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# NOTE TO USERS

# A STUDY OF 2, 3 BUTYLENE GLYCOL AND ITS DERIVATIVES

## BY

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A Thesis Submitted to the Graduate Faculty
for the Degree of

DOCTOR OF PHILOSOPHY

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In charge of Major work

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## FOREWORD

Recognition of their usefulness and extreme versatility has brought about an ever increasing production of organic compounds. New compounds are constantly being developed to meet specific needs and new uses are being discovered for products already known. The sources of raw materials for the *synthesis* of these compounds may be divided into two classes: the organic deposits in the earth, the amount of which, though large, is limited, and the practically inexhaustible supply of agricultural products. The gradual depletion of the first source will force a turn to the greater utilization of the latter. Because of this, and because a greater production and more varied use of agricultural produce will satisfy the long-felt economic need for more stable agricultural prices, it seems expedient to try to enlarge our knowledge of the fundamental compounds obtainable from plants, so that we can produce and apply them most efficiently. 2,3 Butylene glycol is such a compound and the object of this study is to add somewhat to the information relative to its possibilities.

When this project was started, 2,3 butylene glycol was known only as one of several unimportant substances which were produced in small amounts in a great many fermentations. Only a few hundred cubic centimeters had ever been isolated, and, of course, it had no commercial value. It was intended at that time to try to discover the most favorable conditions, with respect to the substrate, temperature, hydrogen-ion concentration, and organism, for the production of the glycol; to work out a suitable means for rapidly and accurately determining its

consideration in a formulation suitable; to develop an efficient and transposed to procedure for isolating it from the heavy; and to look into the possibilities for its practical application.

Since that time, however, a large amount of research has been done on this chemical by many investigators, and much of the work outlined above has been the subject of patents. The glycol is now being produced on a semi-industrial scale and is available at a moderate price. This has necessarily caused this project to depart materially from its original course. Having prepared, at the cost of no little time and effort, considerable quantities of the glycol, it was felt that some attention might well be given the properties of its derivatives, or probably its toluene diether, which has rendered very little attention considering its relative simplicity and its potentialities as a starting point in chemical synthesis.

## INTRODUCTION

The glycols are aliphatic, dihydric alcohols in which two hydrogen atoms attached to two different carbon atoms have been replaced by hydroxyl groups. The simplest member of the series, ethylene glycol, was synthesized by Wurtz (92) in 1854, and thus the gap between mono-hydric alcohols and glycerol was filled in. Wurtz chose the name glycol to indicate the intermediary relation of the new substance to alcohol on the one hand and glycerol on the other. Such words as glycerol, glucose, glycogen, and glycine, are derived from the greek stem, γλυκυς, meaning sweet. Probably the first butylene glycol obtained was the 1,3 glycol synthesized by Kekulé (48) stereo by Weiss (44) in 1876.

In the case of monohydric alcohols the three classes, primary, secondary, and tertiary are distinguished, but by virtue of the repetition of the hydroxyl group in the molecule, the classes of glycols are twice as numerous, there being diprimary, primary-secondary, disecondary, etc. The name according to the Geneva system are obtained by adding to the final syllable "diol," together with the appropriate numbers, to the parent hydrocarbons.

The lower glycols are colorless, odorless, viscous liquids, having a somewhat sweetish taste. They are rather hygroscopic and quite soluble in water and alcohol, the lighter members of the series being miscible in all proportions in these two solvents. Ethylene glycol is only sparingly soluble in ether, but with increasing number of carbon atoms the solubility increases. The ethlyene glycols are somewhat higher than the corresponding saturated hydrocarbons.

Table 1.

TABLE I

BOILING-POINTS AND DENSITIES OF THE GLYCOLS (23)

| | Ethyl | | Propyl | | Butyl | |
|---|---|---|---|---|---|---|
| | alcohol | glycol | alcohol (n) | glycol (1,2) | alcohol (n.) | glycol (2,3) |
| Boiling-point | $78.4^\circ$ | $197.5^\circ$ | $97.4^\circ$ | $188^\circ$ | $117^\circ$ | $183.4^\circ$ |
| Density | .789 | 1.115 | .804 | 1.051 | .810 | 1.046 |

Apparently the boiling-point of the glycols decreases with increase in atomic weight. For a fair comparison, however, the glycols having the hydroxyl groups both on end carbon atoms should be considered, because it is only in this position that the hydroxyl groups have their maximum effect.

The chemistry of the glycols is merely the chemistry of two molecules of a monohydric alcohol superimposed; that is, the oxidation products, aldehydes, ketones, and acids are the same, but combinations can be formed giving the molecule a double function. Mono- and di-halides, esters, ethers, and salts are possible, as well as the many other derivatives of the hydroxyl group.

Though over one hundred glycols are known, ethylene glycol, and, perhaps, tetramethyl ethylene glycol, pinacol, are the only ones to which, until a few years ago, more than passing attention has been given. Ethylene glycol is important because of its value in organic syntheses and its commercial value both as an antifreeze for automobile radiators and the solvent action of its ethers and esters. Pinacol is thought of in connection with the pinacoline rearrangement. Though pinacol as a substance refers to tetramethyl ethylene glycol, it is also the name

applied to the whole class of ditertiary glycols, all of which undergo
the peculiar rearrangement when boiled with dilute sulphuric acid,
whereby one of the radicals attached to the two fundamental carbon
atoms apparently changes places with the opposite hydroxyl group, thus
causing the simultaneous loss of water due to the inability of the
carbon atom to hold the two hydroxyls, with the resultant formation of
a ketone, known because of its derivation as a pinacone.

## HISTORICAL

### Preparation

2,3 Butylene glycol, also designated $\beta,\gamma$ dihydroxy butane, symmetrical dimethyl ethylene glycol, butane diol-2,3, and pseudo-butylene glycol was isolated in 1906 by Harden and Walpole (18) from the fermentation of glucose by *Bacillus lactis aerogenes*. Pere (55), in 1896, had obtained a "volatile red substance" in the aerobic fermentation of mannitol by *Bacillus subtilus* and *Bacillus mesentericus vulgatus*, and of glucose and glycerol by *Tyrothrix tenuis*, but he did not identify it, so it remained for Walpole to show that it was acetyl methyl carbinol, very closely related to 2,3 butylene glycol. The glycol had been produced synthetically by a variety of methods (13) (20) (30) (47) (64) (75) prior to Harden and Walpole's discovery, but they were all difficult, roundabout, and poor in yield. Since that time several investigators have produced 2,3 butylene glycol and also some of the other glycols by the fermentation of a large number of substrates using various organisms. A fairly complete list of 2,3 butylene glycollic fermentations is given in Table II.

The propylene and butylene, but principally the latter, are the only glycols occurring widespread in fermentations. Of the butylene glycols, all excepting the 1,2 are found quite generally in alcoholic fermentations, though because of the greater ease in synthesizing them the 1,4 glycol and 1,3 glycol are better known than the 2,3 glycol. Besides its presence in fermented liquors, 2,3 butylene glycol has been

## TABLE II

### 2,3 BUTYLENE GLYCOLIC FERMENTATIONS

| Organisms | Substrates | Products | Investigators | Reference |
|---|---|---|---|---|
| Bacillus lactis aerogenes | glucose fructose mannose galactose arabinose rhamnose mannitol dulcitol glycerol ethylene glycol erythritol | acetyl methyl carbinol and 2,3-butylene glycol | Walpole, Harden and Morris | (18)(20)(71) |
| | 2,3-butylene glycol | ethylene glycol | | |
| Bacillus cinesus | glucose fructose mannose galactose arabinose rhamnose mannitol dulcitol | 2,3-butylene glycol | Harden and Morris | (20)(21) |
| | | acetyl methyl carbinol 2,3-butylene glycol | Harden, Morris and Thompson | (20) |

destected in the blood of higher animals (43) and in many meats and grains (42).

## Physical properties

2,3 Butylene glycol is a colorless, odorless (46), viscous liquid. The meso form boils at 183-4° and the racemic at 177-80° (6). The density is reported as 1.048 at 0° C (75). It is miscible with water and ether in all proportions.

As there are two asymmetric carbon atoms, there are four possible optical isomers; namely, dextro, laevo, meso, and racemic, all of which are reported in the literature. Kling (30) found that by fermenting the inactive racemic mixture with Sorbose bacterium or Mycoderma aceti the laevo form is converted to acetyl methyl carbinol, but the dextro form is untouched. Walpole (72), who isolated biochemically prepared glycol in considerable quantities for the first time, found it to be made up of two optically inactive glycols in the proportion of nine to one.

Ciamician and Silber (8) describe their preparation as containing equal parts of two optical isomers whose dibenzoates are a liquid and a solid respectively, while Neuberg and Nord (55) found that a laevor-otatory 2,3 butylene glycol results from the action of yeast on diacetyl.

Boeseken and Cohen (5) confirmed in the main and added to Walpole's findings. They fractionated several hundred grams of glycol prepared by fermentation according to Kluyver's (34) directions and having a rotatory power $\alpha_{20°} = + 2.32°$ in a tube of 2 dem. This value is in good agreement with Neuberg and Nord's work. The principal fraction

solidified at + 25° and produced only a feeble rotation due no doubt to the presence of a little of the optically active isomer in much of the optically inactive form.

Bosseken and Cohen (6) attempted to resolve the biochemically prepared glycol by means of the strychnine and brucine salts of the sulphate, but were unsuccessful, so they concluded it was chiefly the internally compensated form. They were also unsuccessful in trying to resolve glycol synthesized by Brainbridge's method, but finally succeeded in preparing an optically active form having a rotation of $[\alpha]_D = + 5°$ and a laevo form with a rotation of $[\alpha]_D = - 2°$ from glycol synthesized by the action of peracetic acid on liquid butene-2 in chloroform. A 54% yield was claimed for this process.

## Chemical properties

The chemistry of 2,3 butylene glycol has so far received but little attention. It is easy, however, to predict from its structure what reactions it will undergo, the products that will be formed, and something of their properties. Experimental evidence substantiates these predictions.

There are several degrees of oxidation and corresponding products. Acetyl methyl carbinol, also known as acetoin and dimethyl ketol, is formed by the action of nitric acid at 100° and also by bacterial action in the presence of oxygen (72). It is a colorless liquid reported to boil at 144-5° (80). It is slightly heavier than water, has a refractive index of 1.42, and is miscible with water and most organic solvents

except ligroin. It has a number of polymers, on which much work has been done. The carbinol is much better known than the glycol. It has been the subject of considerable research, has been prepared by a great many methods, including numerous biochemical, and a number of its derivatives, such as the ethers, sodium sulphite compound, oxime, phenylhydrazone, etc., are known.

Strong oxidizing agents, such as bromine, oxidize the glycol to diacetyl(34). This is a yellow-green liquid with a peculiar odor which in very dilute solutions resembles the aroma of butter. It boils at $87.5-88^\circ$ (14), is slightly lighter than water, and has a refractive index a little below the carbinol. As would be expected, it polymerizes readily. Many derivatives are known.

Varying the conditions of oxidation would probably give rise to a number of other products such as pyruvic, oxalic, and acetic acids and crotonaldehyde.

The proximity of the hydroxyl groups makes the removal of a molecule of water appear fairly easy, and the corresponding dimethyl ethylene oxide is known. Under the proper conditions polyglycols analogous to those of ethylene glycol would undoubtedly form.

