Total Syntheses of Carbohydrates. I. Dihydroxyacetone and DL-Erythrulose

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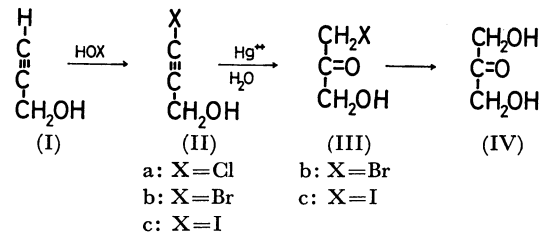
(Received January 24, 1972)

An improved method of preparation of halopropargyl alcohol is described. Hydration of halopropargyl alcohol followed by hydrolysis gave dihydroxyacetone which was identified as its dibenzoate. 2-Butyne-1,4-diol was converted into acetoxymethyl vinyl ketone. 1,4-Diacetoxy-3-bromobutan-2-one obtained by the addition of acetyl hypobromite to the vinyl ketone was treated with silver acetate to yield tri-*O*-acetyl-DL-erythrulose. Hydrolysis of the triacetate afforded DL-erythrulose which was identified as phenylhydrazone.

Since the pioneering work of R. Lespieau,[1] a number of papers have appeared on total syntheses of carbohydrates. Stereoselective synthesis of carbohydrates involves two problems; the construction of asymmetric centers bearing hydroxyl group with particular configuration, and the introduction of formyl- or keto-function at a desired position. The former can be solved in principle by (1) a stereoselective synthesis of an open chain olefinic compound followed by stereospecific hydroxylation, (2) stereospecific reactions of cyclic compounds such as reduced furans or pyrans, or (3) a combination of (1) and (2). Open chain compounds can usually be obtained by stereoselective half-reduction of acetylenic compounds. Construction of more than three asymmetric centers with a particular configuration in an open chain olefinic compound is usually difficult, but the versatile reactivity of an acetylenic compound, the precursor of an olefinic compound, provides various routes for the introduction of carbonyl function. Thus, the total syntheses of DL-erythrulose,[2] DL-apiose,[3] 2-deoxy-DL-*erythro*-pentose,[4,5] 2-deoxy-DL-*threo*-pentose,[5] the four isomers of DL-aldopentose,[6] ethyl glycoside of 3-amino-3-deoxy-DL-arabinose,[7] L-mycarose[8] and ethyl glycoside of DL-picrocin[9] were achieved starting from various acetylenic compounds.

We have studied total syntheses of carbohydrates starting from simple acetylenic or olefinic compounds, and wish to report on the total syntheses of dihydroxyacetone and DL-erythrulose.[10]



Scheme 1. Synthesis of dihydroxyacetone (IV).

The reported methods of preparation of dihydroxyacetone by chemical means such as isomerization of glyceraldehyde,[11] bromine oxidation of glycerol,[12] alkaline treatment followed by acid hydrolysis of 1,2-isopropylideneglyceryl chloride[13] and hydrolysis of 1,3-dichloroacetone[14] do not seem to be very satisfactory. As is shown in Scheme 1, we carried out the synthesis of dihydroxyacetone (IV) employing propargyl alcohol (I) as a starting material. Treatment of an ethynyl compound with hypohalite under strongly alkaline conditions is the usual method of preparation of haloacetylene.[15] However, the reaction conditions can not be applied to propargyl alcohol (I), since I and II are sensitive to strong base. Since the prolonged treatment of I with calcium hypohalite and calcium hydroxide in water resulted in recovery of I, alcohol (I) was converted into α-methoxyethyl ether derivative by the reaction with methyl vinyl ether. Treatment of the ether derivative with sodium hydroxide-calcium hypohalite in water followed by acid hydrolysis of the protective group afforded chloropropargyl alcohol (IIa) in a 53% yield. Bromopropargyl alcohol (IIb) could be prepared in a 65% yield by rapid addition of I to a mixture of calcium hypobromite, calcium hydroxide, water and ether at a temperature below −5°C.[16] When the reaction temperature is higher than this an appreciable amount of bromopropiolic acid is formed accompanied by a significant decrease in the yield of IIb. It is to be noted that calcium hypobromite can oxidize primary acetylenic alcohol to carboxylic acid leaving the acetyl-

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4) M. M. Fraser and R. A. Raphael, *J. Chem. Soc.*, **1955**, 4280.

