from cornstalks by 30% aqueous morpholine-ethanol and in the sulfuric acid lignin digested with a 30% aqueous solution of this base.

The nitrogen content of the isolated lignins (1.97–3.12%) was not significantly greater than that reported by Walde and Hixon[6] as due to contamination in oat hull lignins. These investigators[6] found that caustic alkali lignin contained 1.9% nitrogen and ammonia lignin analyzed 3.04% nitrogen. The increased nitrogen content of sulfuric acid lignin digested with the aqueous bases cannot be due to protein contamination, nor can it be entirely due to a fractionation of contaminating protein material. From these facts it must be concluded that the organic nitrogen bases form nitrogenous compounds with lignin.

(6) Walde and Hixon, THIS JOURNAL, **56**, 2656 (1934).

Summary

1. The action of a series of commercially available organic nitrogen bases on lignin has been studied; cornstalk tissues and isolated lignin (72% sulfuric acid) were used as substrates.

2. It appears that the amount of lignin extracted depends upon the basic strength of the extracting liquors for both the aqueous and anhydrous nitrogen bases. This does not preclude the possibility that anhydrous bases may remove lignin by organic solvent action.

3. Evidence indicating that the aqueous bases form nitrogenous compounds with lignin is presented.

AMES, IOWA RECEIVED JANUARY 13, 1941

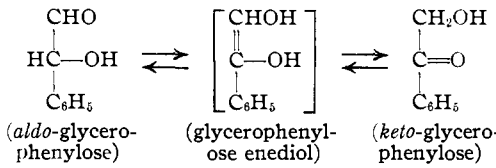
[CONTRIBUTION FROM THE CHEMICAL LABORATORY OF THE OHIO STATE UNIVERSITY]

The Preparation of Glycerophenylose Enedioldiacetate*

BY WM. G. DAUBEN, WM. LLOYD EVANS AND ROBERT I. MELTZER

Many of the results obtained in a study of the chemical behavior of reducing sugars in alkaline solutions have been best understood by assuming as the first step in reaction the intermediate formation of the aldehydo[1] structure which is then converted into a series of enediols. The existence of these enediols was postulated by Fischer, Wohl and Neuberg, and Nef, but their synthesis has not been hitherto achieved.[2] Ascorbic acid, dihydroxymaleic acid and the Redukton of Euler and Martius are some of the well known examples of compounds which contain the enediolic functional group, $\left[\text{HO—C=C—OH}\right]$.

The following experiments deal with the first synthesis of a sugar enediol derivative. Benzoylcarbinol (C_6H_5-CO-CH_2OH) is related to mandelic aldehyde (C_6H_5-CHOH-CHO) as a ketose is to an aldose, respectively. Adapting the nomenclature suggested by Votoček[3] for the methyloses, mandelic aldehyde may be designated as *aldo*-glycerophenylose and benzoylcarbinol as *keto*-glycerophenylose. These two phenyloses should give the same enediol, *i. e.*, glycerophenylose enediol



(*aldo*-glycerophenylose) (glycerophenylose enediol) (*keto*-glycerophenylose)

The experiments of Gomberg, Fuson, Thompson, and Barnes and Tulane[4] suggest methods of approach to the synthesis of the sugar enediols.

The diacetate of glycerophenylose enediol (I) was prepared by the techniques of Barnes and Tulane, through refluxing a mixture of ω-bromoacetophenone, freshly fused potassium acetate and acetic anhydride for three hours. This compound reacted as expected of the enediol as shown by the following: (a) on partial deacetylation with potassium acetate and glacial acetic acid, the reaction mixture yielded keto-glycerophenylose monoacetate (II) (m. p. 49°)[5]; (b) when completely hydrolyzed with water in the presence of $CaCO_3$, keto-glycerophenylose (III) (m. p. 86.5°)

* Presented at the Meeting of the American Chemical Society, St. Louis, Missouri, April 10, 1941.

(1) (a) M. L. Wolfrom, THIS JOURNAL, **51**, 2188 (1929); (b) M. L. Wolfrom, *ibid.*, **52**, 2464 (1930).

