

**SYNTHESIS OF 1,4-DIHYDROXYBUTANEDIONE AND
CERTAIN DERIVATIVES OF dl-2-DEOXYTETROSE**

by

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SYNTHESIS OF 1,4-DIHYDROXYBUTANEDIONE AND CERTAIN DERIVATIVES OF dl-2-DEOXYTETROSE

INTRODUCTION

The occurrence of normal four carbon compounds among metabolic intermediates and products oxalacetic acid (25, p.95), malic acid (25, p.104), erythritol (2, p.43), biacetyl (25, p.138), 2,3-butylene glycol (25, p.138), tartaric acid (2, p.140), and acetoin (25, p.115) to name some suggests that other similar four carbon compounds might be of biological interest.

For this reason the synthesis of 1,4-dihydroxy-2,3-butanedione (III, Fig. 1) was undertaken in order to make it available for comparison with a product obtained by Cheldelin and King¹, of these laboratories, in studies of the metabolism of A. suboxydans. While it was anticipated that the bromine of 1,4-dibromo-2,3-butanedione (8, p.207) could be as easily replaced as the bromine of phenacylbromides (20, p.125) in practice the reaction proved to be very sensitive to conditions. Efforts to effect the reaction with sodium hydroxide in water or alcohol; with sodium bicarbonate, sodium carbonate, potassium carbonate, sodium acetate, silver acetate, silver oxide or barium carbonate in water, alcohol or acetone and under various conditions of temperature and mixing invariably gave, upon removal of the solvent, a black tar that quickly became water insoluble. In an effort to prepare the diphosphate ester, 1,4-dibromo-2,3-butanedione (I, Fig.1) was reacted in warm water with potassium

¹ Private communication. V.H. Cheldelin and T.E. King.

dihydrogen phosphate. The pH of the solution was found to decrease with time indicating that a strong acid was being formed and consequently that hydrobromic acid or the equally strong phosphate ester was a reaction product.

Extraction of this solution with chloroform gave a small amount of a tarry substance that contained bromine and decomposed easily. Extraction of the solution again with *n*-butanol gave upon removal of the butanol a glass that gave a faint test for phosphate and that decomposed only slowly, was slightly hygroscopic and remained soluble in water. These results suggested that 1,4-dihydroxy-2,3-butanedione could possibly be obtained if the hydrolysis was conducted under slightly acidic conditions and in such a way that only water insoluble or gaseous inorganic compounds were formed. Thus when 1,4-dibromo-2,3-butanedione was reacted with the theoretical quantity of silver carbonate in a stoppered ruby red container it was found that 97.8% of the calculated quantity of silver bromide was obtained after 72 hours and only traces of reduced silver. Removal of the water by lyophilization gave a glass which changed to a powder in the presence of 2-butanone. Analysis indicated that the carbonate ester was not formed nor would it be expected since under the conditions employed the concentration of carbonate ion would be very low and bicarbonate esters decompose spontaneously to carbon dioxide and the corresponding alcohol.

The material itself melts at 125.5-6.0° and readily forms a bis(2,4-dinitrophenyl hydrazone) (IV, Fig.1) in glacial acetic acid which decomposes at 283-5°. A material which appears to be the same compound is obtained when

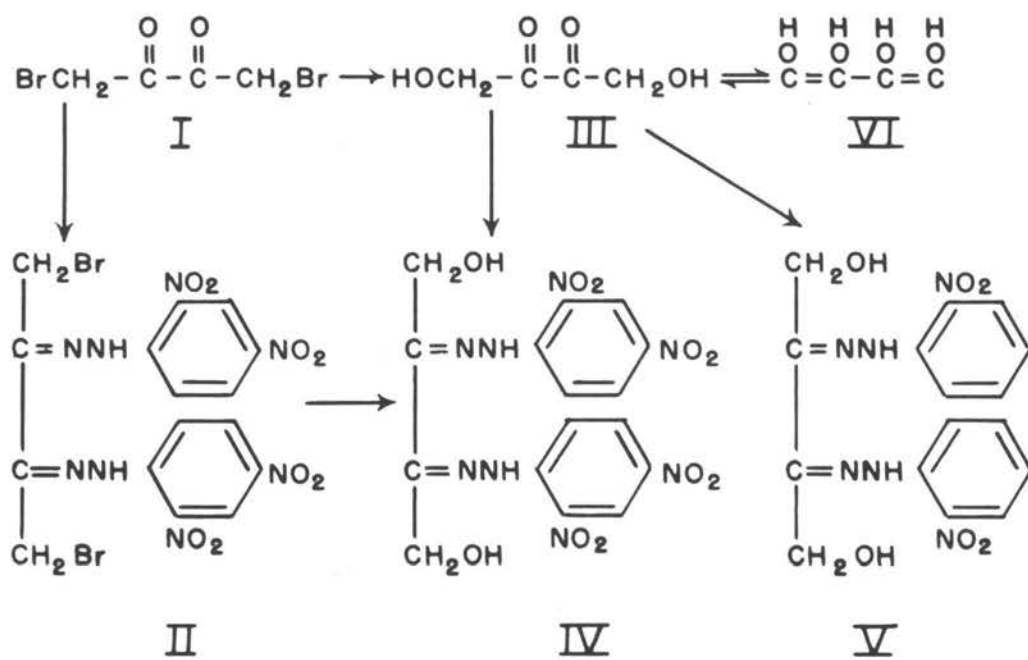


FIGURE 1

the bis(2,4-dinitrophenylhydrazone) of 1,4-dibromo-2,3-butanedione (II, Fig. 1) is reacted with 2,4-dinitrophenylhydrazine in a methanol-water solution.