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13) H. O. L. Fischer, E. Baer, and L. Feldmann, *Ber.*, **63**, 1732 (1930).

14) E. Waldmann and V. Prey, *Monatsh. Chem.*, **82**, 861 (1951).

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16) The reported method of preparation of IIb [L. F. Hatch, W. E. Blankenstein, and S. H. Chu, *J. Org. Chem.*, **23**, 397 (1958)] gave a much lower yield.

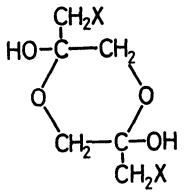
enic bond intact under weak alkaline conditions at a low temperature. The procedure of preparation of iodopropargyl alcohol (IIc) had to be modified because of the unstable nature of hypoiodite, *i.e.*, an aqueous solution of iodine–potassium iodide was added to an aqueous suspension of calcium hydroxide containing I. By this procedure, iodopropargyl alcohol (IIc) was obtained in a 56% yield.

Halopropargyl alcohols (IIa, IIb, and IIc) thus prepared were found to be rather unstable. The stability decreases with the increase in the atomic weight of halogen atom. Iodopropargyl alcohol (IIc) could be recrystallized from ether or petroleum ether to yield pure crystals (mp 39.5—41.0°C). Recrystallization of IIc from methanol or ethanol, however, gave a different substance (mp 153°C), which was assigned to be 2,3,3-triiodo-2-propen-1-ol on the basis of IR spectrum and the elemental analysis.

The hydration of halopropargyl alcohols (IIa, IIb, and IIc) was examined with two catalysts, an aqueous sulfuric acid containing mercuric sulfate (Reagent A)[17] and mercury-impregnated Dowex-60 (Reagent B).[18] Bromo- and iodopropargyl alcohols (IIb and IIc) gave smoothly corresponding haloketones (IIIb, 69% and IIIc, 53%) on treatment with Reagent A. On the other hand, the chloro-compound (IIa) gave no ketone under the same reaction conditions. Treatment of IIa under more drastic conditions resulted in a minor amount of a mercury containing substance, which seems to be an intermediate complex of hydration. Although the hydration of IIa and IIb could not be accomplished by Reagent B, IIc gave iodoketone (IIIc) in an 84% yield under these conditions. The marked difference in reactivity of halopropargyl alcohols (IIa, IIb, and IIc) may be explained in terms of the difference in electron donating power of halogen atoms. The hydration of acetylenic linkage is regarded as an electrophilic addition reaction catalyzed by mercuric ion.[17] Thus, the reaction is considered to be retarded by the presence of an electron attractive substituent and enhanced by an electron donating group. Haloacetylene can be regarded as a resonance hybrid of V and VI.

$$\underset{\text{(V)}}{RC{\equiv}C\text{–}X} \longleftrightarrow \underset{\text{(VI)}}{R\bar{C}{=}C{=}\overset{+}{X}}$$

The increase of contribution of VI in the sequence Cl<Br<I has been confirmed by the measurement of dipole moment of arylhaloacetylenes.[19] The IR spectra of halopropargyl alcohols (IIa, IIb, and IIc) exhibit absorptions due to $\nu_{C\equiv C}$ at 2250, 2240, and 2195 cm^{-1}, respectively, and the absorption intensity was found to be in the sequence IIa≈IIb>IIc. The IR spectral behavior observed in IIa—c is consistent with the conclusion obtained from the dipole moment measurement.



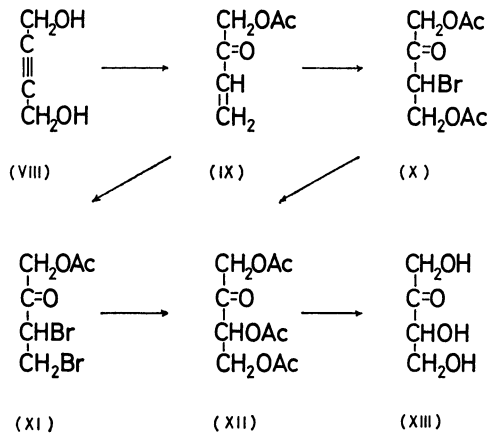
(VII)

