4. Ethyl Benzoate and Phthalyl Chloride.—This reaction was carried out as under (3) by heating 2 moles of ethyl benzoate with one of phthalyl chloride. The reaction started at about 180° and after heating at 180–200° for two hours gave a 65% yield of ethyl chloride.

Summary

Equimolecular amounts of phthalyl chloride and diethyl phthalate react in presence of traces of zinc chloride to give excellent yields of phthalic anhydride and ethyl chloride. Other alkyl esters of phthalic acid react similarly, except that the yields of the alkyl chlorides are lower due to the formation of larger amounts of alkylenes. Succinic esters and succinyl chloride react in the same manner.

Ethyl benzoate and benzoyl chloride react in the presence of zinc chloride at higher temperatures to give fair yields of benzoic anhydride and ethyl chloride.

Benzoyl chloride and phthalic esters react to give alkyl chlorides and presumably a mixture of the anhydrides of the acids as the main reaction products. The same is also true of the reaction of phthalyl chloride with ethyl benzoate.

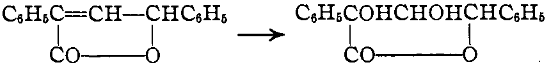
ST. LOUIS, MISSOURI
RECEIVED JULY 14, 1933
PUBLISHED NOVEMBER 7, 1933

Hydroxyl Derivatives of Alpha,Gamma-Diphenylbutyric Acid

BY E. P. KOHLER AND R. H. KIMBALL

The work herein described began many years ago with an attempt to add nitromethane to phenyl benzoyl ethylene oxide in the hope of finding an explanation for the peculiar behavior of certain aliphatic nitro compounds.[1] Addition appeared to occur readily enough but experiments carried out under the most diverse conditions invariably ended with an intractable oil from which no substance containing nitrogen could be isolated. By digestion with hydrochloric acid this oil was in part converted into a solid in which all that remained of the nitromethane was an atom of carbon and possibly one or two atoms of oxygen.

From a series of transformations which need not be discussed here we came to the conclusion that the nitrogen-free solid was a dihydroxy lactone. This conclusion has been confirmed by a synthesis of the substance that adequately establishes its structure



$$\begin{array}{l} C_6H_5\underset{|}{C}{=}CH{-}\underset{|}{C}HC_6H_5 \\ CO\text{———}O \end{array} \longrightarrow \begin{array}{l} C_6H_5\underset{|}{C}OHCHOH\underset{|}{C}HC_6H_5 \\ CO\text{————}O \end{array}$$

I

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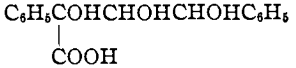
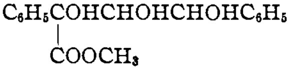
(1) Kohler and Goodwin, THIS JOURNAL, **49**, 219 (1927).

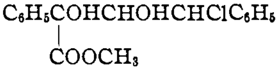
Our solid product, therefore, is the gamma lactone of an α,β,γ-trihydroxy acid. Since comparatively few substances of this type are known we have studied it with some care. By well-known methods it was easily converted into the trihydroxy acid, its methyl ester and the methyl ester of the corresponding gamma chloro acid; all of these substances thus became available for comparison


$C_6H_5\underset{\substack{|\\ COOH}}{C}OHCHOHCHOHC_6H_5$

II


$C_6H_5\underset{\substack{|\\ COOCH_3}}{C}OHCHOHCHOHC_6H_5$

III

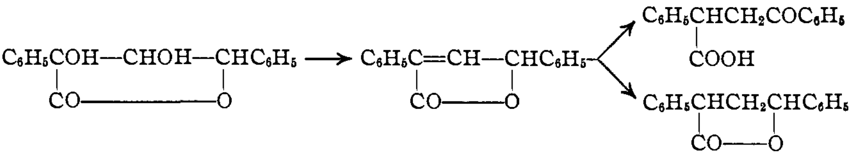

$C_6H_5\underset{\substack{|\\ COOCH_3}}{C}OHCHOHCHClC_6H_5$

IV

The oxidation of these substances yielded no results of general interest. In acid media the lactone is oxidized less readily than its primary oxidation products, consequently when oxidation occurs at all it always ends in carbon dioxide and benzoic acid. In alkaline solution the salts of the trihydroxy acid reduce permanganate with great rapidity, being oxidized to benzoic and phenylglyoxylic acids.