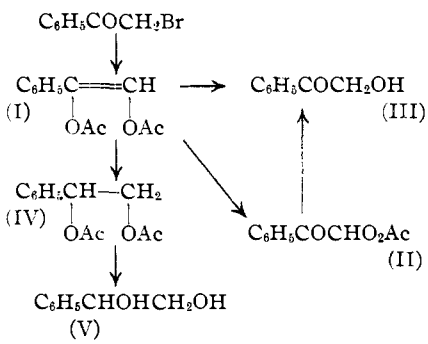
(2) (a) E. Fischer, *Ber.*, **28**, 1149 (1895). (b) Wohl and Neuberg, *ibid.*, **33**, 3099 (1900). (c) Nef, *Ann.*, **335**, 191 (1904).

(3) E. Votoček, *Bull. Soc. Chim.*, [4] **43**, 1 (1928).

(4) (a) M. Gomberg and W. E. Bachmann, THIS JOURNAL, **49**, 236 (1927); (b) R. C. Fuson and J. Corse, *ibid.*, **61**, 975 (1939); (c) R. B. Thompson, *ibid.*, **61**, 1281 (1939); (d) R. P. Barnes and V. S. Tulane, *ibid.*, **62**, 894 (1940).

(5) (a) Th. Zincke, *Ann.*, **216**, 306 (1883); (b) ref. 4d; (c) R. P. Barnes and V. J. Tulane, THIS JOURNAL, **63** 867 (1941).

was obtained[6]; (c) when hydrogenated in the presence of the catalyst of Adams, Voorhees and Shriner, phenyl glycol diacetate (IV) (b. p. 152–153°, 15 mm.) was obtained[7]; (d) on hydrolysis of the reduced enediol with potassium carbonate solution, phenyl glycol (V) (m. p. 67°) was obtained, identical in every respect with that prepared by Evans and Morgan[8] from styrene through the dibromide and diacetate; (e) furthermore, this enediol diacetate reacted with cupric hydroxide in the presence of sodium hydroxide solution in the same manner as this reagent reacts on benzoylcarbinol to give *r*-mandelic acid.[9]



Further work is now in progress in this Laboratory on the preparation of the sugar enediols.

Experimental Part

Preparation of ω-Bromoacetophenone.[10]—One hundred grams of acetophenone was dissolved in 500 cc. of ethyl ether and the solution cooled to ice temperature. With vigorous stirring, 133.5 g. of bromine was added in the course of five minutes. To catalyze this bromination, a small amount of acetophenone and ethyl ether were mixed in a test-tube to which a few drops of bromine were added. This solution was heated gently until the color of bromine had disappeared. The contents of the test-tube were then added to the bromination mixture. After the color of bromine had disappeared the reaction mixture was poured into a large volume of mechanically stirred ice water. The ether solution was then separated, washed well with water and dried over anhydrous sodium sulfate, after which the solvent was removed *in vacuo*. The sirup was crystallized as white needles from absolute ethanol; yield, 132 g. (79.7%); m. p. 50°. This compound possessed strong lachrymatory properties.

Preparation of Glycerophenylose Enedioldiacetate.—Certain modifications of the general method of preparation of Barnes and Tulane were used in this experiment. Bromoacetophenone (60 g.) and freshly fused potassium acetate (50 g.) were dissolved in 450 cc. of acetic anhydride in a one-liter three-necked round-bottom flask equipped with a mechanical, mercury-sealed stirrer and a reflux condenser. After refluxing the mixture in an oil-bath for three hours, it was allowed to stand for forty-eight hours at room temperature, at which time it was poured into mechanically stirred ice water. After the excess of acetic anhydride was hydrolyzed, the brown oil at the bottom of the flask was extracted with chloroform and then dried over anhydrous sodium sulfate. Upon distillation of the chloroform *in vacuo*, a brown oil was left which had none of the lachrymatory characteristics of the ω-bromacetophenone. When this oil was distilled under reduced pressure it yielded a colorless, clear sirup, b. p. 118–120° at 2 mm. (yield 43 g., 64.9%). In the presence of aqueous sodium hydroxide and pyridine, the sirup decolorized Na-2,6-dichlorobenzenone-indophenol and had an index of refraction n^{25} 1.5297.