The crystalline halogenohydroxyacetones (IIIb and IIIc) showed no carbonyl absorption in their IR spectra. This suggests that the halohydroxyacetones (IIIb—c) exist in the dimeric form (VII) in the solid state as in the case of dihydroxyacetone (IV). However, the IR spectrum of IIIc in liquid state exhibits absorption due to carbonyl group (1700 cm^{-1}) and ethylenic linkage (1620 cm^{-1}), which indicates that IIIc in solution exists in monomeric state at equilibrium of keto- and enol-forms. IIIb was found to be extremely unstable. Complete decomposition took place within about 1 hr at 30°C. IIIb could be kept in a refrigerator for a long time without change in appearance, but the melting point (75—76°C) lowered rapidly to *ca.* 50°C.

Dihydroxyacetone (IV) is extremely sensitive to acid and base. It decomposes or polymerizes easily in the presence of acid or alkali. Rearrangement to methylglyoxal or glyceraldehyde is also easily caused by acid or alkali. Consequently, the preparation of IV from its ester or ether derivative is difficult. It has been reported that the hydrolysis of diacetate of IV by means of weak alkali or water alone, or the hydrogenolysis of dityrityl or dibenzyl ether of IV gave fruitless results.[14] The hydrolysis of monoacetate IV with barium carbonate also gave only a trace of IV.[13] We have therefore employed an ester-exchange method which has been successfully applied to the conversion of bromoacetone to acetol[20] or 1-alkoxy-3-halogenopropan-2-one to 1-alkoxy-3-hydroxypropan-2-one.[21] Treatment of both IIIb and IIIc with anhydrous sodium formate in boiling anhydrous methanol gave a syrup. All attempts to crystallize the syrup were unsuccessful. However, the absence of methylglyoxal or glyceraldehyde was confirmed by various color reactions.[22] The syrup gave crystalline dibenzoate which gave a superimposable IR spectrum with that of an authentic specimen and showed no depression in mixed melting point. Syrupy IV obtained from IIIc was contaminated with potassium iodide and its removal was found to be difficult owing to the solubility of the salt in organic solvent. The best results were obtained with the use of bromo-compound (IIIb).

In 1952, Raphael reported on the synthesis of DL-erythrulose (XIII) starting from butynediol (VIII) *via* bromoketone (X).[2] In order to improve the preparation of bromoketone (X), a key substance of the present synthesis, we have studied the conversion of

17) R. A. Raphael, "Acetylenic Compounds in Organic Synthesis," Butterworth, London (1955), p. 40.
18) M. S. Newman, *J. Amer. Chem. Soc.*, **75**, 4740 (1953); J. D. Billimoria and N. F. Maclagan, *J. Chem. Soc.*, **1954**, 3257.
19) C. J. Wilson and H. H. Wenzke, *J. Amer. Chem. Soc.*, **56**, 2025 (1934).
20) P. A. Levene and A. Walti, "Organic Syntheses," Coll. Vol. II, p. 5 (1948).
21) A. Grün and W. Stoll, U. S. 2374283 (1945).
22) C. Neuberg, *Biochem. Z.*, **71**, 150 (1915).



Scheme 2. Synthesis of DL-erythrulose (XIII).

acetoxymethyl vinyl ketone (IX) into bromoketone (X) (Scheme 2). Vinyl ketone (IX) was prepared according to a reported method.[23] It has been pointed out that a terminal double bond usually has low reactivity to electrophilic addition.[24,25] A double bond conjugated with an electron withdrawing group such as carbonyl is also inert to peracid oxidation.[26] Hydroxylation by means of alkaline hydrogen peroxide which is usually applied to double bond conjugated with carbonyl group can not be used, since the ester linkage in IX might be cleaved and the product is considered to be sensitive to alkali. The formation of bromohydrin by the reaction of *N*-bromoacetamide[27] or *N*-bromosuccinimide[2,24] in water is well-known. Bromohydrin acetates have been obtained by the reaction of *N*-bromoacetamide[28] or *N*-bromosuccinimide[29] in acetic acid. However, it is recognized that an ethylenic bond conjugated with carbonyl function except for α,β-unsaturated carboxylic acid reacts sluggishly with these reagents.[27,30]

