cance. The constitutional significance of the results obtained in this investigation is under consideration.

Experimental

Numerous variations of procedure were employed but the following is cited as typical. The electrolysis cell was constructed of 3-inch Pyrex piping.[1] The assembled, 3-compartment cell consisted of two 90° L's for ends, connected by a T. The 3 compartments were assembled with the usual gaskets and metal joint flanges, and with the compartments separated by a membrane of parchment paper. During reaction, the entire cell assembly was immersed in running water to control temperature and both anolyte and catholyte were stirred vigorously. The anode consisted of 99.9% pure lead sheet 6 × 70 × 100 mm. The cathode was a pool of mercury in a beaker 50-mm. in diameter. The distance from anode center to cathode center was about 52 cm.

Twenty grams of dry butanol lignin[2] from western hemlock (*Tsuga heterophylla* Sarg.) was dissolved in 1500 ml. of 1% sodium hydroxide solution. Half of this solution was placed in the anode compartment and half in the cathode compartment. The center compartment was filled to the same level with 1% sodium hydroxide solution.

An e. m. f. of 60 volts was applied which caused a passage of 3 amperes. As the current increased, a small amount of solution from the center compartment was withdrawn and replaced with water, maintaining the current approximately constant at 3 amperes. The center compartment served the important functions of controlling current, preventing undue heating, preventing foaming and providing a visual check on undesirable migration. The temperature of the electrolyte was 30 to 35°, and the time of electrolysis was forty-eight hours. Both anolyte and catholyte became straw-colored in this time, the latter more rapidly, and produced maximum yields of products.

Anolytes and catholytes were acidified and extracted with ether, the volume of each reduced under a 34-plate column, re-extracted, and rough yields determined. The aqueous solution of anolyte was then evaporated to dryness and the solids left were extracted with acetone. Eight or ten cycles of grinding the solids and re-extracting with acetone were necessary to recover all soluble material.

Anolyte–ether extracts from a number of identical electrolyses were combined and fractioned directly (without bicarbonate extraction, etc.) in efficient columns of small size of the helices and twisted-screen types. Low pressure distillation was employed on fractions not sufficiently volatile to ascend the columns. Molecular distillation was used on the fractions of lowest volatility. A pressure of 10^{-6} mm. of mercury at the distilling gap was established by means of a three-stage, four-compartment oil diffusion pump using Octoil-S. Anolyte–acetone extracts were treated separately and similarly.

Identification of Products

1. **Ethyl Methyl Ketone.**—The 2,4-dinitrophenylhydrazone melted at 113.1° and the semicarbazone at 134.3°.

2. **Acetone.**—The 2,4-dinitrophenylhydrazone melted at 126° and the *p*-nitrophenylhydrazone at 147.2°.

3. **Acetic Acid.**—The *p*-nitrobenzyl ester melted at 75–76° and the *p*-phenylphenacyl ester at 109.5°.

4. **β-Resorcylic Acid.**—The *p*-nitrobenzyl ester melted at 187–188°. When methylated with dimethyl sulfate and alkali and purified, yielded acid, m. p. 106.0–106.3° (2,4-dimethoxybenzoic acid, m. p. 108°).

5. **Protocatechuic Acid.**—The *p*-nitrobenzyl ester melted at 186°, the amide at 209–210° and the anilide at 164°.

6. ***p*-Hydroxybenzoic Acid.**—The *p*-nitrobenzyl ester melted at 180–181° and the *p*-phenylphenacyl ester at 238.5°.

7. ***m*-Toluic Acid.**—The S-benzylthiuronium ester melted at 162.6° and the *p*-bromophenacyl ester at 107°.

8. **Oxalic Acid.**—Sublimed below 100°, the *p*-phenylphenacyl ester melted at 164° and the S-benzylthiuronium ester at 192–193°.

9. **Isobutyl Methyl Ketone.**—The semicarbazone melted at 130.0–130.5° and the 2,4-dinitrophenylhydrazone at 131°.

Summary

Lignin was electrolytically oxidized and reduced. Oxidation products were obtained in good yield and identified as ketones and acids.

Seattle 5, Washington Received September 24, 1945

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[1] Corning Glass Works, Pyrex Brand Piping and Heat Exchangers, Bulletin 814, Corning, N. Y., 1940.