The bis(2,4-dinitrophenylhydrazone) of 1,4-dibromo-2,3-butanedione was prepared by reaction of the substituted hydrazine with the dione in glacial acetic acid solution. A mixture was obtained when the reaction was carried out in a water-methanol solution.

A bis(ortho nitrophenylhydrazone) of 1,4-dihydroxy-2,3-butanedione (V, Fig.1) was readily prepared in methanol. It melts with decomposition at 239-40°.

Efforts to prepare derivatives of the hydroxyl groups invariably gave a tar and the product resulting from the reaction of the reagent with water. Phenyl isocyanate, para toluene sulfonyl chloride, 3,5-di nitro benzoylchloride and triphenylmethylchloride were used. Reaction with excess acetic anhydride gave a brown tar upon removal of volatile solvents from which no pure product was isolated.

A dilute water solution of 1,4-dihydroxy-2,3-butanedione is faintly acidic, pH 5-6, which suggests that it may be in equilibrium with the diene-tetraol structure (VI, Fig.1). A flash of purple coloration is given when a drop of ferric chloride solution is added to a dilute solution of 1,4-dihydroxy-2,3-butanedione.

A semimicro hydrogenation of 1,4-dihydroxy-2,3-butanedione in an apparatus similar to the one described by Siggia (21, p.74) resulted in an uptake of 1.57 moles of hydrogen per mole of dione taken. The syrupy residue from

lyophilization of the filtered hydrogenation mixture rapidly reduced cold Tollen's reagent. Since this experiment was only attempted once no particular significance should be given to the incomplete uptake of the theoretical two moles of hydrogen per mole of dione.

When tested with the hydroxylamine reagent (20, p.106) 1,4-dihydroxy-2,3-butanedione gave a positive carbonyl test. However, when an effort was made to prepare the dioxime by the usual method (20, p.202) no pure compound was readily obtained. This effort was therefore abandoned.

Likewise, with semicarbazide a reaction takes place, the yellow color of the dione disappears quickly, but the product could not readily be purified.

With orthophenylenediamine a reaction apparently takes place but removal of solvent gave a black water insoluble material which appeared to be a polymer. The conditions for purification were not worked out. A similar black product was obtained when 2,3-di(bromomethyl)quinoxaline was reacted with alcoholic potassium hydroxide solution or silver carbonate suspension.

Although 2-deoxy-D-ribose has been shown to be the carbohydrate component of deoxyribonucleic acids (18, p.398) and several deoxypentoses and deoxyhexoses have been prepared (18, p.128, 371; 17, pp.66-91) there is only one reference to the preparation of any of the deoxy derivatives of the four carbon sugars namely; the preparation of dl-2,3-dihydroxybutanal by Glattfeld and Straitiff (13, p.1386), isolated as the diacetate, as an extension of Glattfeld's studies on the synthesis of the C₄-saccharinic acids and other possible products of the alkaline degradation of sugars (13, p.1384).

The present synthesis of dl-3,4-dihydroxybutanal was undertaken because of the need in these laboratories for a series of analogs of deoxynucleosides.

In the study of possible methods for the preparation of dl-3,4-dihydroxybutanal (X, Fig.2) note was taken of the known instability of 2-deoxy-sugars in acid media (17, p.63) and therefore methods which maintained essentially basic or mildly acidic conditions were sought. The report by Friedman (9, p.5M) and later by Smith and Rogier (22, p.4048) that the nitrile group could be reduced with theoretical quantities of lithium aluminum hydride to the corresponding imine from which the aldehyde is readily obtained by mild hydrolysis made the use of this reaction potentially possible.

The commercial availability of 3-chloro-1,2-propanediol, (I, Fig.2) with a highly reactive chlorine made this a natural starting point in the synthetic scheme that was adopted (Fig.2). The reaction of this compound with alkali cyanides had been shown to give dl-3,4-dihydroxybutyronitrile (IV, Fig.2). Although the latter compound had not been isolated by those who had previously used it as an intermediate (10, 11, 12), it was found possible to obtain it from the oxidation of allyl cyanide (III, Fig.2) (24, p.46) with calcium permanganate in a carbon dioxide buffered solution. Calcium was removed as the oxalate after evaporation of the solution to a small volume. To remove excess oxalic acid, and any acidic material resulting from oxidation or hydrolysis, the solution was treated batchwise with an anionic exchange resin as the free weak base. Evaporation of the resulting solution at low temperature gave a syrup that did not give a positive test for carbonyl compounds (20, p.126).

