethyl β-phenyl-β-hydroxy-γ,γ-diethoxybutyrate (II), the structure of which was shown by conversion to phenylmalic acid. Elimination of the tertiary hydroxyl group in II presented unexpected difficulties. The compound was remarkably stable to the usual dehydrating agents, and only by the use of phosphorus oxychloride in pyridine was it possible to eliminate the hydroxyl group in question. The product thus obtained consisted largely of the aldehydo ester, III, although analyses indicated contamination with varying amounts of unhydrolyzed acetal or hemiacetal. Catalytic reduction of the double bond in III and hydrolysis of contaminating acetals gave ethyl β-phenyl-β-formylpropionate (IV). Ring closure of this aldehydo ester provided interesting information on the stability of β-phenyl-$\Delta^{\beta,\gamma}$-butenolide. Shemyakin (7) reports that condensation of the hemiacetal of ethyl glyoxylate with phenylacetaldehyde in the presence of acetic anhydride results in the formation of the intermediate ethyl α-hydroxy-β-phenyl-β-formylpropionate (VI) which then either loses water to yield ethyl β-phenyl-β-formylacrylate or undergoes ring closure and acetylation to yield α-acetoxy-β-phenyl-$\Delta^{\beta,\gamma}$-butenolide (VII). No proof of structure of the latter substance was offered. In contrast to this reported behavior of the α-hydroxy aldehyde ester, the unhydroxylated ester, IV, yielded β-phenyl-$\Delta^{\alpha,\beta}$-butenolide (V) on ring closure. The latter was identical with the lactone previously described (1, 2). The easier ring closure to, and greater stability of the α-hydroxy lactone apparently represents another case of the stabilizing effect of an α-substituent (8, 2). As far as we are aware, the reported ring closure of the aldehyde ester of Shemyakin is the only case on record of such a ring closure with an aldehydo acid. With the unsubstituted derivative, the tendency for the unsaturated lactone to assume a structure representing maximum conjugation of the double bonds makes the existence of a stable $\Delta^{\beta,\gamma}$-lactone doubtful.


C6H5COCH(OC2H5)2 + BrCH2COOC2H5
Zn
C6H5C(OH)CH2COOC2H5
CH(OC2H5)2
POCl3
pyridine
I
II
C6H5C:CHCOOC2H5
CHO
H2
C6H5CHCH2COOC2H5
CHO
HBr in
CH3COOH
III
IV
C6H5C:CHCOOC2H5
CH3
SeO2
C6H5C:CHCOOC2H5
CH2OH
C6H5C
CH
CH2
CO
O
VIII
IX
V
C6H5CH2
CHO
+
C2H5O
CH
HO
COOC2H5
Acetic
Anhydride
C6H5CH
CHOH
CHO
COOC2H5
VI
C6H5C
CH
CHO
COOC2H5
III
C6H5C
CH(OAc)
CH
CO
O
VII

In the course of the above work it has been found that if phenylglyoxal hydrate be treated with alcoholic hydrogen chloride, the hemiacetal (X) results. The latter substance undergoes the usual transformation under the influence of alkali which results in the formation of *d,l*-mandelic acid (XI). This apparently is a special case of the benzilic acid rearrangement.

$$C_6H_5COCH(OH)(OC_2H_5) \rightarrow C_6H_5C(OH)_2CH(OH)(OC_2H_5) \rightarrow$$
$$\text{X}$$
$$C_6H_5CH(OH)COOH$$
$$\text{XI}$$

In order to circumvent the difficult dehydration of the hydroxy acetal ester, II, ethyl β-methylcinnamate (VIII) was oxidized with selenium dioxide, with the object of taking advantage of the activation of the hydrogens of the methyl group by the double bond and thus proceeding directly to the unsaturated aldehydo ester III. However, the oxidation proceeded only to the alcohol stage (IX), and the only product isolated was the $\Delta^{\alpha,\beta}$-lactone V. This experiment is of significance, however, in that it provides rigid confirmatory evidence for the structure assigned to this lactone both in this paper and in a preceding one (1).

EXPERIMENTAL

Diethyl acetal of phenylglyoxal (I). A solution of 396 g. of phenylglyoxal (9) in 3 l. of absolute alcohol containing 3% of hydrogen chloride was allowed to stand 36 hours at room temperature and was then refluxed for 10 hours. After neutralizing the solution with basic lead carbonate and filtering off the lead salts, the solvent was removed and the residue was fractionally distilled at 7 mm. After a fore-run of 46 g. which boiled up to 127° and consisted of unreacted phenylglyoxal, the acetal was collected from 129–132°. The yield was 389 g. or 65%, based on the glyoxal reacted. n_D^{25} 1.5012.

Anal. Calc'd for $C_{12}H_{16}O_3$: C, 69.2; H, 7.7.
Found: C, 69.3; H, 7.5.