Anal. Calcd. for $C_{12}H_{12}O_4$: C, 65.5; H, 5.45. Found: C, 64.48, 64.97; H, 5.31, 5.22. *Acetyl value.* (a) By hydrolysis with 0.1 *N* NaOH for three hours.[11] Calcd. for $2(CH_3CO)$: 9.11 cc. of 0.1 *N* NaOH per 100 mg. of sample. Found: 9.11 and 9.15 cc. (b) By hydrolysis with *p*-toluene sulfonic acid[12]: Calcd. for $2(CH_3CO)$: 0.1562 g. acetyl per 0.4017 g. of sample. Found: 0.1496 g. *Mol. wt.* Calcd. for $C_{12}H_{12}O_4$: 220. Found: (cryoscopic in benzene), 212 and 207.

Conversion of Glycerophenylose Enedioldiacetate to Phenyl Glycol Diacetate.—The enediol diacetate (4.147 g.) was dissolved in 50 cc. of anhydrous, thiophene-free benzene. To this solution was added 0.202 g. of the catalyst of Adams, Voorhees and Shriner (PtO_2).[13] The mixture was then agitated mechanically by a device similar to that described by those investigators. The hydrogen entered the reaction flask at just slightly above atmospheric pressure. At the end of three hours, a constant volume of hydrogen had been absorbed. Deducting the volume of hydrogen used to reduce the catalyst, approximately 440 cc. of hydrogen should have been taken up if only one double bond was present; actually 435 cc. was absorbed. Therefore, it was concluded that only one double bond was present in our product.

After the mixture was filtered and the solvent removed *in vacuo*, a clear, colorless sirup with a pleasant odor remained while the enediol diacetate seemed to be odorless. The product distilled at 152–153° at 15 mm., had n^{25} 1.5125 and showed a negative test with the indophenol indicator. As shown by the index of refraction and boiling point, the product was identical in every respect with the phenyl glycol diacetate prepared from styrene by Evans and Morgan.[8] Also as shown by mixed melting point determination, the product on deacetylation yielded the same glycol.

As a further confirmation of the character of the glycerophenylose enedioldiacetate, the following experiments were carried out.

(a) **Conversion to *keto*-Glycerophenylose Monoacetate.**—Barnes and Tulane have shown that enediol diacetates when refluxed[4d, 5c] with acetic acid and potassium

(6) (a) C. Graebe, *Ber.*, **4**, 34 (1871); (b) W. L. Evans and C. R. Parkinson, THIS JOURNAL, **35**, 1770 (1913).

(7) Th. Zincke, *Ann.*, **216**, 295 (1883).

(8) W. L. Evans and L. H. Morgan, THIS JOURNAL, **35**, 54 (1913).

(9) W. L. Evans, *Am. Chem. J.*, **35**, 125 (1906).

(10) F. Kröhnke and H. Timmler, *Ber.*, **69B**, 614 (1936).

(11) A. Kunz and C. S. Hudson, THIS JOURNAL, **48**, 1978 (1926).

(12) K. Freudenberg, *Ann.*, **433**, 230 (1923); **494**, 68 (1932).

(13) "Organic Syntheses," Vol. VIII, 1928, p. 92–98.

acetate undergo a partial deacetylation and a characteristic rearrangement. With these facts in mind, glycerophenylose enedioldiacetate was treated in the following way: a solution of 2 g. (0.0091 mole) of enedioldiacetate, 1 g. (0.0102 mole) of freshly fused potassium acetate and 10 cc. of acetic acid were refluxed for thirty minutes. Upon pouring the mixture into ice water a brown oil separated. The oil was dissolved in ether, decolorized with carboraffin, dried over anhydrous sodium sulfate and the solvent removed with a stream of dry air. The sirup was then dissolved in warm ligroin from which crystals appeared upon cooling; m. p. 49°, yield 0.26 g. (16%).