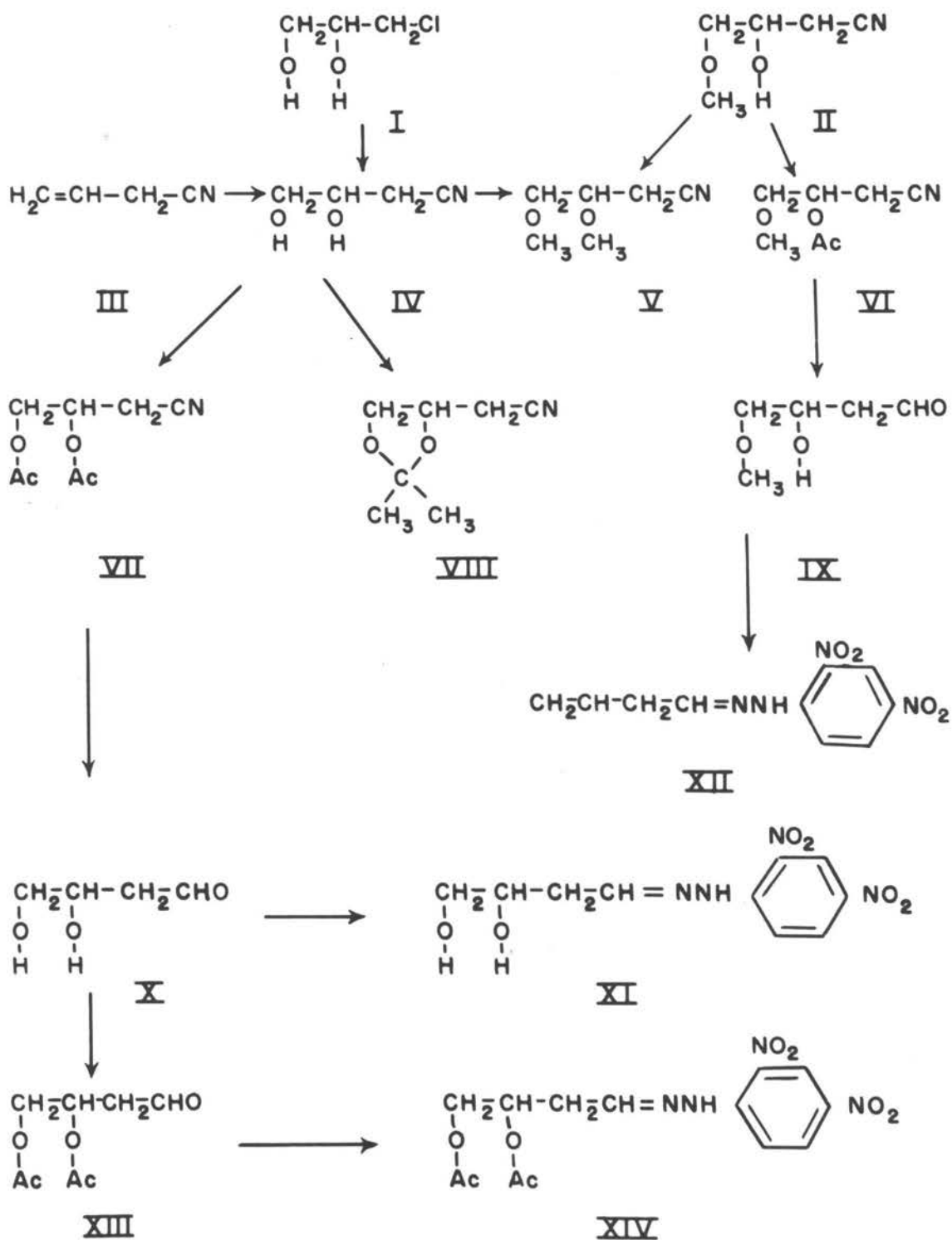


FIGURE 2

In an effort to ascertain when the reaction of 3-chloro-1,2-propanediol with sodium cyanide was complete, aliquots of the reaction mixture were periodically titrated for cyanide ion. Fig.3 is a typical plot of the data obtained and shows that at 50° approximately 80% of the cyanide added had disappeared in two hours from the time of mixing. This represents almost complete reaction since there was an undetermined excess of cyanide present. As a consequence of this determination, the time of reaction was shortened very considerably over that used by previous investigators (11, 12).

From the information available it appeared that for a nitrile to be reduced to the imine only, using lithium aluminum hydride, it would be desirable to have a common solvent for the nitrile and hydride (4, p.486). Because of its availability and of the greater solubility of lithium aluminum hydride in diethyl ether, (4, p.484) it was chosen as the solvent. However, 3,4-dihydroxybutyronitrile is insoluble in ether so it became necessary to form a derivative that would be more soluble. For this reason, the cyclic ketal with acetone, 4-cyanomethyl-2,2-dimethyl-1,3-dioxolane (VIII, Fig.2), was prepared. Efforts to reduce it with the theoretical quantity of lithium aluminum hydride gave the theoretical volume of hydrogen and the starting material upon isolation in the usual manner.

Exactly similar results were obtained from the attempted reduction of dl-3,4-dimethoxybutyronitrile (V, Fig.2) prepared by the methylation of dl-3,4-dihydroxybutyronitrile and of dl-3-hydroxy-4-methoxybutyronitrile (II, Fig.2) with methyl sulfate.

