with increase in time. The 15- and 20-minute plates on comparison with the aniline and zinc chloride plates of the same times and dilution show clearly a stronger antiseptic action. Predicting from the curve obtained from the aniline solution, in order to compare on a time basis with the salt solution, the results would seem to indicate that the salt has about 1.3 times the disinfecting power of aniline and about 5 times that of zinc chloride.

When the salt solution was allowed to stand for a week at room temperature, it became somewhat cloudy and lost the power to kill the bacteria in even the 30- or 35-minute periods.

Summary

1. The double salt of aniline with zinc chloride has been prepared and physical and chemical data have been added to those already existing.

2. Its bactericidal action has been found to be greater than that of either aniline or zinc chloride.

Missoula, Montana

[Contribution from the Department of Chemistry, Yale University]

STUDIES ON REACTIONS RELATING TO CARBOHYDRATES AND POLYSACCHARIDES.[1] V. THE USE OF ACETYLENE FOR THE SYNTHESIS OF CYCLIC ACETALS

By Harold S. Hill[2] and Harold Hibbert

Received October 16, 1923

In a previous communication[3] the authors have pointed out the structural relationship existing between cyclic acetals and polysaccharides, that is, that the carbonyl-hydroxyl condensation reaction involved in cyclic acetal formation is without doubt duplicated, either inter- or intramolecularly, or both, when simple sugars condense to form di-, tri-, or polysaccharides. In view of this relationship the belief was expressed that a thorough investigation of the simpler cyclic derivatives would afford a promising means of attack for the problem of the nature of the complex molecules of starch, inulin, cellulose, etc. It is in the course of this work that a new and improved method for the synthesis of cyclic acetals has been developed.

Earlier investigators have prepared cyclic acetals from acetaldehyde and ethylene glycol,[4] trimethylene glycol,[4b] 1,2-propylene glycol,[5] glycerol,[6]

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[1] The title has been altered so as to be more in accord with present, and proposed future investigations (Hibbert).

[2] Antoine Chiris Co. Research Fellow.

[3] Hibbert and Hill, This Journal, **45**, 734 (1923).

[4] (a) Würtz, *Compt. rend.*, **53**, 378 (1861); *Ann.*, **120**, 328 (1861); (b) Lochert, *Ann. chim. phys.*, [6] **16**, 26 (1889). (c) Clark, *J. Chem. Soc.*, **101**, 1803 (1912).

[5] Gramont, *Compt. rend.*, **97**, 173 (1883); *Bull. soc. chim.*, **41**, 361 (1884).

[6] Harnitzky and Menschutkin, *Ann.*, **136**, 126 (1865).

and mannitol,[7] by heating mixtures of acetaldehyde (or paracetaldehyde) and polyhydroxy derivatives, either alone or with a catalyst which was usually hydrochloric, sulfuric, or phosphoric acid, or iodine.[8]

In a number of interesting researches, Nieuwland and co-workers[9,10] have recently shown that various condensation reactions between acetaldehyde and other products (aniline, toluidine, methyl alcohol, ethyl alcohol) take place as well, or better if, instead of using the free aldehyde, this is generated *in situ* from acetylene, catalytically, by the agency of a small amount of a mercuric salt in the presence of sulfuric acid. Thus, by passing the gas into a mixture of an alcohol and the catalyst it was possible to synthesize the simple acetals.

In view of this, it seemed highly probable that the same process might be applied to the preparation of *cyclic* acetals, and it has, in fact, been found that not only are high yields of uniformly pure products more easily and cheaply obtainable at room or moderate temperature, and in a much shorter time by this method, but it is now possible to synthesize readily a number of cyclic acetals, the preparation of which is rendered difficult, and in some cases even precluded, by the unfavorable experimental conditions associated with the earlier methods of formation.[11]

The procedure used consists essentially in passing acetylene with vigorous stirring into a mixture of a polyhydroxy compound and a small amount of mercuric sulfate and concd. sulfuric acid (93%) as a catalyst. It has been applied with good results to the synthesis of cyclic ethylidene derivatives of ethylene glycol, trimethylene glycol, 1,2-propylene glycol, 1,4-tetramethylene glycol, glycerol-α-bromohydrin, glycerol, 2,3-dimethyl-2,3-butanediol (pinacol), 2-methyl-2,4-pentanediol, and α-methyl glucoside. Attempts to obtain a similar product from glucose yielded a sirup which could not be crystallized or distilled, but which gave every indication of being an acetal.