Hemiacetal of phenylglyoxal (X). When crude phenylglyoxal, as directly obtained from the selenium dioxide oxidation of acetophenone (9) and containing considerable amounts of the hydrate, was subjected to the same treatment with alcoholic hydrogen chloride, the hemiacetal, boiling at 133–137° at 12 mm. was obtained in 56% yield, based on the acetophenone used. n_D^{25} 1.5110.

Anal. Calc'd for $C_{10}H_{12}O_3$: C, 66.6; H, 6.7.
Found: C, 66.8; H, 7.0.

Mandelic acid from the hemiacetal of phenylglyoxal. The hemiacetal was refluxed for 5 hours with an excess of a 4% solution of sodium hydroxide in 50% alcohol. The cooled reaction-mixture was acidified, some of the alcohol was removed under reduced pressure and the aqueous solution was extracted with ether. Upon removal of the ether, *d,l*-mandelic acid was obtained which melted at 117–118° after recrystallization from ether-petroleum ether (Skellysolve B). The acid is reported as melting at 118° (10).

Anal. Calc'd for $C_8H_8O_3$: C, 63.2; H, 5.3.
Found: C, 63.3; H, 5.5.

The *anilide* melted at 150.5–151°, which compares with a value of 151–152° reported by Bischoff and Walden (11).

Anal. Calc'd for $C_{14}H_{13}NO_2$: C, 74.0; H, 5.8.
Found: C, 73.9; H, 6.1.

Ethyl β-phenyl-β-hydroxy-γ,γ-diethoxybutyrate (II). A 5-l. 3-necked flask was equipped with a mechanical stirrer and two very efficient reflux condensers. In the flask were placed 164 g. of granulated zinc (20 mesh), 350 g. of the diethyl acetal of phenylglyoxal, 283 g. of freshly distilled ethyl bromoacetate, and 1200 cc. of sodium-dried benzene. A pinch of good zinc dust and a crystal of iodine were added and the contents of the flask were gently warmed without stirring until the reaction started. The mixture was allowed to reflux spontaneously without stirring for 2 hours. The stirrer was then started and, on breaking up the zinc cake in the bottom of the flask, the reaction became more vigorous. When the reaction had moderated, the mixture was refluxed with stirring for 2 hours and allowed to stand overnight at room temperature. It was poured into 2 l. of 20% hydrochloric acid, the benzene layer was separated and washed successively with dilute hydrochloric acid, sodium carbonate solution, and water. After drying with anhydrous magnesium sulfate and removal of the solvent, the residue was fractionally distilled at 1 mm., the fraction boiling at 145–157° being collected. This was redistilled at 0.4 mm., and gave 170 g. of the product which boiled at 136–140°; n_D^{25} 1.4838.

Anal. Calc'd for $C_{16}H_{24}O_5$: C, 64.8; H, 8.2.
Found: C, 64.6; H, 8.0.

It was possible to obtain the *acetal acid* from the above ester as follows. Twenty-five grams of the ester was refluxed for a few minutes with 75 cc. of 50% alcohol containing 3.4 g. of sodium hydroxide. Hydrolysis of the ester was prompt and the solution turned deep brown. The alcohol was removed and the aqueous solution was extracted with ether for the removal of any unchanged ester. The alkaline solution was then chilled to 0°, carefully acidified with ice-cold dilute hydrochloric acid, and immediately extracted with ether. After thorough washing of the ether extract and removal of the solvent, the acetal acid remained as a reddish-brown oil which could not be crystallized. The acetal group was still intact, as shown by the negative Tollens test displayed by this substance in dilute pyridine solution. However, after warming the acetal acid with 50% acetic acid a prompt strong Tollens test was obtained.

The above acetal acid was converted to the *methyl ester* with diazomethane. The ester boiled at 127–132° at 0.4 mm., n_D^{25} 1.4867.

Anal. Calc'd for $C_{15}H_{22}O_5$: C, 63.8; H, 7.9.
Found: C, 63.8; H, 7.9.

On warming the above methyl ester with 2,4-dinitrophenylhydrazine in dilute alcoholic hydrochloric acid solution, hydrolysis of the acetal occurred and the 2,4-*dinitrophenylhydrazone* of the aldehyde ester was formed. It melted at 179.5–180°.

Anal. Calc'd for $C_{18}H_{18}N_4O_7$: C, 53.7; H, 4.6; N, 14.0.
Found: C, 53.9; H, 4.6; N, 14.1.

Oxidation of β-phenyl-β-hydroxy-β-formylpropionic acid to phenylmalic acid. The acetal and ester groups in ethyl β-phenyl-β-hydroxy-γ,γ-diethoxybutyrate (2 g.) were hydrolyzed by boiling for several hours with dilute sulfuric acid. The free aldehydo acid was extracted with ether and oxidized by stirring with silver oxide, prepared from 1.9 g. of silver nitrate and 0.5 g. of sodium hydroxide in 25 cc. of water, for 12 hours. The phenylmalic acid was extracted from the filtered solution with ether and crystallized from ether-petroleum ether (Skellysolve B). It melted at

186–187° with decomposition, which compares with 187–188° reported by Alexander (12).

Anal. Calc'd for $C_{10}H_{10}O_5$: C, 57.1; H, 4.8.
Found: C, 57.0; H, 5.1.