The pinacoline rearrangement has already been referred to; Fairn (67) always found methyl ethyl ketone in the distillate from the 2,3 glycol and 25% sulphuric acid. He identified it as the p-nitro phenyl hydrazone.

By oxidation of the glycol to diacetyl and treatment of this substance with methyl magnesium bromide, pinacol itself could be synthesized.

This is a rather valuable chemical and difficult to make by other methods. If other Grignard reagents were used a variety of tertiary glycols could be prepared, all of which should undergo the rearrangement. This would be an interesting study.

Mono- and di-metallic salts can be formed by treating the glycol with alkali metals, using benzene or toluene as a solvent. The salt crystallizes out and is soluble in alcohol. Cross and Jacobs (10) prepared sodium salts of glycols by the action of sodium hydroxide. These metallic salts are valuable in the synthesis of ethers and esters.

Either one or both of the hydroxyl groups may be replaced by a halogen, using the halogen acid, phosphorus trihalide, or other halogenating agents. Fourneau and Puyal (15), as well as Likhosherstov and Alekseev (45), have prepared the bromohydrin and chlorohydrin from butene-2 and the hypohalous acid. When the halohydrins areheated with water or lead oxide and water they undergo a rearrangement similar to the pinacoline, whereby the halogen acid splits out and methyl ethyl ketone is formed (29).

By the action of the dialkyl amines on the halohydrins, Fourneau and Puyal formed 3 dimethylamino 2 butanol, and 3 diethylamino 2 butanol. The p-nitro benzoates were then made and these reduced by means of tin and hydrochloric acid to the p-amino benzoates. These compounds have pronounced local anesthetic action. The p-amino benzoate hydrochloride of 3 diethylamino 2 butanol is dimethyl novocaine, and its anesthetic effect is much more intense than novocaine.

These same investigators produced symmetrical dimethyl ethylene

oxide in excellent yield by treating the butylene halohydrins with dry caustic soda. It has a pleasant odor and is a very good anesthetic, as might be expected from the close resemblance of its structure to that of diethyl ether.

Many mixed-type compounds could be, and have been, prepared. Wieland and Bossert (73) found 2,3 hydroxy amino butane among the products from the reaction of diethyl peroxide and ferrous sulphate on alanine. It could more readily be prepared, however, by treating symmetrical dimethyl ethylene oxide with ammonia. Likhosherstov and Alekseev report the acetates of 2,3 butylene chlorohydrin and bromohydrin and the benzoate of the bromohydrin. Palomaa and Jansson (55) have synthesized a number of the halo-ethers of other glycols by the action of phosphorus trihalide on the monoethers in pyridine. These compounds could readily be used for further synthetic work through formation of the Grignard reagents or treatment with organic salts.

If the halides be treated with potassium cyanide, the halogen will be replaced by a cyanide radical. This will, of course, add water to form the acid amide, hydrogen to form the amine, and hydrogen sulphide or halide to form the corresponding sulpho- or halo-amine. Complete hydrolysis would result in a carboxyl group.

In general, sulphur may be substituted for oxygen throughout, giving rise to the thioalcohols, thioethers, etc. A large number of new compounds could be prepared, and many known compounds probably could be formed from the glycol more easily than by present methods.

## Physiological properties

The presence of 2,3 butylene glycol in the blood (48) and physiolog-
ical experiments on rats indicate the comparative non-toxicity of this
compound, in contrast to ethylene glycol which R. Hunt (24)(25) declares
to be as toxic as methyl alcohol. The key to the difference in the
physiological behavior of these two glycols is probably to be found in
the nature of the products to which their oxidation in the body give
rise. The butylene glycol forms diacetyl and acetic acid, while
ethylene glycol produces oxalic acid (24)(25).

## Determination

Several qualitative tests for 2,3 butylene glycol and acetyl methyl
carbinol have been advanced, such as Voges and Proskauer's (19), which
consists in making the solution strongly alkaline with potassium hy-
droxide and letting it stand open for a number of hours. The acetyl
methyl carbinol is supposedly oxidized under these conditions to
diacetyl, which in turn reacts with enzymes present to give an  eosin-
red coloration. This color can often be observed in butylene glycollic
beers that have been made alkaline to stop fermentation.

Other qualitative tests include Kluyver, Donker, and Hooft's (34)
modification of Lemoigne's (40) test, as used by Wilson, Peterson, and
Fred (74), which is based on the oxidation of the glycol and carbinol
to diacetyl and the subsequent formation of a fine, red-needle precipitate
of nickel dimethyl glyoxime, and Thomas and Winn's (68) test for a

variety of polyhydric compounds using $\beta$-naphthol 3,6 disulphonic acid.

Until a few years ago a good quantitative determination for 2,3 butylene glycol had not been devised. Recently, however, Brockmann and Werkman (6), A. R. Kendall (27), and Mouren and Dodé (51) have each developed methods that appear satisfactory. The last named workers use a modification of Lemoigne's qualitative test and claim it to be quite successful, even for very low concentrations.

## EXPERIMENTAL

### Biochemical Synthesis of 2,3 Butylene Glycol

#### Fermentation

The fermentation work was done in conjunction with the study on which have been reported by A. R. Kendall (27). The medium consisted of 5.25 g. magnesium sulphate, 10.5 g. ammonium chloride, 4.0 g. secondary potassium phosphate, .45 g. calcium chloride, 6 g. calcium carbonate, and 200 g. sucrose made up to 3500 cc. with distilled water. Concentrated solutions of the soluble chemicals were prepared in order to facilitate measuring the components for each batch.

The fermentations were run in four-liter Erlenmeyer flasks. The media were sterilized in an autoclave at 15 pounds pressure for one hour, inoculated with 50 cc. of 24 hour cultures of _aerobacter aerogenes_ grown on a similar medium, and incubated for 14 days at a temperature of 37.5°. Calcium carbonate was used to neutralize the acid formed during the course of the fermentation, but for maximum yield the pH should be kept constant at about 6 by addition of sodium carbonate.

The fermentations were essentially anaerobic, but not strictly so. For the flasks were shaken twice daily to stir up the calcium carbonate and keep the mixture homogeneous. Care was taken not to wet the cotton plugs. In general, anaerobic conditions produce mostly glycol, while aeration tends to increase the yield of acetyl methyl carbinol or acetoin and diacetyl.

tion of the vapor, and by centrifugalization of the solid material to remove occluded glycols. With the amounts involved these are impractical in the laboratory.

The extractions were carried out in a continuous extractor, a diagram of which appears in Fig. 1, which could handle 5 liters of the concentrate. Several solvents were tried, but because of its low boiling point and the relative insolubility of water and inorganic salts in it, ether is by far the best.

Again, for large-scale production extraction probably would not be resorted to, but steam distillation under low pressure, with or without the addition of other substances, would be used.

As extractions are never complete, there is the problem of when they should be discontinued. As this is best estimated by plotting a curve showing the rate of extraction, it was done for each run. One of these curves is shown in Fig. II. The comparative extration of successive fractions apparatus is indicated when such graphs are compared.

The extractions were run, on an average, for 48 hours, but the untreated material was removed from them to then the fractionated material from petroyther and nearly odorless during the first few hours, to darkbrown and an odor of sour potatoes toward the last of the run. Upon cooling, these fractions all deposited a variety of crystals, in which was found calcium, potassium, phosphorus and organic matter. In latter was probably sucrose and calcium lactate.

One batch of fermentation was run with molasses substituted for sucrose. Though the fermentation proceeded nearly as well, great difficulty Apparently