Of the above derivatives, ethylidene glycerol was prepared by Harnitzky and Menschutkin[6] in 1865 by heating glycerol and acetaldehyde together

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[7] Meunier, *Compt. rend.*, **107**, 910 (1888).

[8] Hibbert, THIS JOURNAL, **37**, 1762 (1915).

[9] Vogt and Nieuwland, *ibid.*, **43**, 2071 (1921).

[10] Reichert, Bailey and Nieuwland, *ibid.*, **45**, 1552 (1923).

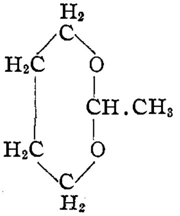
[11] The possibility of synthesizing cyclic acetals by the use of acetylene was suggested to Dr. J. A. Nieuwland by the writer some eighteen months ago. He was kind enough to intimate that in view of our greater interest in this particular phase of the subject he would be glad to see the work carried out by us. We desire to express to him and his co-worker, Mr. Hoffmann, our appreciation of the kindness accorded, especially since the latter, due to a misunderstanding, later prepared, independently and almost simultaneously with ourselves, one or two identical acetals, namely, those from trimethylene glycol and pinacone.

In further agreement, and with Dr. Nieuwland's kind consent, it is our intention to extend his acetylene method to the synthesis of cyclic acetals from polyglycols.

at 180° in a sealed tube. Their product boiled at 184–188° and was only slightly soluble in water, whereas the ethylidene glycerol obtained by the new acetylene method boils at 189–195° and is miscible with water in all proportions. Nef[12] also obtained an ethylidene glycerol, soluble in water. It is to be noted in this connection that somewhat the same discrepancies exist between the benzylidene glycerol described by Harnitzky and Menschutkin and that prepared later by Fischer,[13] and also by Irvine, Macdonald and Soutar.[14] It is probable that in both cases the earlier investigators were dealing with impure products. The question as to whether ethylidene glycerol exists as a 5- or a 6-membered cyclic structure will be taken up in a later paper.

The cyclic acetals of 2,3-dimethyl-2,3-butanediol (pinacol) and of its isomer 2-methyl-2,4-pentanediol, representing 5- and 6-membered rings, have not been obtained previously. Their synthesis by the acetylene method is noteworthy in that the ethylidene cyclization takes place in preference to dehydration and rearrangement to pinacolone derivatives, in spite of the presence of concd. sulfuric acid which presumably should tend to favor the two latter reactions. Both of these acetals are colorless, volatile liquids having a strong odor of camphor and menthol.

The cyclic acetal of 1,4-tetramethylene glycol, I, is also of interest in that it represents a new type of comparatively rare 7-membered ring.[15]



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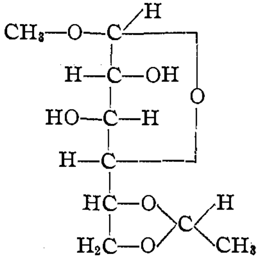

Ethylidene α-Methyl Glucoside

II

The existence and ease of formation of this acetal would seem to indicate that speculations regarding the structure of polysaccharides are by no means limited to the probabilities of only five- and six-membered heterocyclic groups.

[12] Nef, *Ann.*, **335**, 216 (1904).

[13] Fischer, *Ber.*, **27**, 1536 (1894).

[14] Irvine, Macdonald and Soutar, *J. Chem. Soc.*, **107**, 344 (1915).

[15] As far as can be ascertained this is the only known example of a simple, saturated, heterocyclic structure containing 5 carbon and 2 oxygen ring atoms. In fact, the only 7-membered heterocyclic carbon-oxygen derivatives of any kind appear to be the ε lactone, 2-6-dimethyl-octane-carboxylic-acid-3,8-olid, and its isomer, 5-isopropyl-heptane-carboxylic-acid-2,7-olid, both isolated by Baeyer and his co-workers [*Ber.*, **29**, 29 (1896); **32**, 3619 (1899); **32**, 3629 (1899); **33**, 860 (1900)].