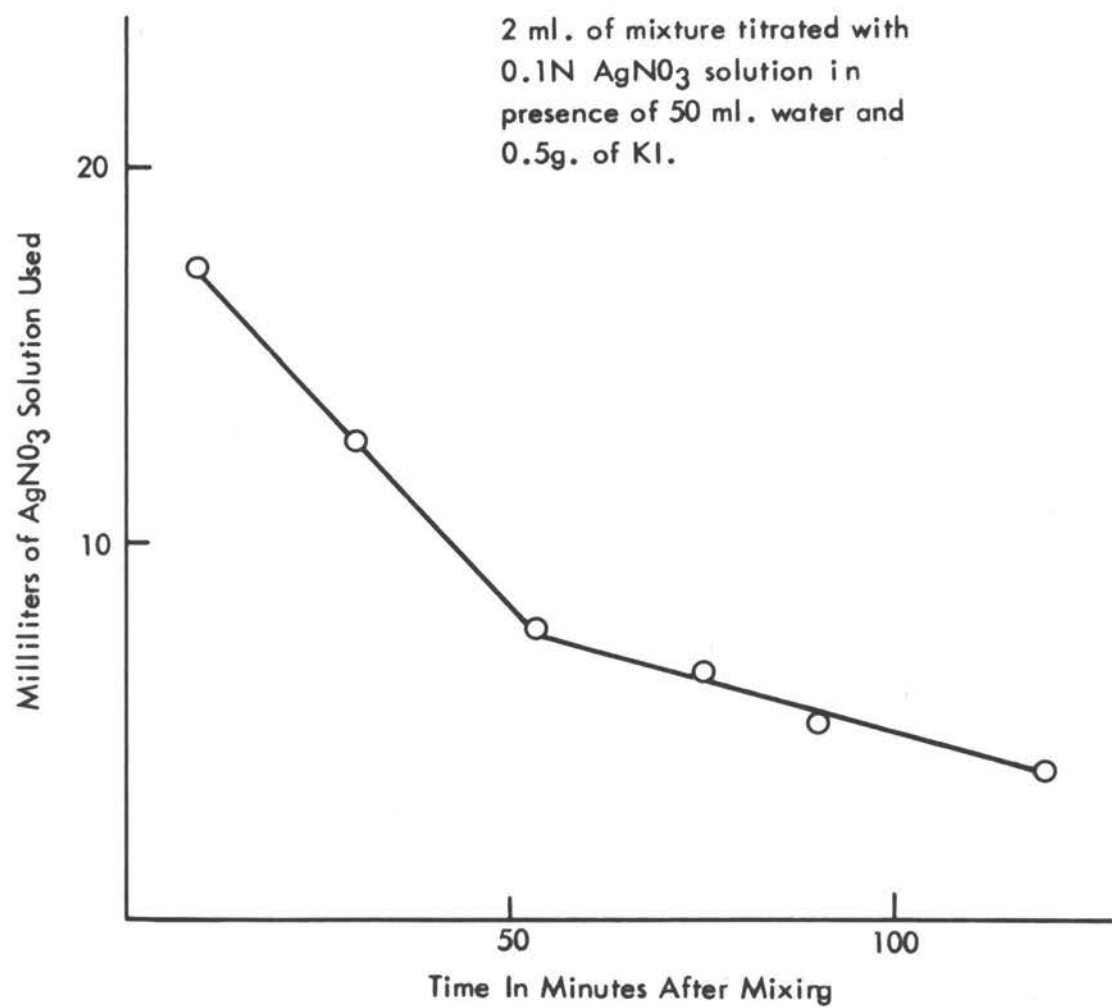


FIGURE 3

These results can be explained if one assumes that the ether linkage on the beta carbon enhances the known activity (16, pp.263-90) of hydrogens alpha to the nitrile group. This is in agreement with the work of Soffer and Parrotta (23, p.3581) who found that hydrogen was evolved when beta-alkoxypropionitriles were reduced with excess lithium aluminum hydride. In a private communication to the author Dr. Soffer states, "On the matter of the evolution of hydrogen we have known for some months that a nitrile containing alpha-hydrogen is essential."

The preparation of dl-3,4-diacetoxybutyronitrile (VII, Fig.2) by the reaction of the crude dihydroxynitrile with excess acetic anhydride was readily accomplished.

The reduction of dl-3,4-diacetoxybutyronitrile with 125 mole percent of lithium aluminum hydride proved possible and dl-3,4-dihydroxybutanal (X, Fig. 2) was isolated as the diacetate (XIII, Fig.2) and as the 2,4-dinitrophenylhydrazone (XI, Fig.2). The 2,4-dinitrophenylhydrazone of the diacetate (XIV, Fig.2) was also prepared.

The reduction of dl-3-acetoxy-4-methoxybutyronitrile (VI, Fig.2) (15, p.2463) with 75 mole percent of lithium aluminum hydride gave the dl-4-O-methyl derivative (IX, Fig.2) of this new deoxy sugar isolated as the 2,4-dinitrophenylhydrazone (XI, Fig.2)

The mixed aldol condensation of benzyloxyacetaldehyde and acetaldehyde was suggested by the work of Eisler and Pollak (5, p.1139) who condensed ethoxy acetaldehyde in basic medium with acetaldehyde and reported

4-ethoxy-3-hydroxybutanal as the principal product. dl-4-Benzyloxy-3-hydroxybutanal (II, Fig.4) was obtained as the product of the condensation of benzyloxyacetaldehyde (I, Fig.4) with acetaldehyde at 0° using potassium carbonate as the catalyst.

The failure of the product obtained to give a positive iodoform test would indicate that very little if any of the benzyloxyacetaldehyde acted as a carbonyl acceptor since if it had 2-benzyloxy-3-hydroxybutanal (III, Fig.4) would have been formed. This latter compound contains a methyl carbinol grouping which would give iodoform (20, p.139) as a result of sodium hypoiodite oxidation.

Apparently the benzyloxy substituent makes the carbonyl carbon more positive and thus increases the reactivity of the carbonyl group towards addition reactions (I, p.155). If this increase in the positive character of the carbonyl carbon is due to an increased negativity of the alpha carbon, because of the presence of the benzyloxy group, it would also explain the failure of benzyloxyacetaldehyde to donate a proton in an addition reaction either with itself or with acetaldehyde when in the presence of acetaldehyde.

This view is in line with the work of Hurd and Abernethy (14, p.1966) who obtained very low yields of 2,4-dimethoxy-3-hydroxybutanal by the self condensation of methoxy acetaldehyde.