Condenser

Asbestos

Ether layer

Aqueous layer

Oil bath

Hot plate
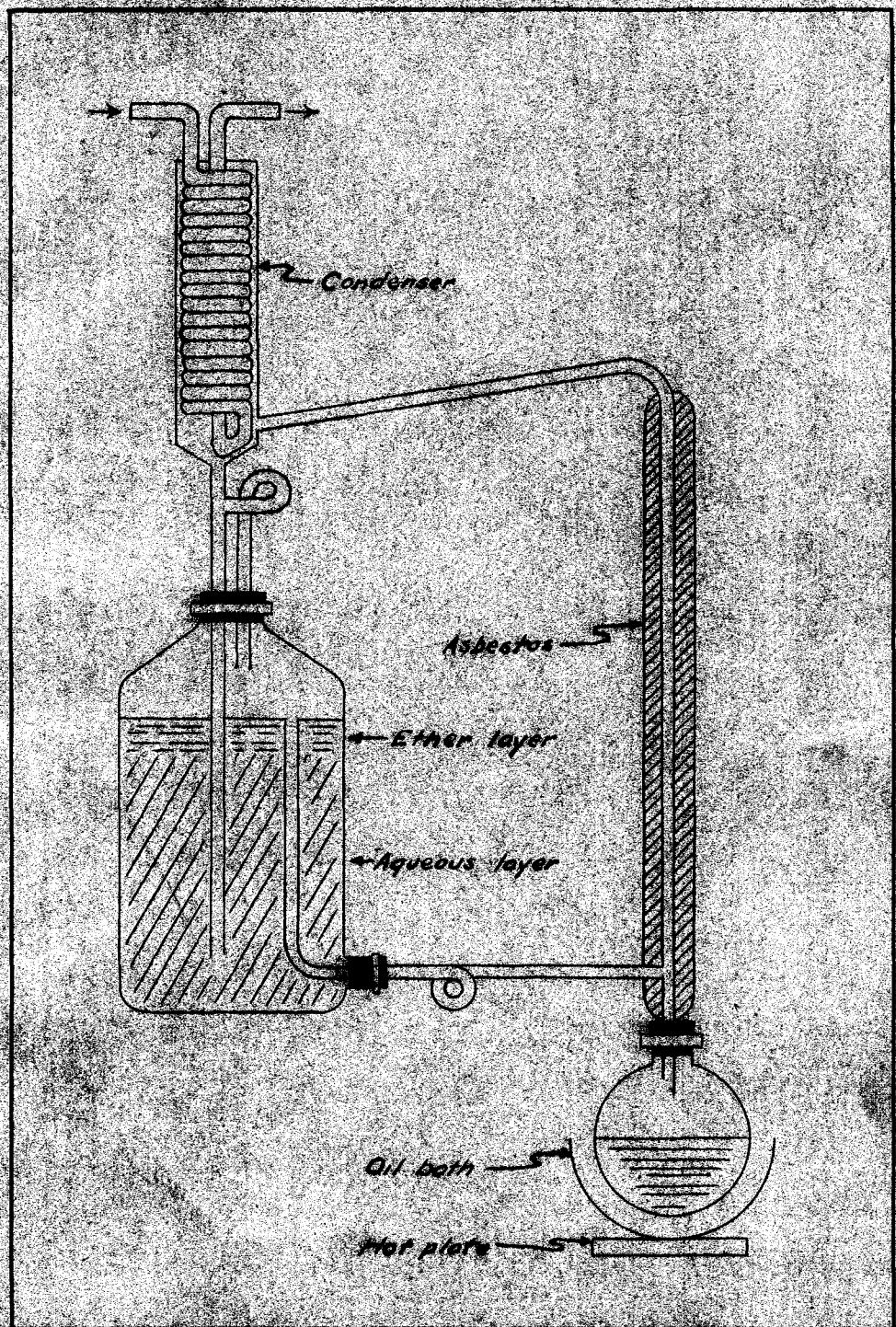
Fig I
Extraction Apparatus

Fig II
Rate of Extraction
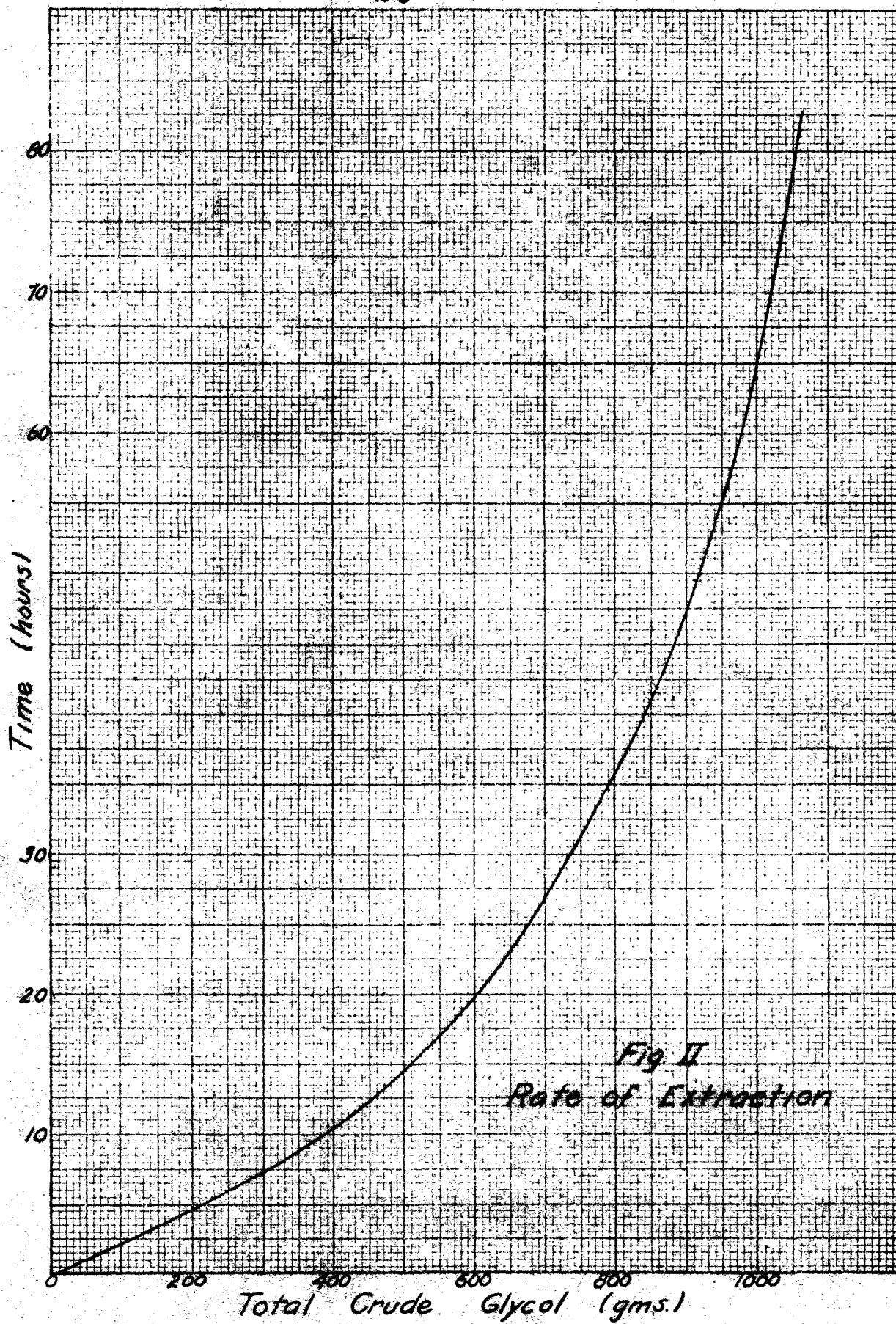
was experienced in filtering and extracting the concentrated material.

## Purification

The several portions of crude glycol were, in each case, combined, distilled, treated with activated carbon, and fractionated. A number of low-boiling, pleasant-smelling fractions were obtained, but, with the exception of acetyl methyl carbinol, which was characterized as the phenylhydrazone, m.p. 83-4°, none of the substances were identified.

## Physical properties

By repeated fractionation, two fractions of the glycol were obtained, boiling 177-79° and 183-4° respectively, and in the proportion of about one part low-boiling form to four parts high-boiling. The low-boiling form was optically active $[\alpha]_D^{25°} +2.41$, but the high-boiling form had only a feeble dextro rotation. For the high-boiling form, which according to Boeseken and Cohen (5) is meso, the following constants were determined: $D_4^{20}$ 1.061; $\eta^{25}$ 1.437.

% C   Calc.: 53.3   Found: 53.2; 53.2

% H   Calc.: 11.18  Found: 11.17; 11.2

The vapor pressure of the high-boiling form was measured at various temperatures as it seemed that this information would be of value for determining optimum conditions for concentrating glycol liquors. The following data have been plotted in Fig. III.

TABLE III

VAPOR PRESSURE OF 2,3 BUTYLENE GLYCOL

| Temperature °C. | Pressure mm. Hg. |
| --- | --- |
| 100 | 24.0 |
| 110 | 44.5 |
| 120 | 76.0 |
| 130 | 120.0 |
| 140 | 177.0 |

On the basis of these data, the latent heat of vaporization calculated by means of the Clausius-Clapeyron equation for several temperatures is given in Table IV.

TABLE IV

LATENT HEAT OR VAPORIZATION OF 2,3 BUTYLENE GLYCOL

| Temperature °C. | Latent heat cal/g. |
| --- | --- |
| 106 | 196.8 |
| 116 | 177.8 |
| 126 | 160.6 |
| 136 | 145.2 |

Thus the heat required to distil 2,3 butylene glycol is considerably less than that required for ethylene glycol, as the latter compound has a latent heat of vaporization equal to 226.2 cal/g. at 180.6°C.

Fig. III
Vapor Pressure
of 2,3 Butylene Glycol

Preparation of derivatives of 2,3 butylene glycol

BUTADIENE 1,3 and 1,4 DIBROMOBUTENE-2. Butadiene, a quite interesting compound, is of considerable value in the synthesis of artificial rubbers and 1,4 di-substituted butenes. As its preparation from 2,3 butylene glycol has never been reported, it was undertaken, and 1,4 dibromobutene-2 was chosen to characterize it.

To a mixture of 50 cc. of concentrated sulphuric acid and 5 g. of pumice heated to 175° in a Claisen flask, 9 g. of glycol were added dropwise. Each drop produced quite an evolution of gas. The gas was passed through an absorption train containing two small tubes of bromine. The temperature of the flask was maintained a few points in its. The temperature of the flask was maintained a few points in its. The excess bromine was evaporated from the contents of the tubes and the crystalline residue recrystallized twice from alcohol. The colorless crystals, obtained in good yield, had a sharp odor, and melted at 54°, as reported by Griner (17) for 1,4 dibromobutene-2.

2,3 BUTYLENE HALOHYDRINS AND 2,3 BUTYLENE DIBROMIDE. The chlorohydrin, bromohydrin, dichloride, and dibromide are all recorded in the literature, but as they were needed for further synthesis considerable quantities were prepared.

Symmetrical butylene was generated readily by allowing secondary butyl alcohol to slowly run into a mixture of glacial phosphoric acid and pumice held at 300°-350°. A condenser and trap in the absorption train removed the water produced. For the dibromide and bromohydrin

liquid bromine and 2% bromine water, respectively, were used as the re-
actants, while for the chlorohydrin, a hypochlorous acid solution pre-
pared according to Koschnin and Mielie's (46) directions was used.

In the preparation of halohydrins the absorption flasks were shaken
quite vigorously by a small shaking device during the pumps of the
butylene.

The amount prepared, the percentage yield based on the secondary
butyl alcohol used, and the physical constants observed were for the
dibromide 247(of 76% bolling-point, 158-158.5° at 735 mm; $D_4^{20}$ 1.7853
and $n_D^{25}$ 1.4667 for the chlorohydrin 29.5 (of 54% bolling-point 117-
118.5° at 735 mm; $D_4^{20}$ 1.1461 and $n_D^{25}$ 1.4531 and for the bromohydrin
48.7 (of 65% bolling-point, 152-153.5° at 735 mm; $D_4^{20}$ 1.4667, and $n_D^{25}$
1.4731.

H. Lepingle (44) reports for the meso dibromide a boiling-point of
157.3° and $D_4^{15}$ 1.7813 and for the racemic dibromide a boiling-point of
160.5° and $D_4^{15}$ 1.7951. Fourneau and Fugal (15) give a boiling range
of 158-160° for the chlorohydrin, and Leithenerber and Aldemec (45)
give a boiling range of 152-5° $D_4^{18}$ 1.472 and $n_D$ 1.4740 for the bromo-
hydrin. The other constants could not be found.

Being mixtures of isomers, these products have higher and lower boil-
ing components, but as no attempt was made to separate these isomers,
the physical constants determined are more averages. The dibromide does
appear, however, to consist mainly of the low boiling, or meso, form.

All the refractive indices reported in this thesis were measured
by means of an Abbé refractometer.

The halohydrins are unpleasant to handle because, even in great dilution, they irritate the eyes.

2,3 BUTYLENE DICHLORIDE. The dichloride was prepared by the action of thionyl chloride on 2,3 butylene glycol. 50 g. of glycol were slowly added to 150 g. of thionyl chloride in a balloon flask equipped with a reflux condenser. No stirring was necessary due to the vigorous evolution of sulphur dioxide. The reaction appears to be endothermic because, though it proceeded quite readily, the flask became rather cold. After all the glycol had been added, the mixture was heated on water bath for three hours, water cautiously added to decompose any excess thionyl chloride, and the dichloride separated, washed, and distilled. The yield was 19.20 g. or 27%, based on the glycol used. The product distilled at 112-113.5° at 755 mm. $D_4^{20}$ 1.100; $\eta^{25}$ 1.401. Schleschukow (65) reports a boiling-point of 113-115° and $D^{18}$ 1.107. The refractive index could not be found in the literature.

## Ethers

2,3 BUTYLENE GLYCOL MONOMETHYL ETHER. The Williamson synthesis was the first one attempted for the preparation of the simple mono- and di-aliphatic ethers. 10 g. of glycol were refluxed with 2.5 g. of sodium in 100 cc. of toluene until all the sodium had reacted. The reaction, which was fairly rapid at first, went very slowly toward the end, requiring nearly an hour for completion, and as only one equivalent of sodium had been added, the di-sodium salt would probably be difficult to make by this method. The salt was jelly-like for quite awhile, but

eventually became quite crystalline. The toluene was filtered off, and the salt dried in an oven at 105° for a few minutes. The second reaction could have been run in the toluene, but it was felt that rectification of the ether would be more difficult with another substance of similar boiling-point present.

The sodium salt was refluxed with 109 g. of freshly distilled methyl iodide on the sand bath over night. The next morning quite a change could be noticed in the solid; it was of finer texture and the crystals seemed much harder, so the reaction was thought to be complete. The liquid was filtered and the large excess of methyl iodide distilled off. The residue was fractionated and 7.6 g. of a liquid boiling 128-130° at 731.5 mm. Hg. was obtained. This amounts to a 65% yield. $D_4^{20}$ .9004; $n_D^{25}$ 1.409..