(b) **Conversion to *keto*-Glycerophenylose.**—Evans and Parkinson have shown that *aldo*-glycerophenylose, a possible rearrangement product of the free enediol, is unstable[6b] in aqueous solution and rearranges to *keto*-glycerophenylose. Thus, the reaction product of the deacetylation of this enediol diacetate should be *keto*-glycerophenylose, as borne out by the following experiment. To a mixture of 5 g. of calcium carbonate in 25 cc. of water was added 1 g. (0.0045 mole) of pure glycerophenylose enedioldiacetate. The reaction mixture was refluxed for four hours under a reverse condenser and filtered while hot. The precipitate was washed well with acetone and ethanol. The filtrate was extracted with ether, dried over anhydrous sodium sulfate and high-boiling petroleum ether was then added to turbidity. Upon standing in the ice chest a short time, bold, plate-like crystals of *keto*-glycerophenylose formed, m. p. 86.5°, yield 0.17 g. (27.5%).

(c) **Glycerophenylose Enedioldiacetate, Copper Sulfate and Sodium Hydroxide.**—To a mixture of 1.62 g. (0.0074 mole) of the diacetate and 3.62 g. (0.0227 mole) of copper sulfate in 80 cc. of water was added 1.60 g. of sodium hydroxide in 5 cc. of water. The solution turned yellow almost immediately. The mixture was then heated for fifteen minutes on a steam-bath, filtered and filtrate evaporated to dryness at 100° under reduced pressure.[9] A few cc. of dilute hydrochloric acid was added and the solution extracted with ethyl ether. Upon addition of petroleum ether, white crystals formed. These crystals melted at 118.5° and with an authentic sample of *r*-mandelic acid no depression was noticed, yield 0.90 g.

Summary

1. Glycerophenylose enedioldiacetate has been prepared from ω-bromoacetophenone with acetic anhydride and potassium acetate.

2. The structure of this enediol has been proved by its hydrogenation to phenyl glycol diacetate and the conversion of this diacetate to phenyl glycol which was in turn shown to be identical with phenyl glycol prepared by an independent method.

3. The enedioldiacetate on deacetylation, partial and complete, rearranges to *keto*-glycerophenylose monoacetate and *keto*-glycerophenylose, respectively.

4. The enedioldiacetate in sodium hydroxide solution is oxidized to mandelic acid with cupric hydroxide, a reaction similar to that of *keto*-glycerophenylose with the same reagent.

COLUMBUS, OHIO RECEIVED APRIL 14, 1941

[CONTRIBUTION FROM THE VENABLE CHEMICAL LABORATORY OF THE UNIVERSITY OF NORTH CAROLINA]

Sulfur Studies. XVII. The Synthesis of Sulfathiophene, 2-Sulfanilamidothiophene

BY R. W. BOST AND CHAS. F. STARNES[1]

Due to the extensive interest shown in sulfanilamide compounds and more particularly in sulfapyridine, sulfathiazole and sulfaguanidine, it seemed desirable to prepare and investigate the properties of their isolog, sulfathiophene. It was felt that sulfathiophene might offer certain therapeutic advantages over the aforementioned compounds or perhaps might even have a specificity for certain organisms which previous compounds have not hitherto shown.

In this paper are described the synthesis and physical properties of 2-sulfanilamidothiophene. Tests of the pharmacological properties have been carried out by the Wm. S. Merrell Company, through the courtesy of Dr. Robert S. Shelton, and will be reported elsewhere.

(1) Present address, Dow Chemical Company, Midland, Michigan.

Considerable difficulty was encountered at first in obtaining good yields in the synthesis of 2-sulfanilamidothiophene. The low yields in the preparation of this compound were largely due to improper decomposition of the stannic chloride salt of thiophenine hydrochloride. The decomposition of this salt was best accomplished by slow addition of alkali to the aqueous solution, under ether, while being stirred in a nitrogen atmosphere. The ether solution was then added to a slurry of *p*-acetamidobenzene sulfonyl chloride in ether, in the presence of pyridine, and allowed to stand ten to fourteen hours under nitrogen. Due to the amphoteric nature of 2-sulfanilamidothiophene, some difficulty was also experienced in the isolation of the compound after hydrolysis. Only small amounts of the compound