2. Neither ketones nor ketone chlorides could be condensed with the *o*-aminophenyl mercaptan under the conditions of our experiments.

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[CONTRIBUTION FROM THE FELLOWSHIP OF RESEARCH IN PURE CHEMISTRY, MELLON INSTITUTE OF INDUSTRIAL RESEARCH, AND COLLEGE OF PHARMACY, UNIVERSITY OF PITTSBURGH]

THE SYNTHESIS OF 5-β-HYDROXYETHYL-BARBITURIC ACID AND ITS ALKYL DERIVATIVES

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Continuing the study of the effect of the introduction of an hydroxyl group on the toxicity and pharmacological action of medicinal substances[1] a number of β-hydroxyethyl derivatives of barbituric acid have been synthesized.

The parent substance, 5-β-hydroxyethyl-barbituric acid, has been prepared by Johnson and Shepard[2] by hydrolysis of 5-β-phthalimidobarbituric acid with concd. hydrochloric acid. So far as the authors are aware, no other members of this series are known.

The synthesis of these substances was first undertaken by the senior author in conjunction with Dr. Ivan P. Lambrette.[3] Sodium diethylmalonate was converted into β-hydroxyethyl-diethyl malonate by a reaction with ethylene oxide.[4] This substance was condensed with urea and with thio-urea in the presence of sodium ethylate. In this manner 5-β-hydroxyethyl-barbituric acid and 2-thio-5-β-hydroxyethyl-barbituric acid, described below, were prepared. Owing to decomposition on distillation, it was impossible to obtain hydroxyethyl-malonic ester and its alkyl derivatives of sufficient purity for our work. Furthermore, the yield of product obtained on condensation with urea was low. Because of these difficulties, this method was abandoned in favor of a procedure mentioned in a previous paper from this Laboratory.[5]

It has been found that β-chloro-ethyl-vinyl ether readily reacts with sodium diethylmalonate and mono-alkyl substituted malonic esters to form diethyl-vinyloxyethyl-malonate and its corresponding alkyl-substitution products. These esters are stable and can be purified by distillation. They condense smoothly with urea and with thio-urea, forming 5-vinyloxyethyl-barbituric acids; these compounds, on treatment with dilute

[1] (a) Cretcher and Pittenger, THIS JOURNAL, **46**, 1504 (1924); (b) **47**, 2560 (1925).

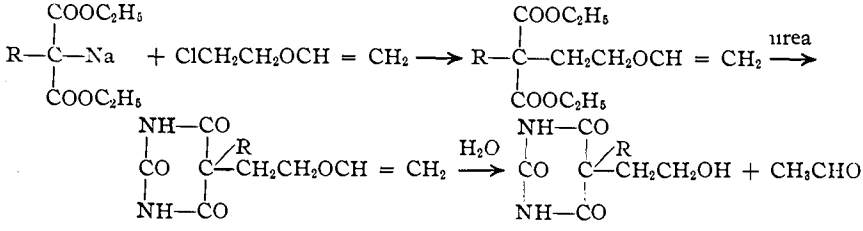
[2] Johnson and Shepard, THIS JOURNAL, **35**, 1003 (1913).

[3] Belgian American Foundation Student, whose untimely death occurred in Brussels, Belgium, in 1924.

[4] Traube and Lehmann, *Ber.*, **32**, 720 (1899).

[5] Cretcher, Koch and Pittenger, THIS JOURNAL, **47**, 1176 (1925).

mineral acid, form acetaldehyde and the product desired. The following scheme will illustrate the process.



Experimental Part

Preparation and Properties of the Esters.—Mono-ethyl, propyl, and butyl derivatives of ethyl malonate were prepared in the usual manner. The sodium salts of these esters were formed by addition of sodium ethylate, in alcohol solution, and boiled with an excess of β-chloro-ethyl-vinyl ether until neutral. About 36 hours was required to complete the reaction. The salt was then removed by filtration and the product distilled under reduced pressure. The yields averaged between 40 and 50%.

TABLE I

ESTERS PREPARED

Diethyl malonate	Formula	B. p., °C.	Pressure, Mm.	d_{15}^{15}	Analyses—Calcd. C, %	Calcd. H, %	Found C, %	Found H, %
Ethyl-vinyloxyethyl	$C_{13}H_{22}O_5$	151	18	1.0264	60.46	8.52	60.71	8.42
Propyl-vinyloxyethyl	$C_{14}H_{24}O_5$	157	17	1.0145	61.79	8.83	62.16	8.83
Butyl-vinyloxyethyl	$C_{15}H_{26}O_5$	165	17	0.9992	62.93	9.15	62.59	9.15
bis(Vinyloxyethyl)	$C_{15}H_{24}O_6$	133	3	1.0566	60.00	8.00	59.60	8.09

Preparation and Properties of the Barbituric Acids.—The details of the preparation of ethyl-vinyloxyethyl- and ethyl-β-hydroxyethyl-barbituric acids will illustrate the general method developed for the synthesis of this class of compounds.