The reduction of the lactone was studied with greater care in an attempt to secure the corresponding diphenyl tetrose. Fischer and Stewart[2] prepared a monophenyl tetrose by reducing, with sodium amalgam in a feebly acid solution, a dihydroxy lactone which differed from ours only in that it lacked the phenyl group in the alpha position. In our case this method failed completely; all of the lactone was recovered. By the prolonged action of a large excess of sodium amalgam in aqueous methyl alcohol which was maintained at a *P*H of approximately 4, we obtained a neutral product which reduced Fehling's solution, but the quantity was too small for identification. Apparently the factors which hinder the esterification of highly substituted acids also interfere with the reduction of highly substituted lactones.

The lactone is much more readily reduced with hydrogen iodide and red phosphorus but, naturally, the reduction is not to the tetrose. The principal reduction products are phenyl benzoyl propionic acid and diphenyl butyrolactone. Evidently the dihydroxyl compound is first reduced to the unsaturated lactone, and this lactone then in part is reduced further but for the most part is opened to the ketonic acid


V

Since the reduction to an unsaturated compound here, as elsewhere, depends on the presence of hydroxyl groups on adjoining carbon atoms, it can be avoided by acylating these groups. Thus both the dibenzoate of

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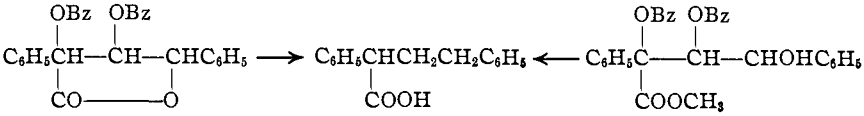
(2) Fischer and Stewart, *Ber.*, **25**, 2559 (1892).

the lactone and the dibenzoate of the trihydroxy ester (III) when reduced under the same conditions pass quantitatively into diphenyl butyric acid. Here the hydroxyl groups are reduced, one by one, as they appear.

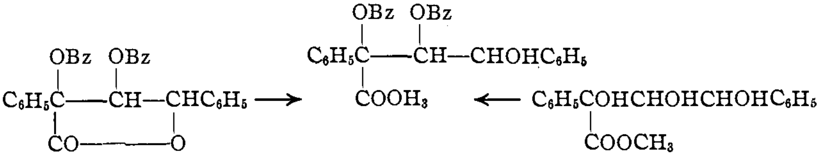


$$\underset{\text{CO}}{\overset{\text{OBz}}{C_6H_5CH}}-\overset{\text{OBz}}{CH}-\underset{\text{O}}{CHC_6H_5} \longrightarrow \underset{\text{COOH}}{C_6H_5CH}CH_2CH_2C_6H_5 \longleftarrow \underset{\text{COOCH}_3}{\overset{\text{OBz}}{C_6H_5C}}-\overset{\text{OBz}}{CH}-CHOHC_6H_5$$

VII VI VIII

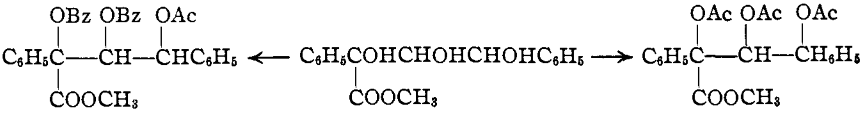
The diacetate of the lactone, which is much more easily hydrolyzed than the dibenzoate, on reduction gave a mixture composed of equal parts of phenyl benzoyl propionic and diphenylbutyric acids.