A $CH_3O$     Calc.: 29.8     Found: 29.5; 29.8

With a view toward a better yield and a cheaper process, methylation with dimethyl sulphate was next tried. 30 g. of glycol and 42 g. of dimethyl sulphate were mixed in a three-necked flask provided with a reflux condenser and a mercury-sealed mechanical stirrer. The mixture was heated to a near-boil for an hour, allowed to cool, and then treated with powdered sodium hydroxide, a little at a time, over a period of an hour and one-half, until the reaction mixture became basic, occasional additions of water being necessary to keep the mixture fluid. The contents of the flask were then filtered and fractionated. The yield of mono-ether was 11.2 g., or only 21.5%. About 1.5 g. or glycol dimethyl ether was also formed.

The next method tried gave better results. 6.1 g. of sodium were dissolved in 100 g. of glycol. The reaction proceeded slowly at first, but as it progressed the glycol became quite hot, the sodium melted, and the reaction became so vigorous as to require cooling. It was necessary to heat the mixture finally, however, in order to speed up the solution of the sodium. When all the sodium had dissolved, 30 g. of dimethyl sulphate were slowly added through a dropping funnel, the mixture being stirred constantly. The heat of the reaction soon started an orderly refluxing. After about an hour the stirring was discontinued, but the mixture was kept on the sand bath over night. The contents of the flask were fractionated under reduced pressure and the excess glycol recovered. The yield was 21.0 g. of mono methyl ether, or 91.5% of theory based on the sodium used, together with a small amount of a low-boiling fraction which was probably mostly the di-ether.

2,3 BUTYLENE GLYCOL DIMETHYL ETHER. 2 g. of sodium was dissolved in 40 g. of glycol monomethyl ether prepared as above, and 12 g. of dimethyl sulphate added, as in the synthesis of the monomethyl ether. The reactions went smoothly, and 7.1 g. of the dimethyl ether boiling 96-97.5° at 731.5 mm. was isolated. Yield: 68%, based on sodium used. $D_4^{20}$ .857; $\eta^{25}$ 1.381.

% $CH_3O$     Calc.: 52.5     Found: 52.3; 52.0

A second method of synthesis was also tried for this compound. To 5 g. of sodium dissolved in 100 cc. of absolute methyl alcohol were added 21.6 g. of the butylene dibromide previously prepared. The mixture was

refluxed on a sand bath for two days, at the end of which time consider-
able salt had formed. The mixture was filtered and repeatedly fraction-
ated. The yield was 7.3 g., or 62% based on the dibromide. Some un-
saturated hydrocarbons undoubtedly formed as there remained no unchanged
dibromide.

C. 3 BUTYLENE GLYCOL MONOETHYL ETHER. The sodium salt was formed
from 10 g. of glycol and 2.6 g. of sodium in toluene in the same manner
as for the monomethyl ether. The salt was refluxed over night with 100 g.
of freshly distilled ethyl iodide. The yield was 9.15 g., or 71% based
on sodium, of a fraction boiling $139.5-141^{\circ}$ at 731.5 mm. $D_4^{20}$ .692; $\eta^{25}$
1.414.

$$\% \text{ C} \qquad \text{Calc.:} \quad 60.96 \qquad \text{Found:} \quad 60.7; \ 60.7$$

$$\% \text{ H} \qquad \text{Calc.:} \quad 11.94 \qquad \text{Found:} \quad 12.1; \ 11.9$$

Another procedure was tried, in which 35 g. of freshly distilled
diethyl sulphate was added to 5.1 g. of sodium dissolved in 100 g. of
the glycol, similar to the dimethyl sulphate synthesis of the monomethyl
ether. The yield obtained was 23.0 g. or 88% based on the sodium used.

The diethyl sulphate, although more pleasant to work with than the
dimethyl sulphate, was quite impure as received. The practical grade
was washed with water twice, with sodium bicarbonate solution, again
with water, was dried over calcium chloride, and distilled under
diminished pressure. The amount of pure diethyl sulphate obtained was
only one-half of that of the crude material.

2.3 BUTYLENE GLYCOL DIETHYL ETHER. This was formed from the

monoethyl ether, sodium, and diethyl sulphate in a manner analogous to the synthesis of the dimethyl ether. From 2 g. of sodium, 50 g. of glycol monoethyl ether, and 13.4 g. of diethyl sulphate, 10.5 g. of a fraction boiling 138-41° at 731.5 mm. was obtained. This is an 82.5% yield based on the sodium used. $D_4^{20}$ .814; $\eta^{25}$ 1.386.

%C    Calc.: 65.7    Found: 64.8; 63.2; 64.6

%H    Calc.: 12.42    Found: 12.3; 12.2

The diethyl ether was also prepared from sodium ethoxide and butylene dibromide in absolute alcohol. To 5 g. of sodium dissolved in 100 cc. of alcohol was added 21.6 g. of butylene dibromide as in the dimethyl ether synthesis. The yield after two days refluxing was 10.0 g., or 68.5% based on the dibromide.

2,3 BUTYLENE GLYCOL MONO n-PROPYL ETHER. As n-propyl sulphate was not available or practical to make, the only synthesis used for the mono n-propyl ether was the Williamson.

The sodium salt was made in the usual manner from 10 g. of glycol and 2.5 g. of sodium. It was refluxed for 16 hours with 100 g. of n-propyl iodide. The yield was 9.9 g. boiling 154.5-156° at 731.5 mm., or 69.5% based on the glycol. $D_4^{20}$ .912; $\eta^{25}$ 1.421.

%C    Calc.: 65.6    Found: 65.6; 65.7

%H    Calc.: 12.17    Found: 12.2; 12.3

2,3 BUTYLENE DI n-PROPYL ETHER. This was made from the alcohol, sodium, and butylene dibromide as in the synthesis of the other

diethers. To 5 g. sodium dissolved in 100 cc. n-propyl alcohol, 21.6 g. of the dibromide were added. The yield after 2 days refluxing was 8.9 g. boiling 172-175.6° at 731.5 mm. This is equivalent to 51% based on the dibromide. $D_4^{20}$ .839; $\eta^{25}$ 1.402.

%C   Calc.: 68.9   Found: 66.4; 68.0; 66.1

%H   Calc.: 12.74  Found: 12.7; 12.9

2,3 BUTYLENE GLYCOL MONO iso-PROPYL ETHER. The sodium salt of 10 g. of butylene glycol was refluxed 14 hours with 100 g. of freshly distilled iso-propyl iodide. The yield of monoether was 10.8 g., or 75% based on the glycol. The boiling point was 147-8° at 731.5 mm. $D_4^{20}$ .847; $\eta^{25}$ 1.418.

%C   Calc.: 65.6   Found: 65.7; 65.7

%H   Calc.: 12.17  Found: 12.2; 12.3

2,3 BUTYLENE GLYCOL MONO n-BUTYL ETHER. The sodium salt of 10 g. of the glycol was refluxed 14 hours with 100 g. of mono n-butyl iodide. 11.1 g., or a 70% yield based on the glycol, was obtained, boiling 174-175.5° at 731.5 mm. $D_4^{20}$ .935; $\eta^{25}$ 1.423.

%C   Calc.: 65.7   Found: 65.6; 65.7

%H   Calc.: 12.42  Found: 12.4; 12.4

2,3 BUTYLENE GLYCOL DI n-BUTYL ETHER. 5 g. of sodium, 100 cc. n-butyl alcohol, and 21.6 g. of butylene dibromide, heated on the sand bath 2 days, yielded 9.5 g. or 47% based on the dibromide, of the di-

ether boiling 188-190° at 731.5 mm. $D_4^{20}$ .859; $\eta^{25}$ 1.417.

% C   Calc: 71.3   Found: 70.3; 70.4

% H   Calc: 12.85   Found: 12.8; 12.8

## Ethyl-type compounds

It has been mentioned that Michaelcroter and Abeleaur (46) prepared the acetate and benzoate of 2,5 butylene chlorohydrin and the acetate of the bromhydrin. However, the 2,5 halo-ethers had never been reported so their synthesis was undertaken, using the method employed by Palomaa and Jansson (56) for the 1,4 halo-ethers.

2 BROMO 3 METHOXY BUTANE. 28 g. of Glycol monomethyl ether were mixed with 4.5 g. of pyridine and slowly added, with constant stirring to 27 g. of ice cold phosphorus tribromide in a three-necked flask. After the reaction had subsided the mixture was warmed on a water bath for three hours. The bromo-ether was distilled off, washed successively with sodium carbonate solution, dilute sulphuric acid, and water. It was dried with sodium sulphate and fractionated. The yield was 14.6 g. or 35% of theory, based on the monomethyl ether. The compound boiled at 138-141.5° at 727 mm. $D_4^{20}$ 1.444; $\eta^{25}$ 1.448.

% Br   Calc: 47.8   Found: 47.1; 47.0

2 BROMO 3 ETHOXY BUTANE. 29.5 g. of Glycol monoethyl ether mixed with 4.5 g. of pyridine were added to 27 g. of phosphorus tribromide under the same conditions as in the preceding synthesis. The yield of

bromo ethoxy butane was 17.5 g. or 39% of theory, boiling 144.5-145.5° at 727 mm. $D_4^{20}$ 1.406; $\eta^{25}$ 1.453.

% Br. Calc.: 44.1 Found: 43.1; 43.4

2 CHLORO 3 METHOXY BUTANE. 26 g. of glycol mono methyl ether were mixed with 4.5 g. of pyridine and added to 13.8 g. of phosphorus trichloride in the same manner as in the preparation of the bromo-ethers. The yield was 12.5 g., or 41% of theory, boiling 114-15° at 727 mm. $D_4^{20}$ .997; $\eta^{25}$ 1.420.

% Cl. Calc.: 29.0 Found: 28.9; 28.9

2 CHLORO 3 ETHOXY BUTANE. To 13.8 g. of phosphorus trichloride were added 29.5 g. of glycol monoethyl ether mixed with 4.5 g. of pyridine under the same conditions as in the three preceding syntheses. The yield of chloro ethoxy butane was 17.75 g., or 52% of theory, boiling 121-5° at 727 mm. $D_4^{20}$ .960; $\eta^{25}$ 1.425.

% Cl Calc.: 25.9 Found: 25.2; 25.2

2,3 BUTYLENE GLYCOL DIACETATE. Though Bainbridge (3) and others had already prepared the diacetate of 2,3 butylene glycol, it was only in small amounts and little mention is made of it. The wide use of ethylene glycol diacetate being considered, it was thought advisable to add a little to the information concerning the butylene glycol diacetate.

To 67 g. of silver acetate in 75 cc. of glacial acetic acid in a balloon flask provided with a reflux condenser, 43 g. of butylene di-

bromide were added, and the flask maintained at about 100° on a sandbath

for 24 hours. The contents of the flask were filtered, neutralised

with aqueous sodium carbonate solution, and the ester layer separated.

The aqueous layer was extracted repeatedly with chloroform, the extract

combined with the ester, and the whole dried over calcium chloride and

fractionated. The yield was 27.5 g. or 70% of theory based on the di-

bromide, boiling 192.5-194° at 738 mm., as compared to Bainbridge's

(3) value of 192°. Density and refraction measurements gave $D_4^{25}$ 1.0581,

$n_D^{25}$ 1.418.