So far as the authors are aware, the crystalline ethylidene product (m. p., 77°) from α-methyl glucoside is the first acetaldehyde derivative of a sugar to be described, although various benzaldehyde[16] and acetone[17] derivatives of carbohydrates are known. By analogy with other derivatives this ethylidene product presumably has the structure II. The benzylidene derivative of α-methyl mannoside contains two aldehyde residues, and it is therefore to be expected that *di*ethylidene α-methyl mannoside will result from the treatment of this glucoside with acetylene.[18]

In the adaptation of the acetylene method of cyclic acetal formation to solid polyhydroxy compounds, such as pinacol, α-methyl glucoside, and glucose, it was found advantageous to use ethylene glycol as a solvent. The treatment of the solution with acetylene yielded a mixture of the acetals of both the solvent and solute from which the two components were readily separated by distillation.

Mechanism of the Reaction

There is no conclusive evidence with regard to the mechanism of the reaction involved in the formation of cyclic acetals from acetylene, although there are two likely possibilities. The first is that acetylene in the presence of mercury salts reacts with traces of water to form acetaldehyde, which in turn condenses with the polyhydroxy compound with regeneration of water. An objection to this scheme lies in the fact that it involves a simultaneous hydration and dehydration which, while not unknown, is hardly plausible, and further that the amount of water present would appear to be too small to account for the rapidity of the reactions, in view of the strong attraction of the acid for it. In every case anhydrous glycols were used, only a small amount of concd. sulfuric acid was added, and the acetylene itself was bubbled through concd. sulfuric acid before it entered the reaction vessel.

A second and more probable alternative is that a direct addition reaction occurs between acetylene and the glycol used. Leaving out of consideration the catalytic role of the mercury salt, for which Nieuwland has postulated an intermediate molecular complex,[9] it would appear that the majority of these acetylene reactions consist essentially in the addition, through the oxygen atom, of an hydroxyl derivative to an unsaturated carbon atom of acetylene with subsequent rearrangement. In the case where dil. sulfuric acid is employed, acetaldehyde is formed, the hydroxy compound in this case being water.

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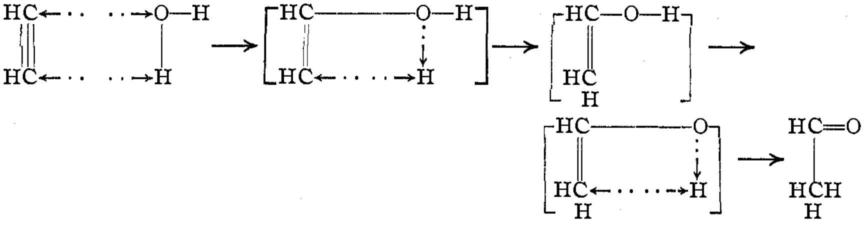
[16] Irvine and Scott, *J. Chem. Soc.*, **103**, 575 (1913).

[17] Macdonald, *ibid.*, **103**, 1896 (1913).

[18] It is our intention to extend the investigation to other carbohydrates and polysaccharides.

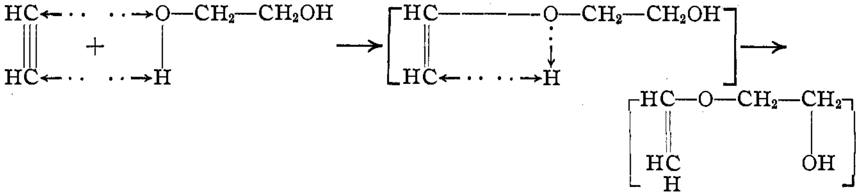


Acetaldehyde

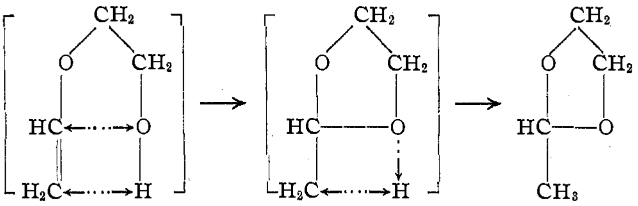
··→ shows the relative direction of free partial valence force.

With a glycol replacing water in the series of changes given above, similar reactions occur, first, *intermolecularly* between acetylene and one hydroxyl group, and second, *intramolecularly* with the other hydroxyl, the whole transformation being practically instantaneous.

I. Intermolecular Addition and Rearrangement



II. Intermolecular Addition and Rearrangement



Ethylidene ethylene glycol

As to the actual changes which render the acetylene capable of effecting such "addition" reactions, it is possible that these may take place in three stages: (1) the formation of an acetylene-mercury derivative; (2) decomposition of this with removal of the mercury and addition of the elements of sulfuric acid; (3) removal of sulfuric acid and addition of water or glycol.[19]

Possibly a similar addition and rearrangement may take place in a variety of reactions involving hydroxyl derivatives, for example: in ester and anhydride formation, etc.