[2] A. Bailey, *Paper Trade J.*, **111**, 63–6 (1940); *Tech. Assoc. Papers*, **24**, 603–11 (1941), entitled "Preparation and Properties of Butanol Lignin."

[Contribution from The Miner Laboratories]

Diglycerol by a New Ether Synthesis[1]

By H. J. Wright[2] and R. N. Du Puis

Diglycerol has been prepared by a new series of reactions between glycerol, calcium hydroxide or calcium oxide, and carbon dioxide. The course of these reactions, which may be carried out to yield diglycerol with substantial absence of higher polyglycerols, has not been definitely established. Theories concerning the mechanism of the reactions have been devised from experimental data and are presented in the following discussion.

The reactions between an alcohol, calcium oxide or calcium hydroxide, and carbon dioxide to yield the ether of the alcohol have never been reported in the literature so far as we are aware. It was thought, therefore, that although such a reaction has been applied only to glycerol in the Laboratory and the data are admittedly incomplete, publication of the procedures used and results obtained might be of interest to workers in related fields.

Reactions between glycerol and calcium hydroxide to form calcium glyceroxides have been studied previously.[3,4] Briefly, it has been found that heating calcium oxide or calcium hydroxide with glycerol results in formation of calcium monoglyceroxide, I, $Ca[C_3H_5(OH)O_2]$ or calcium diglyceroxide, II, $Ca[C_3H_5(OH)_2O]_2$ and water.

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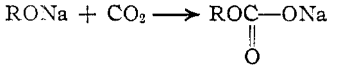
[1] This research was sponsored by the Association of American Soap and Glycerine Producers, Inc.

[2] Present address: 700 Desnoyer Street, Kaukauna, Wisconsin.

[3] Grün and Bockisch, *Ber.*, **41**, 3476 (1908).

[4] Wheeler, *Chem. News*, **142**, 241–243 (1931).

It was also found that the type of glyceroxide obtained could be controlled by the temperature used during the reaction. Below 120°, the diglyceroxide is formed and above 120°, the monoglyceroxide is the main product. Another literature reference[5] has indicated that sodium alcoholates will add carbon dioxide under anhydrous conditions in the following fashion



$$\mathrm{RONa} + \mathrm{CO_2} \longrightarrow \mathrm{RO}\underset{\underset{\displaystyle \mathrm{O}}{\|}}{\mathrm{C}}\mathrm{{-}ONa}$$

We have found that if calcium glyceroxides are treated with carbon dioxide under anhydrous conditions and then heated at elevated temperatures, calcium carbonate and diglycerol will be formed.

Experimental

Preparation of Diglycerol.—Thirty-four parts of calcium oxide was heated with 400 parts of glycerol under water-pump vacuum at 140° until the water from the reaction had been removed. Carbon dioxide was passed into this mixture at 140° until approximately one mole of carbon dioxide had been absorbed for every mole of calcium present. The reaction mixture was heated to 200°, at which temperature the whole mixture solidified for a short period and then liquefied again. The mixture was diluted with water and filtered to remove calcium carbonate. Any remaining calcium salts were removed from the filtrate by treatment with ammonium carbonate. The filtrate was concentrated and distilled. Glycerol (287 parts) was obtained at 140° (3 mm.) and diglycerol (59 parts) distilled at 225° (3 mm.). The residue amounted to less than 1% of the weight of distilled products. The diglycerol thus obtained had the constants: $n^{20}\mathrm{D}$ 1.4890, $d^{20}{}_{20}$ 1.2774. Estimation of the diglycerol content of the above fraction by the acetin process showed it to contain 95.8% diglycerol.

The acetates of mixtures containing glycerol and polyglycerols may be fractionated to yield pure fractions of the individual components, whereas purification of diglycerol itself by fractionation is difficult. Hence, this method was used regularly in determining the purity of our diglycerol samples. Diglycerol tetraacetate, b. p. 179° (2 mm.), has $n^{20}\mathrm{D}$ 1.4440. The saponification number of the sample from which the above constants were obtained was 671.9. The theoretical saponification number of diglycerol tetraacetate is 671.9.