The acylation of the lactone presented no complications; boiling acetyl chloride converted it smoothly into the diacetate and benzoyl chloride in pyridine into the dibenzoate. Benzoylation of the sodium salt of the trihydroxy acid in pyridine likewise led to the dibenzoate of the lactone—doubtless because the lactone ring is closed early in the process. Benzoylation of the methyl ester of the trihydroxy acid, however, stopped with the formation of the dibenzoate of the ester. Since this same dibenzoate is formed also by the action of methyl alcoholic hydrochloric acid on the dibenzoate of the lactone, presumably the same hydroxyl groups are benzoylated in both cases



$$\underset{\text{CO}}{\overset{\text{OBz}}{C_6H_5C}}-\overset{\text{OBz}}{CH}-\underset{\text{O}}{CHC_6H_5} \longrightarrow \underset{\text{COOH}_3}{\overset{\text{OBz}}{C_6H_5C}}-\overset{\text{OBz}}{CH}-CHOHC_6H_5 \longleftarrow \underset{\text{COOCH}_3}{C_6H_5COH}CHOHCHOHC_6H_5$$

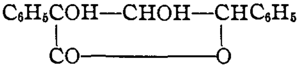
The dibenzoate of the ester does not, however, like the trihydroxy ester itself, lose methyl alcohol and form the lactone when it is heated. It is possible, therefore, that the prolonged action of methyl alcoholic hydrogen chloride causes a shift of one of the benzoyl groups—hence the structure of the benzoylated ester cannot be regarded as certain. Although the third hydroxyl group of the ester cannot be benzoylated it can be acetylated; the resulting triacyl derivatives supply the final proof of the presence of all three hydroxyl groups:



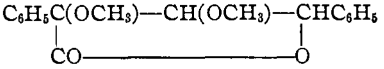
$$\underset{\text{COOCH}_3}{\overset{\text{OBz}}{C_6H_5C}}-\overset{\text{OBz}}{CH}-\overset{\text{OAc}}{CHC_6H_5} \longleftarrow \underset{\text{COOCH}_3}{C_6H_5COH}CHOHCHOHC_6H_5 \longrightarrow \underset{\text{COOCH}_3}{\overset{\text{OAc}}{C_6H_5C}}-\overset{\text{OAc}}{CH}-\overset{\text{OAc}}{CH_6H_5}$$

IX X

The methylation of the lactone likewise presented no complications. Depending upon the temperature and the amount of methylating agents employed, it gave either a mixture of two monomethyl derivatives or the completely methylated lactone. Each of the monomethyl derivatives is converted into the same dimethyl derivative by further methylation; these substances are therefore structural isomers. An attempt to determine which of them is the alpha and which the beta methoxyl compound by oxidation was unsuccessful because each of them was oxidized to a mixture of benzoic and phenylglyoxylic acids.

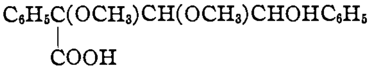


$$\begin{array}{lcl}C_6H_5COH & —CHOH— & CHC_6H_5\\ | & & |\\ CO & ——— & O\end{array}$$



$$\begin{array}{lcl}C_6H_5C(OCH_3) & —CH(OCH_3)— & CHC_6H_5\\ | & & |\\ CO & ——— & O\end{array}$$

XI



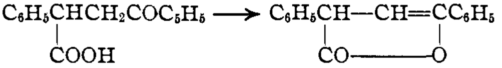
$$\begin{array}{l}C_6H_5C(OCH_3)CH(OCH_3)CHOHC_6H_5\\ \quad\ \ |\\ \quad COOH\end{array}$$

XII

Methylation of the trihydroxy acid gave results which are more difficult to interpret. Here the principal product is a mono methylated acid in which the methoxyl group is in the gamma position. Accompanying this acid are small quantities of the alpha or beta methoxy acid corresponding to the higher melting monomethylated lactone, the α,β-dimethoxy acid XII and another dimethylated acid in which one of the methoxyl groups is in the gamma position. The completely methylated acid could not be obtained. More than 70% of the product has methoxyl in the gamma position and more than 66% in this position alone—a result which could not have been anticipated either from the relative acidity of the hydroxyl groups or from the space relations.