Experimental Part

Description of Apparatus

Acetylene was supplied from a commercial tank, the gas being first passed into a gasometer in order to afford a means of pressure control and volume measurement.

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[19] The fact that dry acetylene can condense directly with anhydrous amines and alcohols, in the presence of concd. sulfuric acid, has been shown by Nieuwland and coworkers. (Refs. 9, 10.)

The arrangement used consisted in mounting two 20-liter glass bottles (having openings at both top and bottom), one above the other. The outlets near the bottom of both were connected by means of heavy rubber tubing, and the securely attached stopper of the lower vessel contained the inlet from the acetylene tank, as well as the outlet leading to the reaction flask, both of these connections being equipped with stopcocks. After the lower bottle was filled with water and this forced into the upper one by means of acetylene from the tank, the valve of the latter was closed, as well as the stopcock on the inlet in order to prevent any leakage taking place through the connection on the tank. An opening to the atmosphere was left in the top of the upper bottle, and in filling the gasometer with acetylene care was taken to admit the gas from the high-pressure tank cautiously and only when the proper stopcocks were open. The amount of gas used was determined from the readings on the lower bottle, this having been calibrated for temperature and pressure to give directly the volume under standard conditions.

From the gasometer the acetylene was passed through a single wash bottle containing concd. sulfuric acid, and from this into the reaction vessel. The latter, in the majority of the experiments described later, was a large-neck, 2-liter, round-bottom flask, having a well-fitted rubber stopper through which passed an inlet tube extending nearly to the bottom of the flask, an outlet tube near the top equipped with a stopcock and a mechanical stirrer. The stirring device operated through a mercury seal, deep enough to hold the maximum gas pressure employed (about 5 cm. of mercury) and was designed to produce a splashing effect so as to insure an efficient mixing of gas and liquid.

Description of Method

The preparation of ethylidene ethylene glycol may be taken as illustrative of the acetylene method of synthesizing cyclic acetals.

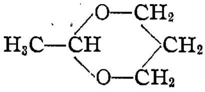
Four g. of mercuric sulfate was triturated in a mortar with 4 cc. of ordinary concd. sulfuric acid (93%), the resulting paste transferred to 62 g. of pure ethylene glycol while the mixture was cooled and shaken, and the whole then poured into the reaction flask. The stopcock on the outlet tube of the latter was opened and the air in the apparatus displaced by acetylene. The outlet was then closed, the contents vigorously stirred, and acetylene led in under the full pressure of the gasometer. Absorption started at once and the rate increased rapidly as the reaction mixture became less viscous due both to the spontaneous rise in temperature and the progressive transformation of glycol into its acetal.

In the preparation of the majority of cyclic acetals the temperature could be allowed to rise with safety to 60–70°, but in the case of such compounds as pinacol, α-methyl glucoside, etc., it was advisable to operate at a lower temperature, not higher than 10–25°, and to use a cooling bath. The time required for the absorption of the calculated amount of acetylene was in general about 30 minutes, this varying somewhat with the nature of the glycol, the temperature used, and the viscosity of the material.

When the required amount of acetylene had been run in, the stirrer was stopped, the flow of gas cut off, the reaction mixture transferred at once to another flask, and the residue washed out with ether. More ether was added and the combined ether solutions were washed once with a 10%

solution of sodium carbonate to neutralize any sulfuric acid present. Since a number of cyclic acetals are soluble in water it is advisable to use as little of the carbonate solution as possible and to extract the wash liquor once or twice with ether. The combined ether solution was dried over solid potassium carbonate, and fractionated through a 30cm. bead column to remove the solvent. In this way 66 g. of ethylidene ethylene glycol, b. p. 82–85°, was obtained. Except for small traces of other derivatives, this was the sole product formed in the reaction. The yield obtained, calculated on the weight of glycol taken, was equal to 75%.