√ 2,3 BUTYLENE GLYCOL MONOMETHYL ETHER ACETATE. To 25 g. of silver

acetate in 25 cm. of glacial acetic acid, were added 12.5 g. of 2 bromo

3 methoxy butane and the mixture heated on a sandbath to 100° for 24

hours in a balloon flask provided with a reflux condenser. The con-

tents of the flask were filtered, neutralised with aqueous sodium

carbonate solution, and the ester layer separated. The aqueous layer

was extracted several times with chloroform, the combined extracts

added to the ester, and the solution dried over calcium chloride and

fractionated. The yield was 5.2 g. or 47.5% of theory based on the

bromo methoxy butane, boiling 149-51° at 730 mm. $D_4^{20}$ .9691, $n_D^{25}$ 1.406.

% C   Calc: 57.6   Found: 57.2, 57.0, 57.0

% H   Calc: 9.66   Found: 9.4, 9.5

2,3 BUTYLENE GLYCOL MONOETHYL ETHER ACETATE. To 25 g. of silver

acetate in 25 cm. of glacial acetic acid, 13.6 g. of 2 bromo 3 ethoxy

butane were added and the mixture heated on a sandbath to 100° for 24

hours in the same apparatus used in the preceding synthesis. The

yield was 6.8 g., or 57% of theory, boiling 160-163.5° at 738 mm. $D_4^{20}$ .957; $\eta^{25}$ 1.413.

% C   Calc.: 60.9   Found 59.4; 59.3

% H   Calc.: 10.06   Found 9.9; 9.9

Preparation and properties of 2,3 butylene diamine

### Historical

Until Prajka and Zahlova (16) prepared 2,3 butylene diamine, in 1926, by the reduction of dimethyl glyoxime in acetic acid, very little work had been done on this interesting and important, from a theoretical standpoint, at least, compound. Angeli (2) had prepared a small quantity by reduction of dimethyl glyoxime with sodium in alcohol, and Morgan and Hickinbottom (50) had shown the diamine to be present in a small fraction of basic material obtained from the prolonged action of ammonia on 2,3 butylene dibromide.

Prajka and Zahlova reduced dimethyl glyoxime by means of hydrogen at slightly above atmospheric pressure, using platinum black as a catalyst, and obtained a 50% yield. The reduction required fourteen hours for completion. They purified the compound, showed that it formed two hydrates, determined its elementary constants, and prepared quite a number of its derivatives.

In 1933, Krajcinovic and Vranjican (35) obtained a 44% yield of 2,3 butylene diamine by hydrogenation of dimethyl glyoxime in an alcoholic hydrochloric acid solution using platinum black as a catalyst. Though

their yield was a little short of Prejma and Zahlova's, as a result, no
doubt, of greater hydrolysis of the glyoxime, the time required for re-
duction was only three hours.

## Preparation

The following experimental work was nearly finished before the
appearance of the research of Krajcinovic and Uranjican. The butylene
diamine was desired in order to resolve it and then convert it to the
optically active, 2,3 butylene glycol. At first, an attempt was made
to obtain the amine from the glyoxime by several of the common reduction
reactions in an effort to eliminate the expensive catalyst and the neces-
sity for quite small runs. The yields from reductions using stannous
chloride or zinc with hydrochloric, sulphuric or acetic acids were
negligible. Prejma and Zahlova (16) had shown that reduction by means
of sodium in alcohol was impractical. To eliminate the costly hydrolysis
of the glyoxime by acids, alkaline reducing agents were tried, such as
sodium hyposulphite, but they, too, were unsuccessful. Gabriel's
phthalimide synthesis, using butylene dibromide, was also without fruit.

Morgan and Hickinbottom (20) had obtained only a very small fraction
of impure butylene diamine from two weeks action of alcoholic ammonia
on butylene dibromide, so more drastic conditions were tried. Ammonia
gas under a pressure of four atmospheres was allowed to react, in a
steel bomb, with pure 2,3 butylene diamine for ten days at a temperature
of 105°. A run was also made under identical conditions, excepting an
alcoholic solution of the dibromide was used. In the latter reaction a
much greater amount of ammonia was present, as considerable was required

to saturate the alcohol.

In both cases a large quantity of ammonium bromide had crystallized out and about three-quarters of the dibromide had reacted, but in neither case was the yield of diamine worth reporting. The reaction seems to favor the formation of unsaturated compounds by the removal of hydrogen bromide from the molecule.

A reversion to catalytic hydrogenation was, therefore, necessary. However, a medium was sought which would remove the diamine from the reaction as fast as it was formed, and yet would not hydrolyze the dimethyl glyoxime. Acetic anhydride seemed to meet these conditions.

DIMETHYL GLYOXIME DIACETATE. One of the chief drawbacks, and the probable reason for the long time necessary for reduction, in Frejka and Zahlova's (16) method is that a suspension of dimethyl glyoxime is used, rather than a solution, because of the low solubility of the glyoxime in glacial acetic acid. As it dissolves readily in acetic anhydride, it was apparent that acetylation must take place. Accordingly, 10 g. of dimethyl glyoxime were dissolved in 100 cc. of acetic anhydride and the excess anhydride distilled off under low pressure. The colorless needles which crystallized out of the residue were recrystallized twice from alcohol and analyzed. They melted at 112° sharply and, allowing for losses during recrystallization, the reaction is quantitative.

$\%$ N   Calc.: 14.0   Found: 14.07; 14.05

The catalyst used in all reductions was platinum oxide, prepared according to the directions given in Organic Syntheses (1).

CALIBRATION of APPARATUS. The reductions were made in a high-
pressure hydrogenation apparatus similar to the one described in Organic
Syntheses. As the amount of hydrogen used in the reaction was measured
by the change in pressure in the system, a calibration is necessary.

11.6 g. of maleic acid and .1066 g. of platinum oxide were placed
in the reduction bottle, and 125 cc. of 95% ethyl alcohol added. The
bottle was fitted in the apparatus, the air quickly displaced by
hydrogen, and the pressure rapidly raised to about 95 pounds per square inch.
The exact reading was taken as 95.55 pounds and the shaking started.
Readings were taken at minute intervals until the pressure change per
minute became less than one-half pound. Readings were then taken at
five minute intervals until the pressure drop became constant. This
constant pressure decrease was due to leakage and the total pressure
change was corrected accordingly. The leakage amounted to .9 pound per
hour and the total pressure drop corrected for this value was 17.85
pounds. The figure obtained for the apparatus, making due allowance for
the hydrogen consumed by the catalyst, was 176.73 pounds per mol of
hydrogen when operating between 95 pounds and 76 pounds. This procedure
illustrates the manner in which all reductions were run.

REDUCTION in GLACIAL ACETIC ACID. Several reductions of dimethyl
glyoxime were made using glacial acetic acid in order to compare results
with Freṇ̃a and Kahlson(1). Though the catalyst used was not prepared
in the same way the data are quite parallel. A typical run was made
with 2.9 g. of dimethyl glyoxime and .81 g. of platinum oxide in 25 cc.
of glacial acetic acid. The data is given in Table V.

TABLE V

REDUCTION of DIMETHYL GLYOXIME in
GLACIAL ACETIC ACID

| Time | Minutes elapsed | Pressure | Lbs. used |
|---|---|---|---|
| 8:45 | 0 | 95.65 | 0.00 |
| 8:47 | 2 | 95.45 | 0.20 |
| 8:50 | 5 | 95.30 | 0.35 |
| 9:00 | 15 | 94.80 | 0.85 |
| 9:15 | 30 | 94.10 | 1.55 |
| 9:30 | 45 | 93.85 | 2.30 |
| 10:00 | 75 | 91.90 | 3.75 |
| 11:00 | 135 | 89.55 | 6.10 |
| 1:00 | 255 | 85.35 | 10.30 |
| 3:00 | 375 | 82.60 | 13.05 |
| 5:00 | 495 | 80.70 | 14.95 |
| 7:00 | 615 | 79.25 | 16.40 |
| 10:00 | 735 | 77.95 | 17.70 |

The above data has been plotted in Fig. IV in order to compare it more easily with subsequent data.

The reduction product usually contained some white needles, which probably were ammonium acetate or the acetate of the amine. A little water was added to the mixture to dissolve the crystals, and the liquid was decanted from the platinum black. The catalyst could be used for about five reductions, on the average, before it became too sluggish.

The water and excess acetic acid were distilled under reduced pressure from the combined solutions of several reductions until the mixture became quite mushy. An excess of sodium hydroxide was then added and the mixture steam-distilled into dilute hydrochloric acid until the condensing liquid was no longer appreciably basic. The distillate was evaporated to a mush on a sandbath and placed in a small

Fig. IV
Reduction of Dimethyl Glyoxime
in Glacial Acetic Acid
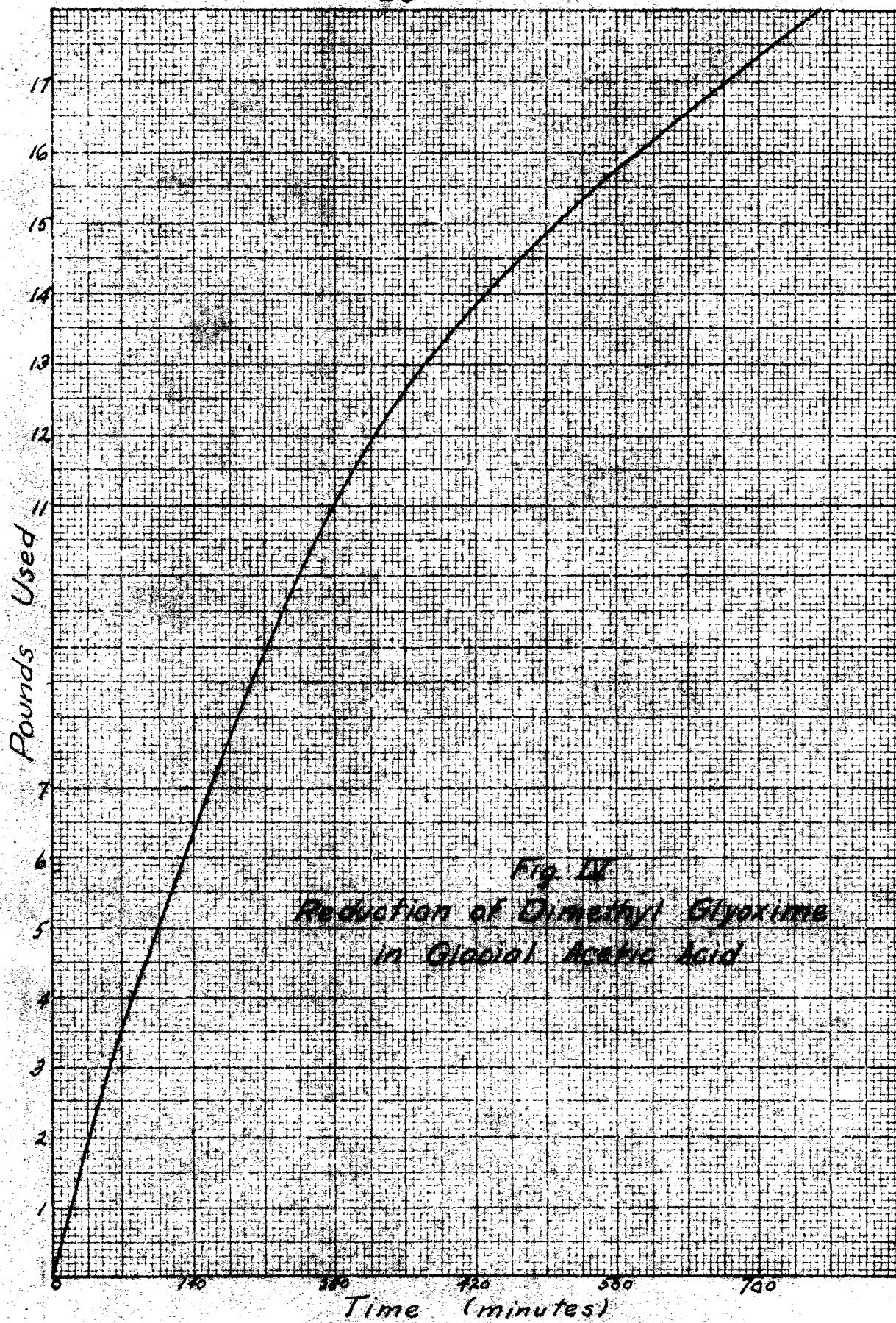
volumetric flask having a quite narrow neck. The flask was packed in
ice and to its contents, saturated potassium hydroxide solution and
solid potassium hydroxide were slowly added until the liquid was high
in the neck. The base which was a light-yellow in color, quickly
separated, and was removed by means of a long medicine-dropper. The
diamine was dried for a day over solid potassium hydroxide, distilled,
dried over sodium metal, and redistilled. The yield of the pure product
averaged 32-33% of theory based on the dimethyl glyoxime used.