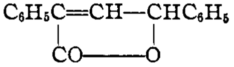
Experimental Part

Dihydroxy diphenylbutyro lactone is now most easily made from phenyl benzoyl propionic acid. A long time ago Anschütz and Montfort[3] found that when this acid is heated with acetic anhydride it loses water and forms a diphenyl crotonic lactone. In view of the method of formation they naturally assumed that the lactone was unsaturated in the β,γ-position and consequently represented it with formula A.



$$\begin{array}{l}C_6H_5CHCH_2COC_6H_5\\ \quad\ \ |\\ \quad COOH\end{array} \longrightarrow \begin{array}{lcl}C_6H_5CH & —CH= & CC_6H_5\\ | & & |\\ CO & —— & O\end{array}$$

A



$$\begin{array}{lcl}C_6H_5C & =CH— & CHC_6H_5\\ | & & |\\ CO & —— & O\end{array}$$

B

Some years later Thiele[4] after an extensive study of unsaturated gamma lactones decided that in most of them the double linkage was in the α,β-position. Thiele also showed that it is possible to distinguish between the two types of unsaturated lactones by oxidation with permanganate because only those which have the double linkage in the α,β-position can be oxidized to dihydroxy lactones. In view of Thiele's work it seemed probable to us that the lactone prepared by Anschütz and Montfort should be represented by formula B and that consequently it should be oxidizable to

[3] Anschütz and Montfort, *Ann.*, **284**, 3 (1895).

[4] Thiele and Wedemann, *ibid.*, **347**, 132 (1906).

dihydroxy diphenylbutyro lactone. We have found that it is oxidizable and that the yield of dihydroxyl compound is excellent. Our procedure is as follows.

In a 4-liter bottle, provided with an efficient mechanical stirrer and surrounded with a freezing mixture, is placed a solution of 60 g. of the unsaturated lactone in 750 cc. of acetone and 10 cc. of water. Into this solution is stirred first 25 g. of very finely powdered anhydrous magnesium sulfate, then a well-cooled solution of 50 g. of potassium permanganate in 300 cc. of water and 1700 cc. of acetone. The permanganate is added as fast as possible without raising the temperature above −4°. Oxidation is rapid and the reaction is complete in an hour. Excess of permanganate is removed by adding bisulfite and acid until the solution clears. The oxides of manganese are then collected on a filter, washed well with acetone and discarded.

The filtrate is distilled to about 750 cc. then gradually diluted to 2 liters with water and cooled in a freezing mixture. It deposits 38–40 g. of practically pure dihydroxy lactone melting at 145–146°. The pure lactone, obtained by recrystallization from aqueous acetic acid, melts at 149°.

Anal. Calcd. for $C_{16}H_{14}O_4$: mol. wt., 270; C, 71.1; H, 5.2. Found: mol. wt., 262; C, 71.1; H, 5.3.

The lactone is readily soluble in ether, alcohol and acetone; moderately soluble in hot water and in benzene. It crystallizes well from benzene and from dilute acetic acid in colorless prisms.

α,γ-Diphenyl-α,β,γ-trihydroxybutyric Acid II.—The pure sodium salt of the trihydroxy acid was prepared by dissolving the lactone in excess of hot sodium carbonate, evaporating the solution to dryness, and extracting the organic sodium salt from the residue with absolute ethyl alcohol. It crystallized from the alcoholic solution in needles containing a molecule of alcohol.

Anal. Calcd. for $C_{16}H_{15}O_5Na\cdot C_2H_5OH$: C_2H_5OH, 12.9. Found: loss at 105°, 13.2. Calcd. for $C_{16}H_{15}O_5Na$: Na, 7.4. Found: Na, 7.4.

When a mineral acid is added to an aqueous solution of the sodium salt it produces an amorphous precipitate which is probably a hydrated form of the trihydroxy acid. The precipitate is sparingly soluble in nearly all organic solvents. It melts at 150–157°, loses water with effervescence, and passes into the lactone. The crystalline acid was obtained but once by concentrating and cooling an ethereal solution. It separated in needles which melted with loss of water at 151°.