In was found that the vinyl ketone (IX) is stable in acetic acid and a prolonged treatment with *N*-bromosuccinimide at room temperature affords the desired bromoketone (X) in a 46% yield. Bromoketone (X) which has been reported as a liquid[2] was obtained as fairly unstable crystals and gave a reasonable IR spectrum and satisfactory data of elemental analysis. As so far this seems to be the first instance of addition of acryl hypohalite to a double bond conjugated with carbonyl group. By the Raphael method,[2] bromoketone (X) was treated with silver acetate in acetic acid to yield tri-*O*-acetyl-DL-erythrulose (XII). Hydrolysis of triacetate (XII) by means of barium hydroxide[2] gave DL-erythrulose (XIII) as a syrup, which was identified as phenylhydrazone. Treatment of dibromoketone (XI) obtained by the addition of bromine to IX with silver acetate in acetic acid gave unsatisfactory results, and XIII could not be isolated in pure state.

Experimental

All the melting points are uncorrected. IR spectra were obtained on a Hitachi EPI-2 Spectrophotometer by Nujol mull method unless otherwise stated. Anhydrous acetic acid was prepared by the fractionation of acetic acid containing 5% of acetic anhydride which had been refluxed for 1 hr.

1-Methoxyethyl Propargyl Ether. Propargyl alcohol (I, 56 g) was added over a period of 50 min to methyl vinyl ether (110 m*l*) containing phosphoryl chloride (2—3 drops) at 0—8°C. After the mixture had been stirred for 3.5 hr at this temperature, it was left to stand overnight at room temperature. Excess methyl vinyl ether was removed by distillation, and the residue was washed successively with 10% sodium carbonate, 4N sodium hydroxide and water and dried (potassium carbonate). The propargyl ether was obtained as colorless liquid, 120.5 g (70%), bp 47—48°C/32—33 mmHg.

3-Chloro-2-propyn-1-ol (IIa). To a stirred mixture of sodium hydroxide (173 g), bleaching powder (85.2 g, corresponding to 0.72 molar equivalent of hypochlorite) and water (100 m*l*), was added 1-methoxyethyl propargyl ether (68.4 g, 0.6 mol) over a period of 25 min at 0°C. The mixture was stirred for 3.5 hr at room temperature and then left to stand overnight. After excess hypochlorite had been reduced by addition of sodium hydrogen sulfite (30 g), concentrated hydrochloric acid (430 m*l*) was added under cooling. The mixture was kept overnight at room temperature to complete hydrolysis of the protective group. The mixture was extracted with ether. The extract was washed with 1% sodium hydrogen carbonate solution and water and dried (sodium sulfate). The residue obtained by evaporation of the solvent was distilled twice *in vacuo* under nitrogen stream. IIa was obtained as colorless liquid, 29.2 g (53%), bp 49.5—50.5°C/13 mmHg, n_D^{20} 1.46916 [lit,[31] bp 68°C/35 mmHg, n_D^{20} 1.4727], IR (neat): 3300, 2920, 2870, 2250, 1420, 1360, 1225, 1080, 1005 cm^{-1}.

Found: C, 40.14; H, 3.40%. Calcd for C_3H_3OCl: C, 39.81; H, 3.38%.

p-*Nitrobenzoate*: Colorless rods, mp 113.4—114°C [lit,[32] mp 112°C].

3-Bromo-2-propyn-1-ol (IIb). Bromine (77 m*l*, 1.5 mol) was added over a period of 30 min to a stirred suspension of calcium hydroxide (185 g, 2.5 mol) in water (2 *l*) maintained at 0°C. An appreciable drop in temperature of the mixture was observed. Ether (800 m*l*) was added to the hypobromite solution (again the temperature decreased to −8°C) and propargyl alcohol (I, 72.9 g, 1.3 mol) was added over a 7 min-period under vigorous agitation. After the mixture had been stirred for 30 min below −5°C, the cooling bath was removed and stirring was continued for 3.5 hr. Sodium hydrogen sulfite (52 g, 0.5 mol) was added under cooling. After 20 min, concentrated hydrochloric acid (250 m*l*) was added to dissolve calcium hydroxide, and the organic layer was extracted with ether repeatedly (total 1700 m*l*). The combined ether solution was washed with a solution of ferrous sulfate (22 g) in dilute sulfuric acid (concd. sulfuric acid,