Experiments carried out, using concd. sulfuric acid (93%) to which several per cent. of water had been added, resulted in decreased yields of the ethylidene derivative and the formation of objectionable by-products. Larger amounts of the pure concentrated acid did not favor the yield, and four times the amount employed as above produced considerable charring during the reaction.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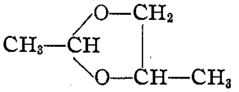
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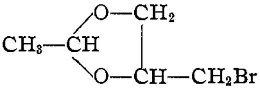
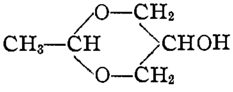

V

Preparation of Ethylidene Trimethylene Glycol. III.—One hundred and fourteen g. of trimethylene glycol gave 115 g. of the cyclic acetal; b. p., 108–111°; yield, 75%. The absorption of gas took place even more rapidly than in the case of ethylene glycol. There were no by-products.

Preparation of Ethylidene 1,2-Propylene Glycol. IV.—One hundred and fourteen g. of glycol yielded 106 g. of the acetal; b. p., 92°; yield, 70%.

Preparation of Ethylidene Glycerol Bromohydrin. V.—One hundred and fifty-five g. of pure glycerol-α-bromohydrin, b. p. 132° (15 mm.), gave 85 g. of the corresponding cyclic acetal; b. p., 170–182°; yield, 40%. In this experiment the absorption of acetylene became very slow after about one-half of the calculated amount had been added, and finally ceased altogether. In the ether extract there was a considerable quantity of a higher boiling material which could not be distilled. The bromine atom in the molecule appears to hinder the reaction with acetylene, since the same difficulty was encountered with other bromine derivatives. Ethylidene bromohydrin, however, may be easily prepared with a 70% yield by heating α-bromohydrin with paracetaldehyde and a trace of iodine as catalyst.[3]


VI

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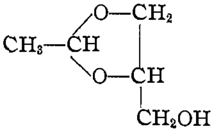
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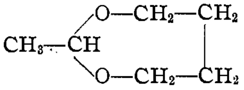

VIII

Preparation of Ethylidene Glycerol. VI or VII.—One hundred thirty-eight g. of glycerol (anhydrous) gave 110 g. of ethylidene derivative; b. p., 189–196°; yield, 63%. In this preparation efficient stirring was rendered difficult on account of the high viscosity of the glycerol, and this resulted in a decrease in the rate of absorption of the acetylene. It was found, however, that by surrounding the reaction flask with a water-bath maintained at about 70°, the speed of the reaction was greatly increased without the production of any injurious effect, and in this way the required 34 liters of gas was absorbed in $1^1/_2$ hours.

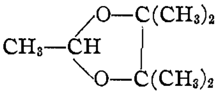
Ethylidene glycerol as prepared by this method, is a colorless, limpid sirup, completely miscible with water, ether, and alcohol. It has only a slight odor when freshly prepared but on standing, especially in moist air, acquires the odor of acetaldehyde. It is hydrolyzed into glycerol and acetaldehyde by dilute acids.

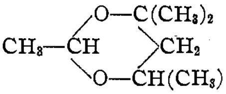
Preparation of Ethylidene 1,4-Tetramethylene Glycol. VIII.—Owing to the small quantity of tetramethylene glycol available because of the difficulties involved in its preparation, this experiment was performed on a small scale. Eighteen g. of the glycol was treated with 4.6 liters of acetylene, using 0.6 cc. of concd. sulfuric acid and 0.8 g. of mercuric sulfate as a catalyst. The addition of the acetylene required several hours, the slow rate of absorption being due to some extent to the inability to stir such a small amount of material efficiently. The ether extract after two fractionations gave 4.6 g. of a colorless liquid, b. p. 125–127°, equivalent to a 20% yield. In the flask there remained an equal amount of a thick sirup which could not be distilled but gave every indication of being an acetal, as it yielded acetaldehyde on treatment with acids, etc.

The product boiling at 124–127°, namely, ethylidene tetramethylene glycol, has the same characteristic odor as the cyclic acetals from ethylene and trimethylene glycols, as well as the same general physical and chemical properties. Its boiling point is also in harmony with those of the corresponding acetals from ethylene and trimethylene glycols.

Analyses. Calc. for $C_6H_{12}O_2$: C, 62.94; H, 10.3. Found: C, 60.9; H, 9.97.

The low value for carbon was doubtless due to a slight amount of impurity, which it was not possible to remove from the acetal due to the small amount of material available for fractionation. The low yield was also due to some extent to the small weight of glycol used, since a parallel experiment on the same scale with ethylene glycol gave a relatively small yield of the corresponding acetal.