Anal. Calcd. for $C_{16}H_{16}O_5$: C, 66.7; H, 5.5. Found: C, 66.2; H, 5.6.

The methyl ester (III) of the trihydroxy acid was made by means of the silver salt which was obtained from the sodium salt in the usual manner. After it had been washed with absolute alcohol and dried *in vacuo* it was found to be anhydrous.

Anal. Calcd. for $C_{16}H_{15}O_5Ag$: Ag, 27.3. Found: Ag, 27.2.

A suspension of the dry silver salt in absolute ether containing excess of methyl iodide was left to itself overnight, then boiled for several hours, and finally evaporated to dryness under diminished pressure. From the residue the ester was extracted with boiling benzene, from which it crystallized well on cooling, and it was finally purified by recrystallization from ethyl acetate and petroleum ether. The yield was 14.6 g. from 20 g. of the silver salt.

Anal. Calcd. for $C_{17}H_{18}O_5$: C, 67.6; H, 6.0; active H, 3.0. Found: C, 67.4; H, 6.1; active H, 3.0.

The ester crystallized in fine colorless needles. Owing to the ease with which it loses methyl alcohol, it has no true melting point. In a capillary tube it softens at about

115°, liquefies with frothing at about 125°, then resolidifies and finally melts at the same temperature as the lactone.

Methyl α,γ-Diphenyl-α,β-dihydroxy-γ-chlorobutyrate, IV.—A solution of 6 g. of the lactone in 50 cc. of dry methyl alcohol was saturated with dry hydrogen chloride, left to itself for forty-eight hours, then poured into ice water. The product crystallized from ether–petroleum ether in fluffy needles melting at 124°. An analysis proved that but one hydroxyl group is replaced by chlorine, and the ease with which the lactone was regenerated from the chloro ester showed that the chlorine is in the gamma position.

Anal. Calcd. for $C_{17}H_{17}O_4Cl$: C, 63.8; H, 5.3. Found: C, 63.4; H, 5.3.

Reduction.—The unsuccessful attempts to reduce the lactone to diphenyltetrose that were discussed in the introduction need not be described in detail. The reduction with hydrogen iodide was carried out as follows. A mixture of 2 g. of lactone, 0.8 g. of red phosphorus and 12 g. of 45% hydriodic acid in glacial acetic acid was boiled for fifteen hours, then filtered and greatly diluted with water. The water solution, manipulated in the usual manner, yielded 1.0 g. of pure phenyl benzoyl propionic acid and 0.2 g. of α,γ-diphenylbutyro lactone (V) which melted at 103–104.5° and which was identified by comparison with an authentic sample.

When the dibenzoate of the lactone was reduced in the same manner the principal product was an acid which crystallized from petroleum ether in prisms and which melted at 75°.

Anal. Calcd. for $C_{16}H_{16}O_2$: C, 80.0; H, 6.7. Found: C, 79.9; H, 6.8.

Since the composition of the acid indicated complete reduction to diphenyl butyric acid we undertook the preparation of this acid by a Clemmensen reduction. To this end we boiled 10 g. of phenyl benzoyl propionic acid and 100 g. of amalgamated zinc with concentrated hydrochloric acid for fifteen hours during which time a total of 130 cc. of hydrochloric acid was added in steps. From the product we isolated 6.9 g. of the same acid that had been obtained from the dibenzoate.

Acetylation.—The general methods employed in acetylating and benzoylating both the lactone and the methyl ester of the trihydroxy acid have been adequately indicated in the introduction. The products were recrystallized either from methyl alcohol or from ether–petroleum ether. Their composition and properties are shown in the table.