The 2,4-dinitrophenylhydrazone (IV, Fig.4) of dl-4-benzyloxy-3-hydroxybutanal was readily obtained.

Reaction of dl-4-benzyloxy-3-hydroxybutanal with dilute hydrochloric

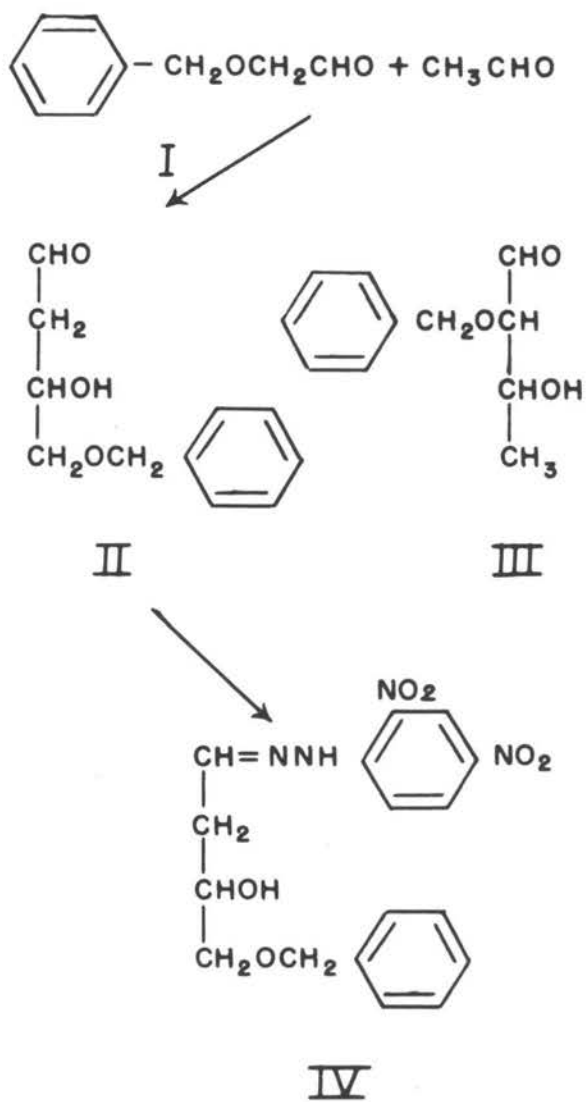


FIGURE 4

acid at room temperature did not result in hydrolysis of the benzyl ether.

EXPERIMENTAL

All melting temperatures are uncorrected.

1,4-Dibromo-2,3-butanedione (I, Fig.1): was prepared by the method of Fittig (8, p.207) in 56% yield and recrystallized from benzene. Melting point 117° .

Bis(2,4-dinitrophenylhydrazone) of 1,4-dibromo-2,3-butanedione (II, Fig.1): To 400 mg. of 2,4-dinitrophenylhydrazine in 15 ml. of glacial acetic acid was added 244 mg. of 1,4-dibromobutanedione. The mixture was heated for a few minutes on a steam bath and allowed to cool overnight. A bright orange powder precipitated. The precipitate was collected and dried. Melting point $236-8^{\circ}$ with decomposition.

Analysis: Calc'd. for $C_{16}H_{12}N_8O_8Br_2$; C, 31.80; H, 2.00

Found; C, 32.0; H, 2.0.

1,4-Dihydroxy-2,3-butanedione (III, Fig.1): To 50 ml. of water in a ruby red flask were added 5.52 g. (0.02 mole) of dry powdered pure silver carbonate and 4.88 g. (0.02 mole) of 1,4-dibromo-2,3-butanedione. The flask was tightly stoppered and the mixture stirred with a magnetic stirrer until the solution no longer gave a positive test for bromine. The stirrer motor kept the temperature at about 35° . The solution was then filtered and the water was removed by lyophilization. The drying was continued three hours after the glassy mass appeared to be dry. Fifteen ml. of anhydrous 2-butanone was then added and the flask vigorously shaken. The glass changed to a flocculent

solid. It was collected in a fritted glass crucible which, after the addition of the slurry was completed, was protected with a calcium chloride drying tube. Yield 1.6 g. (68%) of a yellowish white hygroscopic powder, melting at 125.5-6.0° and decomposing at higher temperatures. A further small amount was obtained by evaporation of the filtrate to 5-7 ml.

Analysis: Calc'd for $C_4H_6O_4$; C, 40.68; H, 5.12.

Found; C, 40.3; H, 5.4.

Bis(2,4-dinitrophenylhydrazone) of 1,4-dihydroxybutanedione (IV, Fig. 1): To 10 ml. of a glacial acetic acid solution containing 150 mg. of 2,4-dinitrophenylhydrazine was added 30 mg. of 1,4-dihydroxybutanedione. The solution was heated a few minutes on the steam bath then set aside to cool slowly. The brown orange precipitate which formed was removed and dried. Yield 90 mg. (76%). Melting at 283-5° with decomposition.

Analysis: Calc'd for $C_{16}H_{14}N_8O_{10}$; C, 40.17; H, 2.95.

Found: C, 40.2; H, 2.9.

A solution of 200 mg. of the bis(2,4-dinitrophenylhydrazone) of 1,4-dibromo-2,3-butanedione in 200 ml. of methanol and 100 ml. of water was refluxed for six hours with 200 mg. of 2,4-dinitrophenylhydrazine. The mixture was then evaporated to about 75 ml. and filtered. The precipitate was recrystallized twice from glacial acetic acid. Yield 54 mg. of an orange red powder. Melting 282-3° with decomposition. Mixed melting point with bis(2,4-dinitrophenylhydrazone) of 1,4-dihydroxy-2,3-butanedione 282-3° with decomposition.