In one instance, the mush remaining after the removal of the excess
acetic acid was treated with excess sodium hydroxide and extracted with
ether. The ether extract was dried over solid potassium hydroxide and
treated with dry hydrogen chloride gas. The diamine hydrochloride pre-
cipitated as a multi-colored gummy mass, which finally became hard after
prolonged addition of hydrogen chloride. It was recrystallized from
absolute alcohol to give very fine, white crystals.

REDUCTION IN ACETIC ANHYDRIDE. 11.6 g. of dimethyl glyoxime and
.86 g. of platinum oxide were placed in the reduction bottle, together
with 75 cc. of acetic anhydride as the solvent. After a lag of about
eleven minutes, the reduction proceeded very rapidly, the pressure-drop
attained a rate of four pounds a minute, and the container got very
hot. When about two-thirds of the amount of hydrogen necessary for
complete reduction had been used, the process stopped quite abruptly.

The procedure was repeated several times. There seemed to be no
correlation between the percentages of hydrogen used at cessation of
the reductions, and in every case the catalyst had a coarse, metallic

appearance after the reduction, and was rendered inert, in spite of

attempts to reactivate it with oxygen.

It was thought that the relatively high temperature the reaction

mixture reached might have caused the inactivation of the catalyst, so

other trials were made in which the jacket of the reduction bottle was

cooled by a coil of running water. The reductions were more complete,

but the results as a whole were still unsatisfactory. The method of

cooling was not very efficient. It was believed that if the reductions

were run at atmospheric pressure the velocity of the reaction might be

sufficiently less that the temperature would not reach the point where

the powers of the catalyst were destroyed.

If the ordinary atmospheric reduction tube, with the side-arms at

each end, was used, plugging of the catalyst invariably resulted when

the acetic anhydride vapor had diffused to the rubber connections.

Also, the tubes could not be made sufficiently large to contain twenty-

five to fifty grams of material, nor did they permit the vigorous shaking

necessary for good reductions without allowing some of the solution to

splash out of the side-arms. The reduction flask shown in Fig. V was

developed to eliminate these difficulties.

The flask was charged through stopcock A until the level of the

liquid reached a point just below the bottom of tube B. The air was

replaced with hydrogen by placing a one-hole stopper in bond C to pre-

vent diffusion of air downward, opening stopcock A to allow the air to

escape, barely opening stopcock B to drain the air from that side-arm,

and passing in hydrogen through stopcock D. When the air was completely

Fig V
Reduction Flask
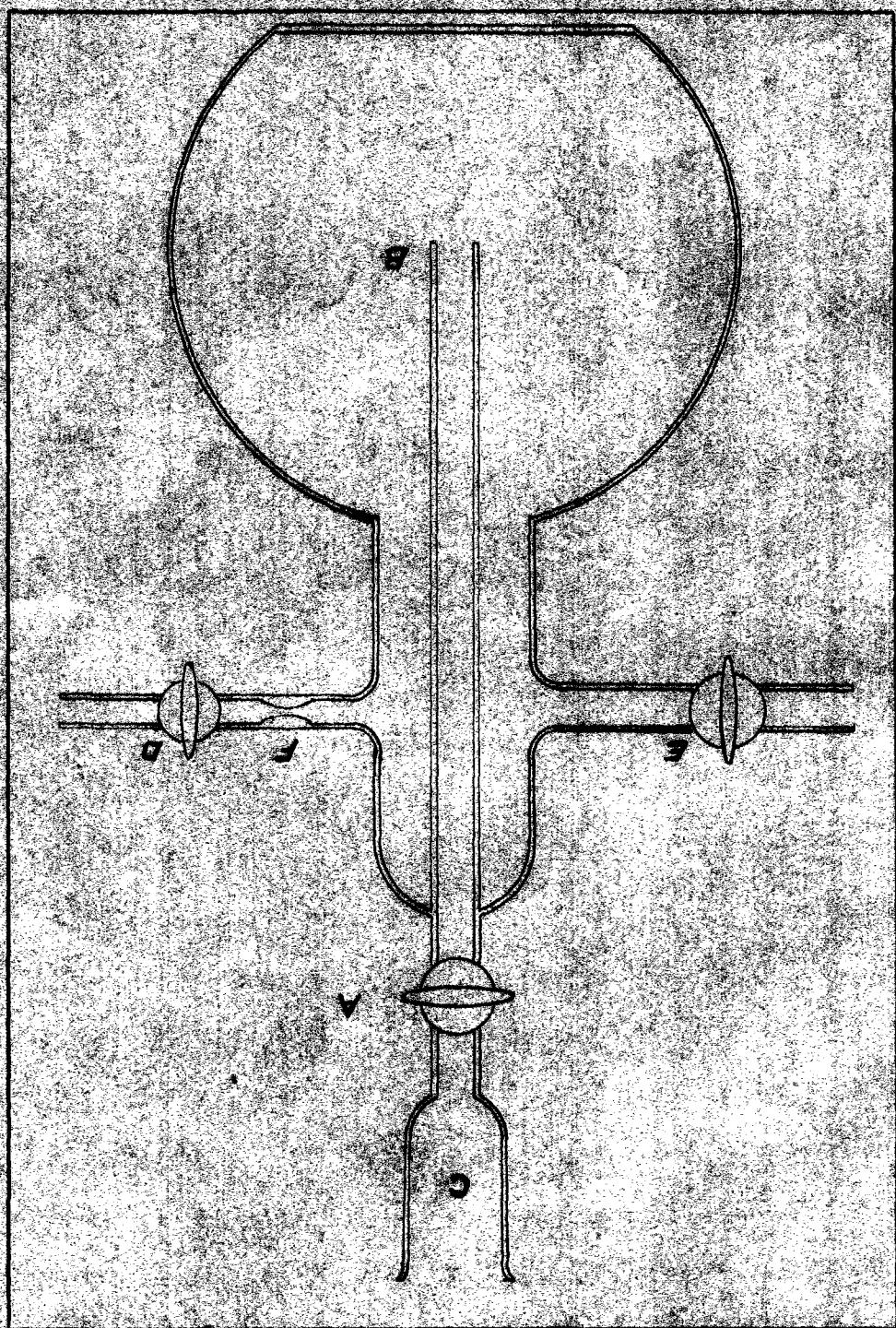
displaced stopcocks A and E were closed, the stopper removed, and shaking begun. The shaking mechanism was the vibrator type, and though the flask was shaken very vigorously, acetic anhydride vapor and spray were prevented from passing backward through stopcock D by the swift current of hydrogen through the constriction F. The flask was emptied through the large stopcock E. All of the stopcocks were lubricated with syrupy phosphoric acid because of the possible harmful effects of vaseline.

The flask was charged with 11.6 g. of dimethyl glyoxime, .95 g. of platinum oxide, and 125 cc. of acetic anhydride. After the usual lag in the reduction had passed, the bulb of the flask was immersed in ice-cold brine during the remainder of the shaking. The reduction was quite successful, and the data in Table VI were obtained.

TABLE VI

REDUCTION OF DIMETHYL GLYOXIME IN ACETIC
ANHYDRIDE

| Minutes elapsed | Hydrogen used (liters, uncorr.) | Minutes elapsed | Hydrogen used (liters, uncorr.) |
|---|---|---|---|
| 1 | .045 | 16 | .510 |
| 2 | .090 | 17 | .570 |
| 3 | .130 | 18 | .645 |
| 4 | .160 | 19 | .750 |
| 5 | .190 | 20 | .920 |
| 6 | .210 | 21 | 1.605 |
| 7 | .240 | 22 | 2.415 |
| 8 | .270 | 25 | 4.830 |
| 9 | .300 | 30 | 8.870 |
| 10 | .325 | 32 | 9.755 |
| 11 | .350 | 34 | 10.025 |
| 12 | .380 | 36 | 10.195 |
| 13 | .405 | 38 | 10.290 |
| 14 | .435 | 40 | 10.335 |
| 15 | .470 | 42 | 10.400 |

Fig. VI

Reduction of Dimethyl Glyoxime
in Acetic Anhydride

Hydrogen Used (liters)

Time (minutes)
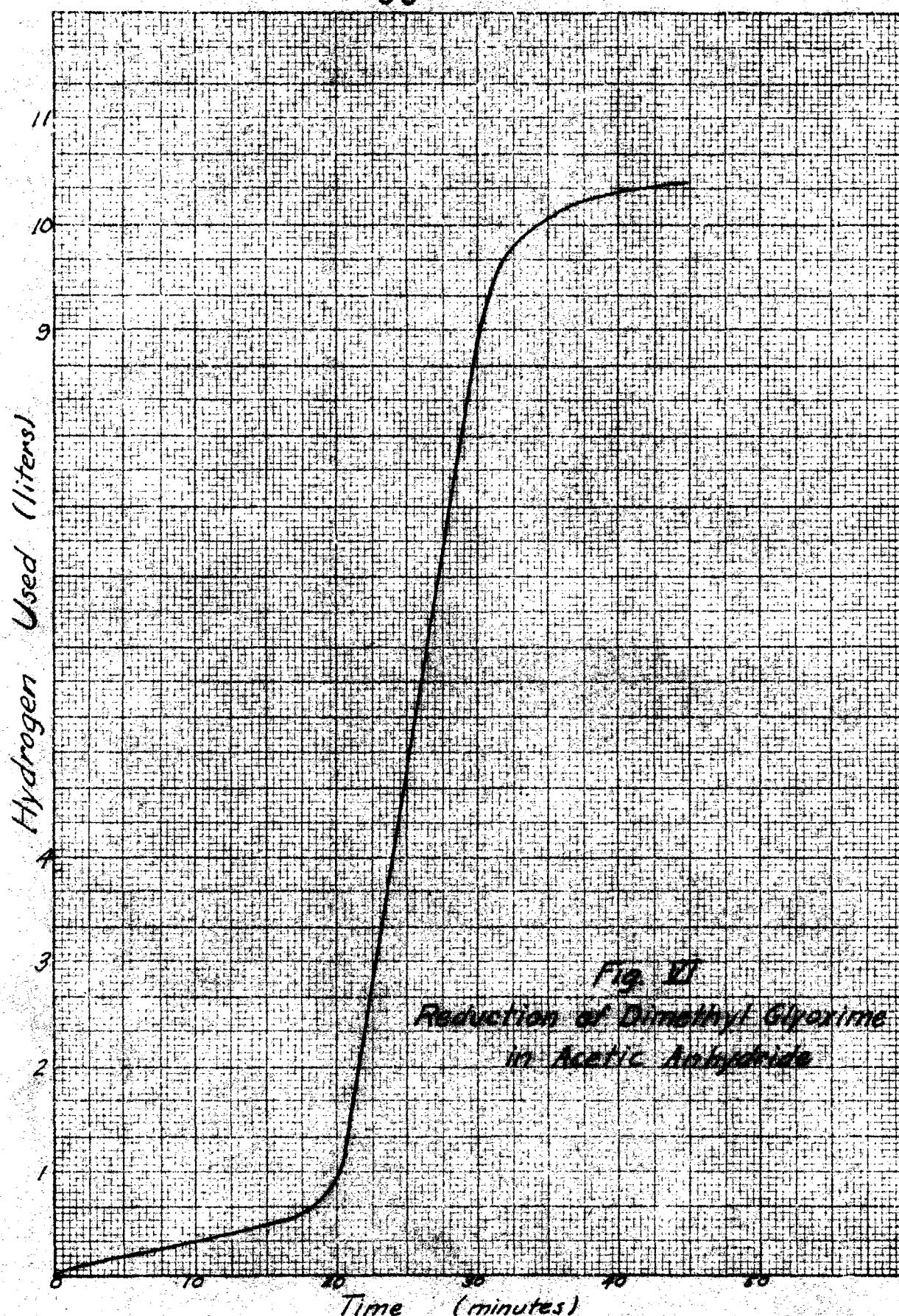
The data in Table VI have been plotted in Fig. VI.