Formulas				Composition					
				Calculated, %			Found, %		
Empirical	Structural	Crystal form	M. p., °C.	C	H	OCH_3	C	H	OCH_3
$C_{20}H_{18}O_6$	VII[a]	Rhombic plates	135	67.8	5.1		67.3	5.2	
$C_{18}H_{16}O_5$	VII[b]	Prisms	138	69.2	5.2		69.0	5.2	
$C_{30}H_{22}O_6$	VII	Prisms	144	75.3	4.6		75.4	4.6	
$C_{31}H_{26}O_7$	VIII	Plates	178	72.9	5.1	6.1	72.5	5.1	5.7
$C_{33}H_{28}O_8$	IX	Prisms	157	71.7	5.1	5.6	71.4	5.1	5.4
$C_{23}H_{24}O_8$	X	Prisms	153	64.5	5.6	7.2	64.2	5.6	7.1

[a] Diacetate of the lactone. [b] Monoacetate of the lactone.

Methylation: α,γ-Diphenyl-α,β-dimethoxybutyro Lactone (XI).—For the purpose of complete methylation a mixture composed of a solution of 10.8 g. of the lactone in 25 cc. of absolute methyl alcohol, 49.7 g. of silver carbonate and 56.8 g. of methyl iodide was boiled under an excess pressure of approximately half an atmosphere. Evolution of carbon dioxide was brisk at first, but soon became slow and regular. After fourteen hours the solvent was evaporated and the residue extracted with boiling methyl alcohol. The resulting solution on evaporation and cooling yielded 6.34 g. of solid and 5.0 g. of a viscous oil. On re-methylation in the same manner, the oil yielded an additional 4.07 g. of solid, making the total 87.3%.

The dimethylated lactone is readily soluble in nearly all common organic solvents. It was purified by recrystallization from methyl alcohol from which it separated in stout prisms melting at 118° and subliming slowly at 100°.

Anal. Calcd. for $C_{16}H_{12}O_2(OCH_3)_2$: OCH_3, 20.8. Found: OCH_3, 20.7.

With a view to partial methylation a similar but more dilute mixture of lactone, methyl alcohol, methyl iodide and silver carbonate was left to itself at the ordinary temperature for forty-three hours, then treated as in the preceding experiment. The proportion of dimethylated lactone was much less and some unmethylated lactone was recovered. By a somewhat laborious fractional crystallization from carbon tetrachloride the residual oil was separated into two isomeric monomethylated lactones, melting, respectively, at 143 and 77°.

The higher melting isomer is sparingly soluble in carbon tetrachloride and much less soluble than the dihydroxy lactone in water or dilute acetic acid. It crystallizes in minute prisms. Like the dimethylated lactone it is practically insoluble in cold aqueous alkalies but is readily soluble in aqueous alcoholic carbonates.

Anal. Calcd. for $C_{16}H_{13}O_3OCH_3$: OCH_3, 10.9. Found: OCH_3, 10.8.

The lower melting isomer is dimorphous. It first crystallized in large lustrous prisms melting at 77°. Later a less soluble form appeared which crystallized in small thin plates and melted at 112°. Once this form had made its appearance it was the only one that could be isolated.

Anal. Calcd. for $C_{16}H_{13}O_3OCH_3$: OCH_3, 10.9. Found: (77°) OCH_3, 10.8; (112°) OCH_3, 10.5.

The relative amounts in which the products were obtained are as follows: unchanged dihydroxy lactone, 13%; dimethylated lactone 22%; monomethylated lactones (112°) 34%, (143°) 14%.

α,β-Dimethoxy-γ-hydroxybutyric Acid (XII).—The methylated lactone is scarcely affected by cold aqueous alkaline hydroxides but is readily soluble in alcoholic hydroxides and in aqueous alcoholic carbonates. The resulting potassium salt, being sparingly soluble in excess carbonate, is readily obtained in a pure condition. It crystallizes from aqueous acetone in needles containing water of crystallization.

Anal. Calcd. for $C_{18}H_{19}O_5K \cdot 1.5H_2O$: H_2O, 7.1; OCH_3, 16.3. Found: H_2O, 7.0; OCH_3, 16.1.

The corresponding acid was purified by recrystallization from ethyl acetate, in which it is far less soluble than the dimethylated lactone. It separated in fine needles melting with decomposition at 129°. After one crystallization from aqueous methyl alcohol about half of it had been converted to the lactone.