23) G. F. Hennion and F. P. Kupiecki, *J. Org. Chem.*, **18**, 160 (1953).
24) R. A. Raphael, *J. Chem. Soc.*, **1949**, s 44.
25) *Inter alia*, D. Swern, *J. Amer. Chem. Soc.*, **69**, 1692 (1947).
26) For theoretical explanation, see F. L. Weisenborn and D. Taub, *ibid.*, **74**, 1329 (1952); I. M. Roitt and W. A. Waters, *J. Chem. Soc.*, **1949**, 3060.
27) I. Salamon and T. Reichstein, *Helv. Chim. Acta*, **30**, 1616 (1957).
28) E. Schmidt, W. V. Knilling, and A. Ascherl, *Ber.*, **59**, 1279 (1926).
29) A. Jovtscheff, *Chem. Ber.*, **93**, 2045 (1960).
30) C. O. Guss and R. Rosenthal, *J. Amer. Chem. Soc.*, **77**, 2549 (1955).
31) M. Julia and J. M. Surzur, *Bull. Soc. Chim. Fr.*, **1956**, 1614.
32) H. G. Viehe, *Chem. Ber.*, **92**, 1950 (1959).

12 ml in water, 220 ml), and then with 10% aqueous solution of sodium carbonate. The residue obtained by evaporating the solvent was distilled to give IIb, colorless liquid, 114.8 g (65.4%), bp 42—46°C/2 mmHg. Redistillation of this material gave pure IIb, bp 45—46°C/2 mmHg, n_D^{25} 1.51486 [lit,[16] bp 41—42°C/1.5 mmHg, n_D^{25} 1.5146]. Pure IIb crystallized in a refrigerator. IR (neat): 3350—3400 (O–H), 2240 (C≡C), 1050 (C–O) cm^{-1}.

Found: C, 26.48; H, 2.45; Br, 58.77%. Calcd for C_3H_3OBr: C, 26.69; H, 2.24; Br, 59.21%.

3,5-Dinitrobenzoate: Yellow rods, mp 122—123°C (from ether) [lit,[16] mp 115—116°C].

Bromopropiolic acid, mp 85—86°C (from benzene followed by vacuum sublimation) [lit,[15] mp 84—86°C] was obtained from the washing (sodium carbonate solution) on acidification. When the reaction mixture was acidified with hydrochloric acid without reduction of hypobromite ion, 2,3,3-tribromo-2-propenoic acid, mp 119—120°C (from benzene followed by a vacuum sublimation) [lit,[33] mp 118°C] was obtained.

3-Iodo-2-propyn-1-ol (IIc). To a stirred mixture of calcium hydroxide (43 g, 0.58 mol), propargyl alcohol (I, 16.8 g, 0.3 mol) and water (500 ml) was added at 0°C a solution of iodine (76 g, 0.3 mol) and potassium iodide (76 g) in water (70 ml) over a period of 13 hr. Sodium hydrogen sulfite (10 g) and then concentrated hydrochloric acid (60 ml) were added to the reaction mixture. Extraction was carried out with ether. After washing (2% sodium hydrogen sulfite and then 10% sodium carbonate solutions) and drying (sodium sulfate), the solvent was removed. The residue, 30.6 g (56%), crystallized in a refrigerator. The crystals were recrystallized twice from petroleum ether to give pure IIc, colorless rods, mp 39.5—41°C [lit,[34] mp 43—44°C], IR: 3150, 2920, 2860, 2195, 1460, 1380, 1355, 1230, 1040, 1030, 980, 965 cm^{-1}.

Found: C, 19.75; H, 1.66; I, 70.45%. Calcd for C_3H_3OI: C, 19.80; H, 1.66; I, 69.75%.

IIc was found to be unstable and could not be kept without decomposition for a long time even in a refrigerator.