Bis(orthonitrophenylhydrazone) of 1,4-dihydroxy-2,3-butanedione (V, Fig.1): To a solution prepared from 5 ml. of methanol, 1 ml. of water and a drop of dilute hydrochloric acid and 150 mg. of orthonitrophenylhydrazine² was added 50 mg. of 1,4-dihydroxy-2,3-butanedione. The mixture was heated for five minutes on a steam bath. The blood red precipitate was collected after the solution was allowed to cool and recrystallized from ethyl acetate. Yield 140 mg. (82.5%), melting point 239-40°.

Analysis: Calc'd for $C_{16}H_{16}N_6O_6$; C, 49.50; H, 4.16.

Found; C, 49.4; H, 4.2.

3,4-Dihydroxybutyronitrile (IV, Fig.2): A liter of water in a 5 liter three necked flask immersed in an ice-salt bath, equipped with an efficient adjustable speed stirrer and a fritted glass gas dispersion tube was aereated slowly with carbon dioxide. After twenty minutes 75 g. (1.12 moles) of allyl cyanide in 500 ml. of methanol were added. With the carbon dioxide aereation continuing the solution was stirred just rapidly enough to form a deep well in the center without splashing.

When the temperature of the solution fell below 0°, the dropwise addition of 113 g. (0.323 moles) of calcium permanganate tetrahydrate in 2 liters of water was begun, so that the drops hit the stirring liquid near the rim of the center well. The rate of addition was adjusted so that the temperature remained between -5 to 2°. When the addition of permanganate had been completed 50 g. of acid washed infusorial earth (Celite) were added, stirred 15

2. Kindly supplied by M.K. Devlin and V. H. Cheldelin.

minutes and the solution filtered. The precipitate was washed well with water and the combined filtrate and washings were quickly evaporated to approximately 400 ml. in a high capacity laboratory evaporator. The temperature of the solution was held below 55°. A precipitate of calcium carbonate and manganese dioxide that formed during this process was removed by filtration after cooling the solution. The resulting golden yellow solution was treated with a slight excess of a saturated solution of oxalic acid and filtered.

To the filtrate was added 100 g. (dry-weight) of IR4B resin that had been activated batchwise by washing five times with 500 ml. portions of a saturated solution of sodium carbonate followed by distilled water until neutral. The mixture was stirred thirty minutes then filtered. The resulting light yellow solution was evaporated under vacuum to an anhydrous oil. Yield 71.5 g. (63.2%) of yellow oily liquid soluble in water acetone and alcohol, $n_D^{26.5}$ 1.4660, decomposes about 85°. Sets to a gummy polymer in about 2 weeks.

Analysis: Calc'd. for $C_4H_7NO_2$; C, 47.51; H, 6.98.

Found; C, 48.0; H, 6.9.

3,4-Diacetoxybutyronitrile (VII, Fig.2): In a flask fitted with an efficient stirrer and provided with an ice water bath that was adjustable to cover the flask to any desired height was placed a solution of 105 g. of sodium cyanide in 110 ml. of water. To this solution was added in one portion 220 g. of 1-chloro-2,3-propanediol. As the temperature of the solution began to rise the bath was adjusted to maintain the temperature between 45-55°. After the temperature dropped (bath removed), the solution was stirred an additional

hour. It was then made faintly acidic by the cautious addition of concentrated hydrochloric acid (Hood III). The precipitate was removed by filtration and washed with acetone. The combined filtrate and washings were added in a thin stream to 1.5 liters of ice cold, well stirred acetone. After one hour in the refrigerator the solution was filtered and the acetone and most of the water were removed at the water pump by the slow addition of the solution to a flask evacuated by a water pump and immersed in a bath at 50°.

The residue was cooled and 220 g. of acetic anhydride and 10 ml. of pyridine were added. There was a rapid rise in temperature which was kept below 80° with a cold water bath. After the heating subsided the mixture was set aside overnight at room temperature. The acetic acid and excess acetic anhydride were then removed under reduced pressure. The residue was distilled in a Claisen flask fitted with a capillary gas inlet reaching to the bottom of the flask through which carbon dioxide was admitted so that the liquid was vigorously agitated. The fraction distilling between 100-15° at approximately 2 mm. was collected; the temperature of the heating bath was between 150-165°.

The crude material was fractionated under reduced pressure at approximately 2 mm. in a 40 cm. Vigreux column. Yield 145 g. (39.2%) of a light yellow oil boiling 100-5°.

Analysis: Calc'd. for $C_8H_{11}NO_4$; C, 51.89; H, 5.98.

Found: C, 51.9; H, 6.1.

3,4-Dimethoxybutyronitrile (V, Fig.2); (Method A): In a liter flask

equipped with a thermometer and a stirrer were placed a solution consisting of 58 g. of sodium cyanide and 60 ml. of water and 110 g. of 3-chloro-1,2-propanediol were then added in one portion. The previously prepared ice water bath was adjusted as the temperature increased so that the reaction proceeded in a temperature range of 45-55°. After the temperature decreased (with the bath removed) the mixture was stirred an additional hour.