Discussion

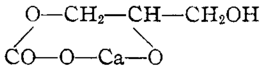
Polyglycerols have been made by heating glycerol above 200° with an alkaline material until a desired degree of polymerization has been obtained as indicated by refractive index or amount of water removed. In order to prove that diglycerol was not being formed in the calcium hydroxide:glycerol:carbon dioxide reaction solely as a result of alkali being present, we have heated glycerol with calcium hydroxide at 200° and with calcium carbonate at 250° for periods of time in excess of those used in the diglycerol procedure. No polyglycerols resulted from the heating of glycerol and calcium hydroxide, and about 5% of the glycerol heated with calcium carbonate was polymerized to polyglycerols. The temperature in the latter experiment was higher than was used in our reaction. From these experiments it may be inferred that the new reaction which results in diglycerol is not due solely to the effect of alkali on glycerol.

The amount of carbon dioxide absorbed during the course of the reaction was studied. It was found that the maximum amount of carbon dioxide absorbed was 1.84 moles per atom of calcium and the average was of the order of one mole. The average amount of carbon dioxide retained as calcium carbonate after heating to 200° was about 0.8 mole. If the carbon dioxide absorption was below 0.8 mole, the yield of diglycerol dropped accordingly.

Excess glycerol served not only to keep the reaction mixture fluid, but also to suppress the formation of polyglycerols higher than diglycerol. Thus the amount of undistillable product in a reaction mixture varied as follows: 34 parts calcium oxide to 200 parts glycerol gave a mixture containing 5.1% undistillable material; 34 parts calcium oxide to 300 parts glycerol gave a mixture containing 3.2% undistillable; and 34 parts calcium oxide to 400 parts glycerol gave a mixture containing 1% undistillable.

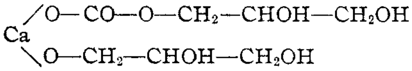
Theoretical yields of diglycerol were calculated on the assumption that one mole of calcium oxide or calcium hydroxide would yield one mole of diglycerol. Thus the theoretical yields in these experiments averaged about 50%. The physical yields based on the amount of glycerol used averaged 15% for the reaction ratio: 34 parts calcium oxide to 400 parts glycerol.

The mechanism of the reaction would, of course, depend on which calcium salt is used and what rearrangements take place, but the following are possibilities. Calcium mono- or diglyceroxide might react with carbon dioxide to form carbonates which might be interconvertible, depending on whether or not there was free glycerol present. For example, a calcium monoglyceroxide carbonate



III

might give a diglyceroxide carbonate such as



IV

in the presence of excess glycerol. On further heating III might lose calcium carbonate with the formation of an unstable intermediate such as glycidol or a free radical which would react with the glycerol present to give diglycerol. Compound IV might conceivably lose calcium carbonate on heating to give diglycerol directly.

If glycidol or a free radical is an intermediate in the reaction, they could presumably react with diglycerol with the result that the amount of undistillable residue would be increased. Since it was found that the amount of residue could be decreased by using excess glycerol, the glycidol or free radical mechanism might be preferred.

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[5] Whitmore, "Organic Chemistry," D. Van Nostrand Co., New York, N. Y., 1937, p. 516.

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Summary

Diglycerol has been prepared by a new series of reactions involving treatment of glycerol with calcium oxide or calcium hydroxide and carbon dioxide.

Some possible mechanisms of the reaction are suggested and experimental procedures and results obtained are reported.

CHICAGO 6, ILLINOIS RECEIVED SEPTEMBER 19, 1945

[CONTRIBUTION FROM THE COLLEGE OF PHARMACY OF THE UNIVERSITY OF MINNESOTA]