SYMMETRICAL 2,3 DIACETAMINO BUTANE. The excess acetic acid and acetic anhydride were distilled from the combined reduction products of several runs made with acetic anhydride as the solvent, and from which the catalyst had been removed. The mushy residue was cooled, filtered, and the precipitate of white needles recrystallized twice from alcohol. They melted sharply at 284.5-285°.

% N    Calc.: 16.3    Found: 16.0; 16.4; 16.4

Frejka and Zahlova (16) found considerable difficulty in preparing this derivative from the diamine and acetic anhydride. They do not give a melting-point for it.

The disadvantage in preparing 2,3 butylene diamine by reduction in acetic anhydride is the difficulty encountered in hydrolyzing the acetyl derivative. Prolonged refluxing with dilute aqueous sodium hydroxide is necessary, and even then the yield is poor.

REDUCTION in ALCOHOL. Because of the troublesome recovery of the diamine from reductions in acetic anhydride, a modification of Krajoinovic and Vranjican's (35) method was tried. As the reason for these investigators' rather low yield was the hydrolysis of the dimethyl glyoxime caused by the acid present, it was believed that if the acid was added in small quantities as it was needed during the reduction, much of the deleterious hydrolysis could be prevented.

Accordingly, 29 g. of dimethyl glyoxime, 2 g. of platinum oxide

and 250 cc. of absolute ethyl alcohol were placed in the reduction flask and after the air had been displaced shaking was started. The catalyst was quietly reduced, but then the reduction came to a standstill, so 1 cc. of concentrated hydrochloric acid was added. Upon starting the shaker, hydrogen immediately began to be taken up. The reduction began to slow down again by the time 500 cc. of hydrogen had been absorbed, so another 1 cc. of hydrochloric acid was added. This procedure was continued until nearly the theoretical quantity of hydrogen had been used, at which time 20 cc. of hydrochloric acid were added. The balance of the hydrogen was taken up and the shaking discontinued. For this reaction immersion of the flask in ice water was unnecessary.

The excess alcohol was distilled, under reduced pressure, from the reaction mixture until the residue in the flask was nearly dry. This mixture of diamine hydrochloride and ammonium hydrochloride was treated in the usual manner with potassium hydroxide to recover the amine. The yields from several runs varied from 65% to 85% of theory, based on the diethyl glyoxime.

TETRAMETHYL PYRAZINE. In one instance the crude 2,3 butylene diamine hydrochloride obtained when the alcohol was distilled from a reduction mixture was made alkaline with sodium hydroxide solution and steam distilled. The first portion that came over solidified as a white mass of substance-like crystals in the condenser. The substance appeared quite pure, but was recrystallized from water in which it was very soluble. It melted at 85-6°. Some of the recrystallized material was dissolved in dry acetone, and hydrogen chloride gas lead into the

solution. A heavy white granular precipitate formed which was filtered out, washed, and recrystallized from 75% aqueous alcohol. It melted at 163°. The picrate was readily formed in alcohol. After recrystallization it melted at 193.5°.

$$\% \ N \quad \text{Calc.:} \ 20.6 \quad \text{Found:} \ 20.6; \ 20.6$$

It may seem strange that an unreduced compound should be present here, but Wallach (71) gives a good explanation of this incongruity. Wallach reduced dimethyl glyoxime in alkaline solution with aluminum and obtained no diamine, but considerable tetramethyl pyrazine. He gives the melting-point of the tetramethyl pyrazine as 86-87° and the picrate 152-5°. No other investigator has reported these compounds, though Frejka and Zahlova (16) obtained a fraction having a nitrogen content of 19-21%, but did not identify it.

In several of the reductions methyl alcohol was substituted for ethyl alcohol, but the yields obtained were poorer. In one run an attempt was made to use acetic acid in place of hydrochloric, in the belief that the weaker acid would produce less hydrolysis. However, the reduction would not proceed until hydrochloric acid was added.

Since the above work was done, Strack and Schwaneberg (66) have reported obtaining as high as 92% of the calculated diamine by reduction of very dilute solutions of dimethyl glyoxime in 99% methanol hydrochloric acid solution using a palladium catalyst. The method reported in this thesis has the advantage of convenience in preparing quantities of the diamine.

## Physical properties

The purified 2,3 butylene diamine is a clear, slightly syrupy liquid possessed with a nauseating, ammonia-like odor. The boiling point was 129-130° at 728.5 mm. The other constants found were $D^{20}_4$ .8655; $\eta^{25}$ 1.446, as compared to Freytag and Zahlon's (54) values of $D^{20}_4$ .86021 and $\eta^{20}_D$ 1.4486. This product is, of course, like the glycol, a mixture of isomers.

% N  Calc.: 31.8  Found: 31.7; 31.7

ELECTROMETRIC TITRATION. Several electrometric titrations were run to ascertain the neutralization equivalent of the diamine prepared and to calculate its dissociation constant. The data for one of these titrations, in which a sample of the amine weighing .2343 g. was taken, are given in Table VII and plotted in Fig. VII. The strength of the hydrochloric acid used was .1525 N. The solution of diamine was made up to 45 cc. with conductivity water, and the titrations were run at a temperature of 25°. A platinum-platinum black hydrogen electrode and a saturated potassium chloride calomel half-cell were used.

Fig. VII
Electrometric Titration of
2,3 Butylene Diamine

Hydrochloric Acid (cc.'s)

E.M.F. (volts)

TABLE VIII

DISSOCIATION CONSTANTS OF 2,3 BUTYLENE DIAMINE

| HCl added (cc) | B.M.F. (moles) | pH | Hydroxyl ion (moles) | Free base (moles) | Degree of dissoc. (x 10) | Undissoc. base (moles) | BOH⁺ (moles) | $K_1$ |
|---|---|---|---|---|---|---|---|---|
| 0 | .651 | 10.14 | $1.36 \times 10^{-4}$ | .607 | 5.75 | .0598 | .01658 | $5.78 \times 10^{-5}$ |
| 11 | .760 | 9.88 | $1.66 \times 10^{-5}$ | .110 | 1.51 | .0109 | .0343 | $5.32 \times 10^{-5}$ |

$$K_1 = \text{HCl}=17.85$$

| HCl added (cc) | B.M.F. (moles) | pH | Hydroxyl ion (moles) | Free base (moles) | | | BOH⁺ (moles) | $K_2$ |
|---|---|---|---|---|---|---|---|---|
| 22 | .651 | 6.95 | $7.84 \times 10^{-9}$ | 4.75 | | | 12.5 | $2.75 \times 10^{-10}$ |
| 30 | .603 | 6.06 | $1.11 \times 10^{-8}$ | 12.75 | | | 4.5 | $3.17 \times 10^{-10}$ |

$$K_2 = \text{HCl}=24.5$$

The following notes are offered in explanation of Table VIII.

1. The molar concentration of the free base present is equal to the cc.'s *molar* base minus the cc.'s normal acid added, divided by the total number of cc.'s present; or that is, 45 plus the cc.'s acid added.

2. The degree of dissociation is equal to the hydroxyl ion concentration divided by the concentration of free base.

3. The concentration of undissociated base is equal to the concentration of the free base multiplied by one minus the dissociation constant.

4. The concentration of the $MOH^+$ ion is equal to the concentration of free base minus the concentration of the undissociated base plus the cc.'s normal acid added divided by the total number of cc.'s present.

5. The first dissociation constant, $K_1$, is then found as the product of the hydroxyl ion concentration and the concentration of the $MOH^+$ ion, divided by the concentration of the undissociated base, according to the Mass Law.

6. The concentration of the $M^{++}$ ion is directly proportional to the cc.'s of acid required for half neutralisation of the base.

7. The concentration of the $MOH^+$ ion is directly proportional to the cc.'s of acid required for complete neutralisation minus the cc.'s of acid added.

8. The second dissociation constant, $K_2$, is, of course, equal to the product of the hydroxyl ion concentration and the concentration of the $M^{++}$ ions divided by the concentration of the $MOH^-$ ions, and for

the latter two figures, the quantities to which they are proportional, as explained in Notes 6 and 7, may be substituted.

9. This calculation makes the assumption that the first amino group of the base is completely neutralized before neutralization of the second amino group has begun. This is a false assumption, but it is very approximate when the two dissociation constants are as far apart as they are in this compound.

## Derivatives

2,3 BUTYLENE DIAMINE DIHYDROCHLORIDE. The preparation of this compound has been given. It was purified by recrystallization from absolute ethyl alcohol. It was found to melt at 262-4° with decomposition, which is the identical value given by Stunek and Schweinsberg (30) for the racemic compound.

% Cl Calc.: 44.3 Found: 44.2; 44.2

2,3 BUTYLENE DIAMINE DIPICRATE. This compound was quickly precipitated when an alcoholic picric acid solution was added to an alcoholic solution of the diamine. It was recrystallized from alcohol and found to melt at 250-51° with decomposition, after darkening at 250°. Morgan and Hickinbottom (30) report darkening at 230° and the melting-point at 264-65°, while Stunek and Schweinsberg (66) give 250° for the melting-point of the racemic form.

2,3 BUTYLENE DIAMINE DIPICROLONATE. An alcoholic solution of picrolonic acid was added to an alcoholic solution of the diamine and

a precipitate of the diplatinate formed. This was recrystallized from alcohol and found to decompose at 285-290°. Strack and Schwanberg (66) give a melting-point with decomposition at 285-270°.

**2,3 BUTYLENE DIAMINE DIPHENYLISOCYANATE.** This derivative was prepared in anhydrous ether according to PrejЗа and Zahlen's (36) directions. It melted at 251.5-252°, as compared with their value of 250°.