The mixture was then cooled to 0° filtered and the salt remaining on the filter was washed with three small portions of acetone. Most of the acetone was evaporated under reduced pressure without heating. The solution was then cooled to 0° or below and a solution of 50 g. of sodium hydroxide in 60 ml. of water was added dropwise so that the temperature did not rise. This operation was followed immediately by the dropwise addition of 315 g. of re-distilled dimethyl sulfate at such a rate that the temperature did not rise above 5°. The solution was stirred two hours following the addition of dimethyl sulfate, then extracted exhaustively with diethyl ether. The combined ether extracts were dried over anhydrous potassium carbonate and the ether removed on a water bath. The residue was distilled under reduced pressure (about 1 mm.) while slowly admitting carbon dioxide through a capillary reaching to the bottom of the flask. It was essential that the receiver be immersed in a dry ice cooling bath to avoid undue loss of material.

The crude product was redistilled through a 40 cm. Vigreux column. The fraction boiling 45-50° at approximately 1 mm. was retained. The yield

was 28.8 g. (22.3%) of a colorless, oily, fragrant substance that does not wet clean pyrex glass. n_D^{26} 1.4232.

Analysis: Calc'd. for $C_6H_{11}NO_2$; C, 55.80; H, 8.58.

Found; C, 55.6; H, 8.7.

(Method B): In a flask equipped with a Hirschberg stirrer was placed a solution of 14 ml. of water and 6 g. of sodium hydroxide pellets. The flask was then surrounded with an ice salt mixture. When the temperature of the contents fell below 5° , 15.4 g. (0.154 moles) of 3-hydroxy-4-methoxybutyronitrile (15, p.2463) were added followed by 13 ml. (0.155 moles) of dimethyl sulfate, added dropwise at such a rate that the temperature remained between 5° to 10° . After the addition of dimethyl sulfate was completed stirring was continued for one hour during which time the temperature dropped to 0° or below. The mixture was then extracted four times with ether. The ether layer was removed, washed with dilute acetic acid and dried over anhydrous sodium sulfate. The ether was then removed and the residue distilled under reduced pressure through a 40 cm. Vigreux column. The colorless fraction distilling $45-50^\circ$ at approximately 1 mm. pressure was retained. The yield was 15 g. (52.8%). n_D^{25} 1.4232.

4-Cyanomethyl-2,2-dimethyl-1,3-dioxolane (VIII, Fig.2): The syrup obtained from reaction of 110 g. of 3-chloro-1,2-propanediol with sodium cyanide (as in the method for preparation of 3,4-diacetoxybutyronitrile) after removal of the precipitated salt and most of the water was placed in a 1 liter

flask with 100 ml. of acetone and 400 ml. of chloroform. An azeotrope of water, acetone and chloroform was distilled off. The distillate was dried with anhydrous sodium sulfate and upturned to the flask. This process was continued until all the water was removed. The contents of the flask were then filtered and returned with 15 ml. of concentrated sulfuric acid. Distillation of the azeotrope of water, chloroform and acetone was continued until no more water was detected in the distillate (approximately 20 hours). The cooled contents of the flask were stirred thirty minutes with an excess of anhydrous finely powdered sodium carbonate then filtered. The light solvents were removed by distillation from a water bath and the residue was distilled under reduced pressure. The fraction boiling at 40-60° under approximately 1 mm. pressure was collected and redistilled under reduced pressure through a 40 cm. Vigreux column. The fraction boiling between 47-9° weighed 9.5g. (6.5%). n_D^{24} 1.4326.

Analysis: Calc'd. for $C_7H_{11}NO_2$; C, 59.56; H, 7.85.

Found; C, 59.5; H, 7.8.

3,4-Diacetoxybutanal (XIII, Fig.2): A 1 liter flask fitted with an efficient stirrer, Ascarite protected condenser, a dropping funnel and a bath for a mixture of dry ice and acetone was used for the reaction.

A lithium aluminum hydride solution was prepared (4, p.485) and analyzed (7, p.347). An amount of 3,4-diacetoxybutyronitrile was weighed that would use 200 ml. of the above solution calculated on a basis of 1 mole of

nitrile to 1.25 mole of hydride.

The nitrile and approximately 200 ml. of anhydrous ether were placed in the reaction flask, stirred and cooled with a dry ice bath. The 200 ml. of lithium aluminum hydride solution was then added dropwise to the well stirred solution.

When the addition was complete the cooling bath was removed. The reaction mixture was allowed to warm up to room temperature and stirred for thirty minutes.

A solution of 10 ml. of acetic acid in 50 ml. of water was added (the first drop very cautiously to insure that all the hydride had reacted) and stirring was continued for thirty minutes more. The ether layer was separated. The aqueous layer was filtered and the filtrate evaporated under reduced pressure to a syrup. An excess of acetic anhydride was added together with a few drops of pyridine and allowed to stand overnight. The acetic acid and excess anhydride were removed under reduced pressure and the residue was distilled using short path distillation at approximately 10^{-4} mm. Yield from 7 g. of nitrile 2.3 g. (32.5%) of a colorless viscous syrup.

Analysis: Calc'd. for $C_8H_{12}O_5$; C, 51.06; H, 6.43.

Found; C, 51.2; H, 6.5.

2,4-Dinitrophenylhydrazone of dl-3,4-dihydroxybutanal (XI, Fig. 2):

To a solution of 200 mg. of 2,4-dinitrophenylhydrazine in methanol containing a few drops of glacial acetic acid was added 0.2 ml. of the syrup obtained

from reduction of 3,4-diacetoxybutyronitrile after removal of water. The mixture was heated for 10 minutes on the steam bath, cooled and placed in the refrigerator. After two days the crystals were collected and washed with methanol and water. Yield 185 mg. of light orange yellow needles melting at 115-117°.