4-Thio and 2,4-Dithio 5,5-Dialkylthiobarbituric Acids

BY JAMES H. BOOTHE[1] AND CHARLES O. WILSON

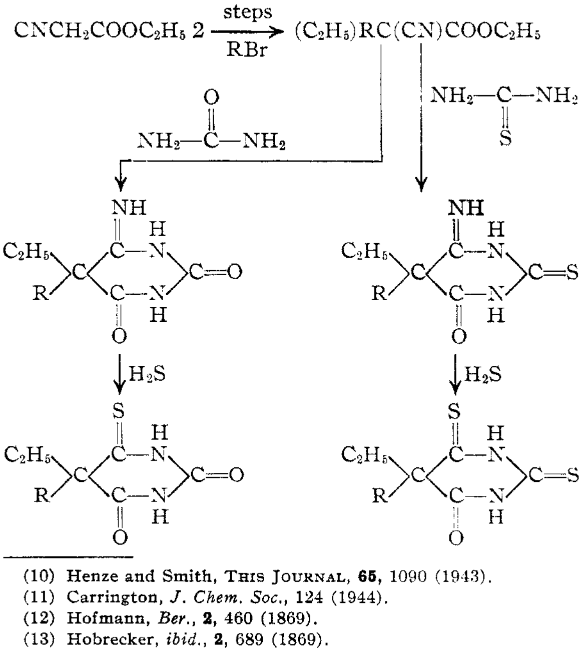
Early in the history of barbituric acid synthesis, a few 2-thiobarbiturates were prepared for the purpose of converting them into the corresponding oxygen analogs. In fact, Fischer and Dilthey[2] reported the preparation of 5,5-diethyl-2-thiobarbituric acid in their original paper in 1904. Until 1935, however, no systematic attempt was made to prepare a series of these compounds and evaluate them pharmacologically. This was probably due to the fact that Fischer and Mering[3] reported that the administration of 120 mg. per kg. of the sulfur analog of barbital to a dog produced a deep sleep, followed by death. This fact was interpreted by Fraenkel[4] as conclusive evidence that sulfur imparted a pronounced toxic character to barbital. Dox and Hjort[5] also reported in 1927 that this compound caused tremors during anesthesia as well as preanesthetic excitement and cyanosis.

In spite of these adverse indications of the toxicity of the thiobarbiturates, two separate groups of workers, namely, Volwiler and Tabern[6] and Miller, Munch and Crossley[7,8] in 1935, reported independently systematic studies of the preparation and pharmacological properties of a number of 2-thiobarbiturates. They found that these compounds had, in general, a rapid onset of action and were destroyed much more rapidly in the body than were their oxygen analogs. Because of these properties, the 2-thiobarbiturates are proving very successful as intravenous anesthetics.

Until recently, no substituted barbituric acids in which more than one of the oxygen atoms were replaced by sulfur were known, although the preparation of 2,4,6-trithiobarbituric acid by the action of potassium hydrosulfide on 2,4,6-trichloropyrimidine had been described.[9] During the course of this study, there appeared a paper by Henze and Smith[10] dealing with polythiobarbiturates in which was reported the preparation of 5,5-diethyl-2,4,6-trithiobarbiturate and 5-phenyl-5 ethyl-2,4,6-trithiobarbiturate. It was stated that these possessed no hypnotic properties. Carrington[11] has prepared the 2-thio, 2,4-dithio and 2,4,6-trithio derivatives of a series of barbiturates. He used those barbiturates that are well-known hypnotics, but reported no pharmacological data.

In view of the fact that no synthesis of 4-thiobarbiturates has been reported in the literature and that the 2,4-dithiobarbiturates reported by Carrington have not been tested pharmacologically, and since such thio compounds might exhibit interesting physiological activity, it was decided to synthesize, if possible, several typical examples of these thio compounds.

Several workers[12–16] have replaced an imino



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[1] Lederle Laboratories, Inc., Research fellow, 1942–1943. Present address. Lederle Laboratories, Inc., Pearl River, New York.

[2] Fischer and Dilthey, *Ann.*, **335**, 334 (1904).

[3] Fischer and Mering, *Therap. Gegen.*, **101**, 97 (1903).

[4] Fraenkel, "Die Arzneimittel Synthese," 6th ed., 1927, p. 510.

[5] Dox and Hjort, *J. Pharmacol.*, **31**, 455 (1927).

[6] Volwiler and Tabern, THIS JOURNAL, **57**, 1961 (1935).

[7] Miller, Munch and Crossley, *ibid.*, **58**, 1090 (1936).

[8] Miller, Munch and Crossley, *Science*, **81**, 615 (1935).

[9] Büttner, *Ber.*, **36**, 2234 (1903).

[10] Henze and Smith, THIS JOURNAL, **65**, 1090 (1943).

[11] Carrington, *J. Chem. Soc.*, 124 (1944).

[12] Hofmann, *Ber.*, **2**, 460 (1869).

[13] Hobrecker, *ibid.*, **2**, 689 (1869).

[14] Bernthsen, *ibid.*, **10**, 1240, 38 (1877).

[15] Matsui, *Mem. Coll. Sci. Eng. Kyoto Imp. Univ.*, **1**, 285 (1908).

[16] Delépine, *Comp. rend.*, **153**, 281 (1911).