On drying at 100° and 10 mm. over phosphorus pentoxide, the acid lost water and gave phenylmaleic anhydride which melted at 119–119.5°. Alexander (12) reports the melting point 119° for the substance.

Dehydration of ethyl β-hydroxy-β-phenyl-γ,γ-diethoxybutyrate. In a 500 cc. flask equipped with a reflux condenser were placed 27 g. of the acetal ester and 150 cc. of dry pyridine. To this mixture 23 g. of freshly distilled phosphorus oxychloride was added gradually and with shaking. The solution was then heated for 8 hours in an oil-bath at 135°. After cooling, the contents of the flask were poured into a mixture of ice and excess dilute sulfuric acid, and the dark mixture was extracted with several portions of ether. The combined ether extracts were washed with dilute sulfuric acid, then with sodium carbonate solution, and finally with water. The residue after drying and removal of the ether was fractionally distilled at reduced pressure, and a fraction of 3 g. of material which boiled at 130–138° was obtained. This material was a mixture of the aldehyde ester with some acetal and hemiacetal. The acetal was partially hydrolyzed during manipulation of the product.

Anal. Calc'd for $C_{16}H_{22}O_4$: C, 67.5; H, 8.0.
for $C_{14}H_{18}O_4$: C, 67.2; H, 7.3.
for $C_{12}H_{12}O_3$: C, 70.6; H, 5.9.
Found: C, 68.6, 68.8; H, 6.2, 6.7.

In accordance with this view, the product of the reaction gave a faint Tollens test. The removal of the hydroxyl group was shown by the preparation of the *2,4-dinitrophenylhydrazone of ethyl β-phenyl-β-formylpropenoate* from the reaction-product. This melted at 163–163.5° after recrystallization from alcohol.

Anal. Calc'd for $C_{18}H_{16}N_4O_6$: C, 56.3; H, 4.2; N, 14.6.
Found: C, 56.3; H, 4.3; N, 14.5.

The effect of the ethoxyl groups in hindering removal of the hydroxyl group in the hydroxy acetal ester is rather remarkable. A similarly situated hydroxyl group in ethyl β-phenyl-β-methylhydracrylate is eliminated without difficulty with hydrochloric acid (13). In the above case we have tried to accomplish the dehydration with a variety of reagents without success.

Ethyl β-phenyl-β-formylpropionate (IV). When the aldehyde ester, III, was reduced with hydrogen in alcoholic solution using platinum oxide as catalyst, one mole of hydrogen was rapidly absorbed and a second mole more slowly. If the hydrogenation was interrupted at the one mole stage, ethyl β-phenyl-β-formylpropionate, boiling at 116–120° at 0.3 mm., n_D^{25} 1.5120, was formed. The compound gave a slow but definite Tollens test.

Anal. Calc'd for $C_{12}H_{14}O_3$: C, 69.9; H, 6.8.
Found: C, 69.8; H, 7.2.

The 2,4-*dinitrophenylhydrazone* melted at 108.5–109° after recrystallization from dilute alcohol.

Anal. Calc'd for $C_{18}H_{18}N_4O_6$: C, 55.9; H, 4.7.
Found: C, 55.5; H, 4.7.

Ring closure of ethyl β-phenyl-β-formylpropionate to β-phenyl-$\Delta^{\alpha,\beta}$-butenolide. A solution of 1 g. of the ester in 2 cc. of glacial acetic acid which had previously been saturated with dry hydrogen bromide at 0° was heated under reflux in an oil-bath at 120° for 2 hours. After pouring the mixture into ice-water and neutralizing with

sodium carbonate, β-phenyl-$\Delta^{\alpha,\beta}$-butenolide was extracted with ether. After recrystallization from water it melted at 91–92°, and the melting point was not depressed when the lactone was mixed with a sample prepared as previously described (1).

Oxidation of ethyl β-methylcinnamate with selenium dioxide. A solution of 44 g. of ethyl β-methylcinnamate (13) in 140 cc. of dioxane and 4.5 cc. of water was heated to boiling under reflux in a 3-necked flask equipped with a mechanical stirrer. To this was added 26 g. of selenium dioxide over the course of 35 min. The mixture was refluxed with stirring for 4 hours. The reaction-mixture was chilled and decanted from precipitated selenium, and the solvent was removed at reduced pressure. The residue was dissolved in ether and filtered from additional selenium which had precipitated. On concentration of the ether solution, crystallization was copious. The crystalline material was filtered off and recrystallized from water. It melted at 93–93.5° and gave no depression of melting point when mixed with a known sample of β-phenyl-$\Delta^{\alpha,\beta}$-butenolide (1).

Anal. Calc'd for $C_{10}H_8O_2$: C, 75.0; H, 5.0.
Found: C, 75.0; H, 5.2.

The mother liquor from the above crystalline material gave 42% of unreacted ethyl β-methylcinnamate on distillation.

The microanalyses here reported were performed by Mr. Saul Gottlieb of these laboratories.

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