1-Bromo-3-hydroxypropan-2-one (IIIb). Mercuric oxide (16 g) was dissolved in a mixture of sulfuric acid (40 g) and water (200 ml) (Reagent A). Bromopropargyl alcohol (IIb, 81.0 g, 0.6 mol) was added under stirring to the solution at such a rate to maintain the temperature of reaction mixture at 40—50°C. The mixture was then stirred for further 1 hr. The insoluble material was filtered and washed with water. The combined washing and filtrate were nearly neutralized by gradual addition of sodium hydrogen carbonate, and repeatedly extracted with ether (total 2.5 l). The extract was washed with a saturated solution of sodium chloride and dried (sodium sulfate). The solvent was removed under reduced pressure at room temperature. Crystalline IIIb thus obtained was washed with ether (63.3 g, 68.7%). The crude material was dissolved in ethanol at 40°C and a small amount of insoluble material was removed by filtration. Concentration of the filtrate under reduced pressure at room temperature yielded IIIb, mp 75—76°C, contaminated with a trace of mercury compound which could not be removed by treatment with ion exchange resin. IR: 3430 (O–H) cm^{-1}. The absorption due to carbonyl group could not be observed.

Found: C, 23.30; H, 3.26; Br, 51.15%. Calcd for $C_3H_5O_2Br$: C, 23.55; H, 3.29; Br, 52.24%.

IIIb reduced Fehling's solution at room temperature, and was found to be extremely heat sensitive.

Benzoate: Fine needles, mp 133.5—134.5°C (from benzene).

Found: C, 47.06; H, 3.54; Br, 30.79%. Calcd for $C_{10}H_9O_3Br$: C, 46.72; H, 3.53; Br, 31.08%.

1-Iodo-3-hydroxypropan-2-one (IIIc). *a) By Means of Reagent A*: Iodopropargyl alcohol (IIc, 3.6 g, 0.02 mol) was added over a period of 40 min to Reagent A prepared from mercuric oxide (0.5 g), concentrated sulfuric acid (2 g) and water (10 ml). The mixture was stirred for further 2 hr at 30°C. The reaction mixture was extracted repeatedly with ether and the extract was washed with 5% sodium hydrogen carbonate, 5% potassium iodide and a saturated sodium chloride solutions, successively and dried (sodium sulfate). The residue obtained by evaporation of the solvent under reduced pressure was kept in a refrigerator to give crystals, 2.1 g (53%). The crystals were recrystallized from ethyl acetate to yield pure IIIc, colorless hexagonal plates, mp 99.5—101°C. IR (liquid): 3420 (O–H) broad, 1700 (C=O), 1620 (C=C); IR (Nujol mull of the crystals): 3300 (O–H) cm^{-1}.

Found: C, 17.90; H, 2.45; I, 64.13%. Calcd for $C_3H_5O_2I$: C, 18.02; H, 2.52; I, 63.46%.

b) By Means of Reagent B: Mercury-impregnated Dowex-60 (Reagent B) was prepared according to the reported method.[18] Iodopropargyl alcohol (IIc, 36.4 g, 0.2 mol) was added over 30 min-period in a stirred mixture of Reagent B (12 g) and water (60 ml) at 35°C. After the mixture had been stirred for further 1.5 hr at the same temperature, the mixture was saturated with sodium chloride and extracted with ether. The extract was washed with 5% potassium hydroxide and a saturated sodium chloride solutions successively and dried (sodium sulfate). The solvent was removed under reduced pressure. The residue crystallized in a refrigerator (33.5 g, 84%). Pure material, 99.5—101°C was obtained according to the above procedure and gave an identical IR spectrum.

Dihydroxyacetone (IV). *a) From 1-Bromo-3-hydroxypropan-2-one (IIIb)*: A mixture of potassium formate (7.6 g, 0.09 mol), 1-bromo-3-hydroxypropan-2-one (IIIb, 9.2 g, 0.06 mol) and methanol (100 ml) was refluxed for 5 hr. The reaction mixture was concentrated to *ca.* 60 ml and mixed with ether (100 ml). The inorganic material deposited was removed by filtration. The filtrate was concentrated under reduced pressure to afford dihydroxyacetone (IV) as a syrup. The syrup was dissolved in ether–methanol and the insoluble material was removed. The syrup obtained by evaporation of the solvent under diminished pressure reduced Fehling's solution at room temperature, and gave positive color reactions characteristic of dihydroxyacetone with sodium nitroprusside, resorcinol, phloroglucinol and orcinol,[22] thus proving the absence of methylglyoxal or glyceraldehyde. Since the syrupy dihydroxyacetone (IV) could not be crystallized after treatment with ion exchange resin (Dowex 50WX8 and Dowex 3), it was converted into a dibenzoate by the usual method. The crude dibenzoate was recrystallized from ethanol to yield colorless needles, mp 120.5—121°C [lit,[11] mp 121°C].