IX


X

Preparation of Ethylidene Pinacol. IX.—Twenty g. of pinacol prepared from pinacol hydrate by dehydrating it over concd. sulfuric acid was dissolved in 30 g. of ethylene glycol, and the solution treated as usual with 16 liters of acetylene, using as catalyst 3 g. of mercuric sulfate and 3 cc. of concd. sulfuric acid. The temperature was kept below 20°, about $1^1/_2$ hours being required for the absorption of the gas. Careful fractionation of the reaction product gave (a) ethylidene ethylene glycol, 35 g., yield 81%; and (b) ethylidene pinacol, 15 g., b. p. 133–134°; yield, 61%.

Analyses. (b) Calc. for $C_8H_{16}O_2$: C, 66.66; H, 10.97. Found: C, 66.22; H, 10.97.

The pinacol derivative, unlike the acetals from ethylene, trimethylene and tetramethylene glycols, is only slightly soluble in water, but resembles them in its other properties. It possesses a powerful, camphor-like odor.

Synthesis of Ethylidene 2-Methyl-2,4-Pentanediol. X.—Twenty-nine g. of the glycol[20] and the corresponding amount of catalyst, on treatment with 5.6 liters of acetylene gave 27 g. of ethylidene derivative, b. p. 139–140°; yield, 71%. Its properties were almost identical with those of the isomeric ethylidene pinacol.

Analyses. Calc. for $C_8H_{16}O_2$: C, 66.66; H, 10.97. Found: C, 66.62; H, 11.08.

Synthesis of Mono-ethylidene-α-methyl Glucoside.—Twenty g. of α-methyl glucoside was dissolved in 80 g. of ethylene glycol, 4 g. of mercuric sulfate and 3 cc. of

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[20] This glycol was supplied through the kindness of Dr. R. R. Read of the University of Vermont, to whom we wish to express our best thanks.

concd. sulfuric acid were added, and the mixture was treated with 34 liters of acetylene. The temperature was kept below 10° to prevent decomposition of the glucoside by the acid present. As a result of the low temperature the rate of absorption was somewhat slower than in the synthesis of the ethylidene glycols. After the completion of the reaction, ether containing a little absolute alcohol was added, the solution washed with a small amount of a concentrated solution of potassium carbonate, filtered, and then dried over the solid carbonate. The solvents (including ether, alcohol, and the ethylidene glycol formed in the reaction) were removed by distillation, first under atmospheric, and during the later stage, under diminished pressure, in order to maintain a temperature below 60° throughout the operation. The resulting sirup was freed from the last traces of solvents by being kept several days in an evacuated desiccator. In the first preparation the crystallization started slowly and was brought about by exposing the product to the air on a watch glass and rubbing with a glass rod. When once a sample of the solid product had been obtained, the sirups were readily crystallized by "seeding." The crude product was recrystallized from ligroin containing a small amount of dry ether, and obtained as silk-like, white crystals; m. p., 77°.

Analyses. Calc. for $C_9H_{16}O_6$: C, 49.0; H, 7.27. Found: C, 48.4; H, 7.22.

Synthesis of Ethylidene Glucose.—The same procedure as used in the preparation of ethylidene-α-methyl glucoside was applied to glucose.[21] A nearly colorless, very sticky, ether-soluble sirup was obtained which, however, could not be crystallized. It was readily hydrolyzed by means of dilute acids to glucose and acetaldehyde. The sirup was not analyzed.

Summary

1. A new method has been developed for the preparation of cyclic acetals from polyhydroxy compounds. This consists in passing acetylene gas into the hydroxy derivative (containing a small amount of mercuric sulfate and concd. sulfuric acid, 93%) at room, or at a moderate temperature.

2. In the case of solid hydroxy derivatives (pinacol, glucosides, etc.), these are first dissolved in glycol and the resulting ethylidene derivatives then separated by a simple distillation process.

3. The mechanism of the reaction possibly consists, at least in part, of an *inter*molecular addition of the glycol to the acetylene, followed by a rearrangement, this being succeeded in turn by an *intra*molecular addition, followed by a second, subsequent rearrangement.

New Haven, Connecticut

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[21] It was observed that pure, dry, powdered glucose when merely mixed with glycol apparently undergoes some physical or chemical change, in that the product sets to a stiff paste, or, with a larger proportion of the glucose, to a solid mass. The phenomenon is being investigated.