**2,3 BUTYLENE DIAMINE DI-d-N-BROMOCAMPHER π SULPHONATE.** The preparation and properties of this compound are given in the next section.

## Optical Studies

### Resolution of 2,3 butylene diamine

As was previously mentioned, the resolution of the diamine was undertaken in order to prepare the optically active 2,3 butylene glycol from the optically active amine. In June, 1954, when this work had been practically completed, Strack and Schwanberg (66) reported the resolution by means of tartaric acid. However, they did not obtain the optical isomers in the pure state, but in solution, and their resolution with tartaric acid had to be supplemented by fractional crystallisation of the hydrochlorides of d-α-bromocampher π sulphonic acid was chosen as the resolving agent. Because it had been used successfully by Morgan and Holmbottom (49) in resolving substituted 2,3 butylene diamines and because of its obvious advantages over tartaric acid, as pointed out by Pope and Peachey (59).

d AMMONIUM $\alpha$-BROMOCAMPHOR $\pi$ SULPHONATE. d Camphor was brominated, and the d bromocamphor sulphonated by means of freshly distilled chlorosulphonic acid, according to the directions given by Kipping and Pope (28). The ammonium salt was isolated and recrystallised three times from water. It melts with decomposition and foaming at 169-90°. The specific rotation was $[\alpha]_D^{20} = +86.2°$ for a .35% solution in water as compared to the value of 84.78° given by Kipping and Pope.

d 2,3 BUTYLENE DIAMINE DI-d-$\alpha$-BROMOCAMPHOR $\pi$ SULPHONATE. The racemic butylene diamine was separated from the mixture with the meso form by the method given by Strack and Schwaneberg (66). d$\alpha$-Bromocamphor $\pi$ sulphonic acid was made from the ammonium salt following the directions given by Pope and Peachey (59). An approximately .8 N solution of the acid in water was titrated with standard sodium hydroxide and the required amount added to a weighed sample of the racemic diamine, also in water solution. The excess water was evaporated on a sandbath. The d-2,3 butylene diamine di-d-$\alpha$-bromocamphor $\pi$ sulphonate crystallised out of the concentrated solution on cooling. It was filtered off and recrystallised several times from water. The rotation of the purified compound finally remained constant at about $[\alpha]_D^{20} = +80.15°$. The yield was 57% of theory based on half the amount of the racemic diamine taken.

d 2,3 BUTYLENE DIAMINE. Solid potassium hydroxide was added to a water solution of 84.6 g. of the d 2,3 butylene diamine di-d$\alpha$-bromo-camphor $\pi$ sulphonate until the amine layer separated. The amine layer was separated and the aqueous layer extracted with three 20 cc. portions

of ether. The combined ether extract and amine was dried over potassium hydroxide for three days and then over metallic sodium for a week. The ether was distilled off and the residue distilled under diminished pressure. The yield was 8.2 g., or 78% of theory. The rotation was $[\alpha]_D^{25} = + 7.3°$. Strack and Schwaneberg (66) give $[\alpha]_D^{18} = + 4.8$ for a 5% aqueous solution of the amine.

d 2,3 BUTYLENE GLYCOL. The d diamine was dissolved in 100 cc. of water containing 15 cc. of concentrated hydrochloric acid. The flask containing the solution was packed in ice and 28.7 g. of silver nitrite added with constant stirring. The ice was removed and the mixture allowed to stand over night. A solution of 15 cc. of concentrated hydrochloric acid in 100 cc. of water was then added, followed by 25 g. of silver nitrite. The mixture was stirred vigorously and left at room temperature for 24 hours. The material was then heated to boiling, neutralized with barium hydroxide solution, and filtered. The filtrate was concentrated to 50 cc. and extracted continuously with ether for three days. The ether was distilled off and the residue distilled under reduced pressure. 3.7 g. of 2,3 butylene glycol, boiling 90-91° at 12.5 mm., was isolated; equivalent to a 44% yield. $\eta^{25}$ 1.439 $[d]_D^{25} = + 6.9°$, in comparison to Boeseken and Cohen's (5) value of + 5°.

Laevo-rotatory 2,3 BUTYLENE DICHLORIDE. The dextro-rotatory glycol was converted to the dichloride by the previously described method using thionyl chloride. 1.1 g., or 21% of theory, was obtained. $\eta^{25}$ 1.410. $[\alpha]_D^{25} = - 15.36°$.

Laevo 2,3 BUTYLENE DIAMINE. The combined filtrates from the crystal-

lization of the d 2,3 butylene diamine di-dα-bromocamphor π sulphonate,
which supposedly contained the dα-bromocamphor π sulphonate of the
laevo base, were concentrated to a thick syrup, but after a little more
of the dd salt had been separated all attempts to crystallize the residue
were fruitless, so potassium hydroxide solution and solid potassium
hydroxide were added until a dark brown layer of amine separated.  This
was removed by means of a medicine dropper and distilled.  As the
quantity obtained was hardly large enough to dehydrate, an approximately
10% aqueous solution was made up and titrated with standard hydrochloric
acid using methyl orange as the indicator.  The optical rotation ob-
served gave $[\alpha]_D^{25} = 5.0°$.

DISCUSSION

It has been mentioned before, that the semi-commercial production

of 2,3 butylene glycol has already begun. It is, however, on a very

small scale, and the price of the compound is high. It is safe to say

that the production of this compound will attain a scale as large as

that of ethylene glycol and, perhaps, as that of glycerol if the price

can be brought to the level of these competing compounds.

The problem to be met in the development of large industrial output

will be easily solved, for they are practically identical with those

already worked out for the biochemical synthesis of glycerol.

The maximum possible yields biochemically obtainable from raw

materials can best is estimated by determining the mechanism of the

fermentation reactions. In developing the scheme presented, the follow-

ing information was considered:

1. Calcium lactate is fermented to acetyl methyl carbinol (41).

2. Acetaldehyde is present during the fermentation (39).

3. Acetic acid is converted practically completely to acetyl

methyl carbinol when transfused to an ordinary alcoholic fermentation (54).

4. It has been confirmed that acetic acid is reduced before com-

fermentation takes place (38).

5. Harden and Norris (20) believe the carbon synthesis involved is

similar to the butyric fermentation of glycerol.

6. Acetaldehyde can be condensed to acetaldol and this reduced by

several methods, such as with aluminum or magnesium amalgams, or electro-

lytically, to yield 2,3 and 1,3 butylene glycols.(4)(7)(11)(12)(32)(31)(55).

7. When mixtures of ethyl alcohol and acetaldehyde or acetone are exposed to light under the proper conditions, 2,3 butylene glycol is formed, among other things (8)(9)(37).

8. Acetaldol, when fermented with an active yeast, produces a good yield of glycol. 15 g. acetaldol and 250 g. yeast form 17.8 g. glycol.(52).

9. Glycol can be oxidized to acetaldol by means of hydrogen peroxide and ferrous sulphate (52).

10. Lemoigne (37) believes <u>Bacillus subtilis</u> ferments sugar in two stages; namely, sugar to glycol, and glycol to acetyl methyl carbinol.

There are a few contradictory elements in the above evidence, but, as a whole, it seems to point to the following relations, which are somewhat the same as those proposed by Kluyver and Donker (33): (Fig. VIII)

The enol form of the acetaldehyde is shown so as to indicate the three possibilities for polymerization (5). It is quite generally accepted that the enol forms, though present in mere traces, are in equilibrium with the aldehydes and ketones and may be the mechanism of addition and polymerization of these bodies.

All of the substances shown, except the unstable compounds in brackets, are found in varying amounts in the fermentation beers. The hydrogen formed from the formic acid probably produces the reductions, only half of it being needed for the maximum yield of 2,3 butylene glycol. The empirical equation for this case would be:

FIGURE VIII

$$C_6 H_{12} O_6$$
(glucose)

$$2\ CH_3-CH-C-OH$$
$$OH\ O$$
(lactic acid)

$$2\ CH_3-C-H \quad + \quad 2\ HC-OH \qquad 2\ CO_2 + 2H_2$$
$$O \qquad\qquad\qquad O$$
(acetaldehyde) \qquad (formic acid)

$$2\ CH_3-CH_2\ OH \xleftarrow{+\ 2\ H_2}$$
(ethyl alcohol)

$$2\ CH_2 = C-H$$
$$OH$$
$$\left(\begin{array}{c}\text{enol form}\\ \text{acetaldehyde}\end{array}\right)$$

$$\left[H-C-CH_2-CH_2-CH_2\right]$$
$$O \qquad\qquad OH$$
$$\downarrow (O)$$

$$HO-C-CH_2-CH_2-C-OH$$
$$O \qquad\qquad\qquad O$$
$$\left(\begin{array}{c}\text{Succinic}\\ \text{acid}\end{array}\right)$$

$$\left[CH_2 = C-CH-CH_3\right]$$
$$HO\ OH$$
$$\begin{array}{c}\text{enol form}\\ \left(\text{acetyl methyl carbinol}\right)\end{array}$$
$$\downarrow [H_2]$$

$$CH_3-CH-CH-CH_3 \xrightleftharpoons[[H_2]]{[O]} CH_3-C-CH-CH_3$$
$$OH\ OH \qquad\qquad\qquad O\ OH$$
$$\left(\begin{array}{c}2,3\text{-butylene}\\ \text{glycol}\end{array}\right) \quad \left(\begin{array}{c}\text{acetyl methyl}\\ \text{carbinol}\end{array}\right)$$

$$\left[CH_3-CH-CH_2-C = O\right]$$
$$OH \qquad\qquad\qquad H$$
$$(\beta\text{-hydroxy butyaldehyde})$$
$$\downarrow$$

$$CH_3-C-CH_2-CH_2$$
$$OH \qquad OH$$
$$\left(\begin{array}{c}1,3\text{ butylene}\\ \text{glycol}\end{array}\right)$$

$$C_{12}H_{22}O_{11} \rightarrow C_6H_{12}O_6 + 2 CO_2 + H_2$$

whereby 100 g. of glucose would produce 50 g. of glycol, and 100 g. of sucrose would produce 52.6 g. grams of glycol. If this conclusion is correct it would mean that the maximum possible yields of 2,3 butylene glycol are 50% and 52.6% from glucose and sucrose respectively. Kendall (27) has already developed conditions and technique which give consistent yields of 45% to 49% from sucrose.

It seems to be Nature's scheme to have a suitable material for every need and purpose, even though it may take man centuries to find it, and, likewise, for every substance there probably is a service to which it is most suited. To say that a thing is worthless is merely to admit that s one has not yet been found for it.

The properties of the derivatives of 2,3 butylene glycol fall midway between those of the simple monohydric alcohols and glycerol. They are very similar to the properties of ethylene glycol, but exhibit a little more of a hydrocarbon nature. Many of the butylene glycol derivatives are excellent solvents and might find application in cases in which their specific properties such as boiling-point, volatility, and viscosity, would make them more desirable than similar derivatives of glycerol or ethylene glycol.

If the present day manifold uses of glycerol and ethylene glycol were combined, many instances undoubtedly would be found in which 2,3 butylene glycol would be superior, and many other cases in which the butylene glycol would be an admirable substitute if the price of glycerol

or ethylene glycol should get out of bounds, as was true during the
World War.

An excellent means, widely practiced, for differentiating between
synthetic and fermented wines and vinegars is analysis for 2,3 butylene
glycol, for it is always found to some extent in all alcoholic fer-
mentations (60)(61)(69)(78).

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