Found: C, 68.49; H, 4.71%. Calcd for $C_{17}H_{14}O_5$: C, 68.45; H, 4.73%.

The dibenzoate showed no depression of melting point on admixture with a benzoate (mp 120.5°C) prepared from an authentic specimen of IV. The IR spectra of both were found to be superimposable.

b) From 1-Iodo-3-hydroxypropan-2-one (IIIc): By the procedure used in the case of bromo-hydroxypropanone (IIIb), IIIc could be converted into a crude IV as a red syrup con-

33) H. B. Hill, *J. Amer. Chem. Soc.*, **3**, 178 (1881).

34) R. Lespieau, *Ann. Chim.*, **11**, 269 (1897); A. M. Sladkov, L. Y. Ukhin, G. N. Gorshkova, M. A. Chubarova, A. G. Makhsumov, and V. I. Kasatochkin, *Zh. Org. Khim.*, **1**, 415 (1965); [*Chem. Abstr.*, **63**, 1718 (1965)].

taining a minor amount of potassium iodide. The crude material gave positive color reactions characteristic of IV[22] and reduced cold Fehling's solution. The crude IV gave a dibenzoate, mp 119—120°C, which was proved to be identical with that of an authentic dibenzoate of IV.

1-Acetoxy-3-buten-2-one (IX). Acetoxybutenone (IX) was prepared according to the reported method[23] with modification. The reaction mixture obtained from 2-butyne-1,4-diol (VIII, 21.5 g, 0.25 mol) was filtered and the filtrate was concentrated under reduced pressure to remove the major part of acetic acid and acetic anhydride. The concentrate was mixed with ether and the insoluble material was removed by filtration. The residue obtained by evaporation of the solvent was distilled *in vacuo*. Acetoxybutenone (IX) was obtained as a colorless liquid, 18.6 g (58%), bp 63—66°C/3.5 mmHg, n_D^{20} 1.43136 [lit,[23] bp 70°C/4 mmHg, n_D^{25} 1.4355].

IX was subjected immediately to the subsequent reaction.

1,4-Diacetoxy-3-bromobutan-2-one (X). Freshly prepared *N*-bromosuccinimide (33.5 g, 0.188 mol) was added to a solution of the vinyl ketone (IX, 18.6 g, 0.145 mol) in dry acetic acid (120 m*l*). The mixture was stirred at room temperature until the crystals of *N*-bromosuccinimide disappeared (3—4 days). The resulting solution was mixed with ether (700 m*l*), and a saturated solution of sodium hydrogen carbonate and then solid sodium hydrogen carbonate were added in small portions. The alkaline aqueous layer was extracted with ether (150 m*l*). The combined ether layer was dried and evaporated under reduced pressure, thus yielding a pale yellow liquid. The colorless crystals, 17.7 g (45.7%) obtained by trituration of the liquid with a small amount of ether were recrystallized from methanol or methanol–water to yield pure X, mp 49.0—49.5°C [lit,[2] bp 100—102°C/10^{-4} mmHg].

Found: C, 36.07; H, 4.24; Br, 29.82%. Calcd for $C_8H_{11}O_5Br$: C, 35.98; H, 4.15; Br, 29.92%.

It was found that X decomposes rapidly on a metal surface and should be handled with a glass spatula. An interesting difference was observed between the IR spectrum of crystalline X by Nujol mull method and that of liquid X by liquid film method. Liquid X exhibits a broad absorption in carbonyl region (1765—1740 cm^{-1}), but the absorption splits into two peaks (1767 and 1725 cm^{-1}) in the spectrum of crystalline X. The sharp absorption observed below 1500 cm^{-1} in the spectrum of crystalline X could not be observed in that of liquid X.