Analysis: Calc'd. for $C_{10}H_{12}N_4O_6$; C, 42.27, H, 4.23.

Found; C, 42.1, H, 4.3.

2,4-Dinitrophenylhydrazone of dl-3,4-diacetoxybutanal (XIV, Fig. 2):

Crude dl-2,4-diacetoxybutanal (1 g.) was added to 15 ml. of freshly prepared Brady's reagent (3, p.757) and the mixture shaken. The precipitate, which appeared almost immediately, was cooled to 0°, allowed to stand for fifteen minutes and then removed by filtration and recrystallized from ethyl acetate. Yield 1.6 g. of orange yellow crystals (86%) mp. 121-122°.

Analysis: Calc'd. for $C_{14}H_{16}N_4O_8$; C, 45.66; H, 4.38.

Found;³ C, 45.5; H, 4.1.

2,4-Dinitrophenylhydrazone of dl-3-hydroxy-4-methoxybutanal (XII ,

Fig.2): A reduction of 3-acetoxy-4-methoxybutyronitrile (VI, Fig.2) (15, p. 2463) was carried out as described in preparation of 3,4-diacetoxybutanal but using 75 mole percent of lithium aluminum hydride. The ether layer was separated, dried over anhydrous magnesium sulfate and the ether evaporated using a water bath at 50°. The resulting syrup gave a positive Schiff's test

3. Analysis by Drs. G. Weiler and F. B. Strauss, Oxford, England.

and reduced Tollen's solution in the cold.

To a solution of 500 mg. of 2,4-dinitrophenylhydrazine in 25 ml. of methanol and 1 ml. of acetic acid was added approximately 0.2 g. of the above syrup. The mixture was heated for 10 minutes then water was added until an opalescence appeared. Upon cooling a yellow precipitate formed which was collected and washed with water.

The dried powder melted at 70°. Yield 85 mg.

Analysis: Calc'd. for $C_{11}H_{14}N_4O_6$; C, 44.30; H, 4.73.

Found; C, 44.1; H, 4.5.

4-Benzoyloxy-3-hydroxybutanal (II, Fig.4): A solution was made at 0° of 15 g. of benzoyloxyacetaldehyde (19, p.1910), 6 ml. of acetaldehyde, 60 ml. of 95% alcohol 125 ml. of water and 15 g. of potassium carbonate. The tightly stoppered flask was placed in the refrigerator and shaken at convenient intervals over a period of three days.

At the end of this time the mixture was saturated with potassium carbonate and extracted with three portions of ether. The extract was dried over magnesium sulfate, evaporated to remove ether and alcohol then heated under high vacuum at 1 mm. until bath temperature reached 142°; a small quantity of low boiling material distilled over. The residue a light yellow oil is 4-benzoyloxy-3-hydroxybutanal. Yield 15.5 g. (80%).

Analysis: Calc'd. for $C_{11}H_{14}O_3$; C, 68.02; H, 7.26.

Found; C, 67.9; H, 7.1.

2,4-Dinitrophenylhydrazide of 4-benzyloxy-3-hydroxybutanal (IV, Fig. 4): 0.5 g. of the aldehyde and 15 ml. of freshly prepared Brady's reagent (3, p. 757) were mixed and shaken for a few minutes. In a short time a heavy bright orange brown tar formed on the sides and bottom of the flask. After decantation of the supernatant liquid and the addition of 25 ml. of methanol the tar gradually crystallized.

Recrystallization from methanol gave 0.8 g. of an orange powder melting 124-125° with preliminary softening at 117°.

Analysis: Calc'd. for $C_{17}H_{18}N_4O_6$; C, 54.54; H, 4.85.

Found; C, 54.8; H, 4.8.

SUMMARY

1,4-Dibromo-2,3-butanedione was reacted with silver carbonate in a weakly acidic solution to obtain 1,4-dihydroxy-2,3-butanedione. The bis-hydrazones of 1,4-dihydroxy-2,3-butanedione were prepared using 2,4-dinitrophenylhydrazine and orthonitrophenylhydrazine. The bis(2,4-dinitrophenylhydrazone) of 1,4-dibromo-2,3-butanedione upon hydrolysis of the bromines gave the same bis-hydrazone obtained from 1,4-dihydroxy butanedione.

Evidence of reaction between 1,4-dihydroxy-2,3-butanedione and hydroxylamine, semicarbazide and orthophenylenediamine was obtained but pure compounds were not isolated.

The isolation of 3,4-dihydroxybutyronitrile from the hydroxylation of allyl cyanide was effected. The dimethoxy, diacetate and isopropylidene derivatives were prepared. Lithium aluminum hydride (125 mole %) was shown to reduce the diacetoxy derivative to the dihydroxy imine. The methoxy and isopropylidene derivatives react to give hydrogen with theoretical quantities of lithium aluminum hydride.

dl-3,4-Dihydroxybutanal was isolated as the diacetate and the 2,4-dinitrophenylhydrazone. The 4-methoxy-derivative was prepared by reduction of 3-acetoxy-4-methoxybutyronitrile and isolated as the 2,4-dinitrophenylhydrazone.

The condensation of benzyloxyacetaldehyde with acetaldehyde in an alcoholic potassium carbonate solution gave 4-benzyloxy-3-hydroxybutanal as the principal product. It was shown that this compound was stable in acid solution at room temperature. The 2,4-dinitrophenylhydrazone was prepared.

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