Four g. of sodium was dissolved in 60 cc. of absolute alcohol and while yet hot the solution was poured into a boiling solution of 6 g. of urea in 20 g. of ethyl-vinyloxyethyl-diethylmalonate and 50 cc. of alcohol. This mixture was heated on a water-bath for five hours. It was then transferred to an autoclave and heated for two hours at 120°. The alcohol was then removed by evaporation, the product dissolved in 50 cc. of water and

TABLE II

BARBITURIC ACIDS PREPARED

Barbituric acid	Formula	M. p., °C. (corr.)	N, % Calcd.	N, % Found
2-Thio-5(ethyl-vinyloxyethyl)	$C_{10}H_{14}O_3N_2S$	136	11.57	11.71
5(Ethyl-vinyloxyethyl)	$C_{10}H_{14}O_4N_2$	158	12.38	12.65
5(Butyl-vinyloxyethyl)	$C_{12}H_{18}O_4N_2$	141	11.02	11.44
2-Thio-5-hydroxyethyl	$C_6H_8O_3N_2S$	181[a]	14.89	14.86
5-Hydroxyethyl	$C_6H_8O_2N_2$	above 300	16.27	16.19
5(Ethyl-hydroxyethyl)	$C_8H_{12}O_4N_2$	176	14.00	14.26
2-Thio-5(ethyl-hydroxyethyl)	$C_8H_{12}O_3N_2S$	143–145	12.96	13.14
5(Propyl-hydroxyethyl)	$C_9H_{14}O_4N_2$	168	13.08	13.04
5(Butyl-hydroxyethyl)	$C_{10}H_{16}O_4N_2$	147	12.28	12.06

[a] Decomposes.

the solution filtered. The filtrate was cooled to 0° and very carefully neutralized with cold hydrochloric acid. The crystalline material so obtained was rapidly filtered off and washed several times with ice water; yield, 60%. The product was purified by crystallization from alcohol or preferably from benzene.

Four g. of ethyl-vinyloxyethyl-barbituric acid, prepared as described above, was placed in 30 cc. of hot water, in which it is insoluble. On the addition of 2 cc. of hydrochloric acid and stirring, the solid dissolved almost immediately while the acetaldehyde formed by the hydrolysis was removed by boiling. The product crystallized on cooling and was purified by crystallization either from alcohol or water; yield of ethyl-β-hydroxyethyl-barbituric acid, 70%.

Summary

1. A method for the preparation of hydroxy-substituted alkyl-barbituric acids has been described.

2. The compounds so prepared may be hypnotics with properties similar to those of veronal and proponal, and should be less toxic. The result of a study of their pharmacology will be reported later.

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

THE MECHANISM OF CARBOHYDRATE OXIDATION. I. *d*-GLUCOSE, *d*-MANNOSE, *d*-FRUCTOSE, *d*- AND *l*-ARABINOSE AND *dl*-GLYCERIC ALDEHYDE

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The work presented in this paper is a continuation of a series of studies being made in this Laboratory on the oxidation of organic compounds.[3]

The principal purpose of these studies is to establish, from exact quantitative data, obtained under definitely chosen experimental conditions, the molecular stages through which some of the organic compounds of the more familiar type pass when they undergo this kind of chemical change. The experiments which are recorded here on the oxidation of *d*-glucose, *d*-mannose, *d*-fructose, *d*- and *l*-arabinose and *dl*-glyceric aldehyde with neutral and alkaline potassium permanganate solutions were carried out with the following definite objectives in view: (a) to determine the effect of alkalinity on the character and amounts of the oxidation products; (b) to ascertain the effect of temperature on the character and amounts of the reaction products; (c) to obtain data which would lead to a better understanding of the oxidation reactions of some of the more common polysaccharides that are wholly or in part composed of some of these well-known hexoses; (d) to learn whether the behavior of *d*- and *l*-

[1] E. I. du Pont de Nemours Fellow, 1922.

[2] E. I. du Pont de Nemours Fellow, 1923.

[3] THIS JOURNAL, (a) **41**, 1267, (b) 1385 (1919); (c) **44**, 1730, (d) 2271, (e) 2276 (1922); (f) **45**, 171 (1923).