1-Acetoxy-3,4-dibromobutan-2-one (XI). Bromine (17.3 g, 0.108 mol) was added dropwise into an ice-cooled solution of IX (13.9 g, 0.108 mol) in carbon tetrachloride (40 m*l*). The mixture was left to stand overnight and the solvent was removed under diminished pressure. Distillation of the residue *in vacuo* yielded XI as a viscous yellow liquid, 24.0 g (76.7%), bp 103—105°C/1 mmHg, n_D^{25} 1.51567, IR (neat): 1765—1735 (C=O of ketone and ester), 1225 (C–O of ester) cm^{-1}.

Found: C, 25.36; H, 2.77; Br, 54.92%. Calcd for $C_6H_8O_3Br_2$: C, 25.06; H, 2.80; Br, 55.50%.

Tri-O-acetyl-DL-erythrulose (XII). *a) From 1,4-Diacetoxy-3-bromobutan-2-one (X):* A mixture of diacetoxybutanone (X, 15.4 g, 0.058 mol), dry silver acetate (16.5 g, 0.099 mol) and anhydrous acetic acid (140 m*l*) was refluxed for 6 hr. The reaction mixture was cooled and the solid deposited was filtered and washed with acetic acid. The combined filtrate and washing were mixed with dry sliver acetate (16.5 g, 0.099 mol). After the mixture had been refluxed for 3 hr, the solvent was removed under reduced pressure and the residue was extracted with ether. The residue obtained by evaporation of the solvent was distilled *in vacuo* to yield a light yellow viscous liquid, 3.4 g (23.9%), bp 73—124°C/6×10^{-4} mmHg. Redistillation of this material afforded XII as a viscous liquid, bp 90°C/3×10^{-4} mmHg, n_D^{18} 1.44946 [lit,[2] bp 108—110°C/10^{-4} mmHg, n_D^{18} 1.4545], IR (neat): 2940, 1770—1740 (C=O of ketone and ester), 1143, 1085, 1055, 1020, 975, 928, 875, 838 cm^{-1}.

Found: C, 48.49; H, 5.77%. Calcd for $C_{10}H_{14}O_7$: C, 48.78; H, 5.73%.

b) From 1-Acetoxy-3,4-dibromobutan-2-one (XI): A mixture of XI (14.4 g, 0.05 mol), dry silver acetate (28.4 g, 0.17 mol) and dry acetic acid (200 m*l*) was treated according to the procedure used in the case of X. A minor amount of viscous yellow liquid, bp 80—125°C/10^{-4} mmHg was obtained. Although the liquid gave a weak positive Beilstein test, the IR spectrum was found to be closely related to that of the product obtained from X [IR: 2920, 1760—1700 (C=O of ketone and ester), 1135, 1075, 1050, 1020, 935, 910, 875, 835 cm^{-1}]. Presumably the liquid contains XII as a major component. Further purification was not performed.

DL-Erythrulose (XIII). A mixture of barium hydroxide octahydrate (8 g), water (80 m*l*) and the triacetate (XII, 2.5 g) was kept at 0°C for 90 min with occasional shaking, after which the mixture was saturated with carbon dioxide and the barium carbonate formed was removed by filtration. 4N Sulfuric acid was added to the filtrate in a slight excess. After the barium sulfate precipitated had been removed by means of a centrifuge, the solution was concentrated *in vacuo* at a temperature below 23°C to one fourth in volume. The concentrated solution was treated with Dowex 30 and again concentrated *in vacuo* at a temperature below 20°C. The syrupy residue was placed in an evacuated desiccator containing phosphorus pentoxide, yielding DL-erythrulose (XIII) as viscous syrup, 0.8 g. The syrup reduced cold Fehling's solution instantaneously.

A mixture of XIII (0.2 g) and a solution of phenylhydrazine in 50% aqueous acetic acid was kept at room temperature for 10 days to give deep brown precipitate. This material was crystallized from benzene to yield DL-erythrulose osazone as yellow needles, mp 168—169°C [lit, mp 166—168°C;[2] mp 167°C[35]].

Financial support from Mr. Tokusuke Egawa, president of Kofuku-sogo Bank, is gratefully acknowledged.

35) H. J .H. Fenton and H. Jackson, *J. Chem. Soc.*, **75**, 1 (1899).