Anal. Calcd. for $C_{18}H_{20}O_5$: OCH_3, 19.6. Found: OCH_3, 19.5.

Methylation of the Trihydroxy Acid: α,γ-Diphenyl-α,β-dihydroxy-γ-methoxybutyric Acid.—To a solution of 5.4 g. of the dihydroxy lactone in 60 cc. of 20% sodium hydroxide was added drop by drop, with vigorous mechanical stirring, 16 g. of dimethyl sulfate, while the temperature was held at 35°. After half an hour, when all the sulfate had disappeared, the addition of the same quantities of sulfate and hydroxide was repeated. Stirring was continued for several hours with addition of sufficient water to keep sparingly soluble salts in solution. The mixture was then made strongly acid, heated for the purpose of converting any hydroxy acids into lactones, and separated into neutral and acid products in the usual manner.

The neutral products were small quantities of the monomethoxy lactone melting at 143° and the dimethoxy lactone. The acid fraction was composed largely of two substances which were most readily separated by treatment with cold chloroform. The residue, insoluble in chloroform, on recrystallization from aqueous methyl alcohol yielded 3.25 g. of the γ-methoxy acid melting at 201° and crystallizing in small rhombic plates.

Anal. Calcd. for $C_{17}H_{18}O_5$: C, 67.5; H, 6.0; OCH_3, 10.3. Found: C, 67.6; H, 6.3; OCH_3, 10.0.

The chloroform solution, on suitable treatment, yielded 0.18 g. of a dimethoxy acid which by recrystallization from very dilute alcohol was obtained in fine needles melting at 148–149°.

Anal. Calcd. for $C_{18}H_{20}O_5$: C, 68.3; H, 6.4; OCH_3, 19.6. Found: C, 68.2; H, 6.5; OCH_3, 19.0.

This same dimethoxy acid was obtained by intensive methylation of the gamma methoxy acid, but the yield was exceedingly small.

Summary

This paper contains a description of the preparation, oxidation, reduction, alkylation and acylation of α,γ-diphenyl dihydroxy butyro lactone.

CAMBRIDGE, MASSACHUSETTS

RECEIVED JULY 15, 1933
PUBLISHED NOVEMBER 7, 1933

[CONTRIBUTION FROM THE KEDZIE CHEMICAL LABORATORY, MICHIGAN STATE COLLEGE]

Chloro Derivatives of Benzyl Phenols. II. Some Monochloro, Dichloro and Trichloro Derivatives of Ortho and Para Benzyl Phenols

BY R. C. HUSTON, R. L. GUILE, P. S. CHEN, W. N. HEADLEY, G. W. WARREN, L. S. BAUR AND B. O. MATE

Continuing our studies on the benzylation of phenols, we have prepared chloro derivatives of ortho and para benzylphenols. A number of the dichloro derivatives of ortho and para benzylphenols have been described in an earlier article from this Laboratory.[1]

Condensations by means of aluminum chloride were carried out according to the technique previously described.[1,2] The mole proportions of reactants used were: one of benzyl chloride (or alcohol), three of phenol and one-half of aluminum chloride except in cases where 2,6-dichlorophenol was a reactant when the phenol and benzyl chloride were used in the ratio of one to one.

Temperatures between 20 and 35° were found to be satisfactory. In some cases with 2,6-dichlorophenol condensation failed to take place at lower temperatures.

In all cases the distillate from the ether extract was examined for benzyl ethers by dissolving in Claisen's alcoholic potash[3] and extracting with petroleum ether. The phenols were then liberated by treatment with hydrochloric acid and again extracted with ether.

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(1) Huston and Eldridge, THIS JOURNAL, **53**, 2260 (1931).

(2) Huston and others, *ibid*, **46**, 2775 (1924); **49**, 1366 (1927); **52**, 448 (1930); **53**, 2379 (1931); **54**, 1506 (1932).

(3) Claisen, *Ann.*, **442**, 224 (1924).