solid esters of organic acids. The properties of these esters render them useful in the identification of organic acids.

3. A number of representative esters have been prepared, and their melting points compared with those of the corresponding *p*-nitrobenzyl esters, phenacyl esters, and *p*-halogen phenacyl esters, where such comparison was possible.

College Park, Maryland

[A Contribution from the Laboratories of the University of Maryland and the U. S. Industrial Alcohol Company]

SOME REPRESENTATIVE CARBONATES AND CARBO-ETHOXY DERIVATIVES RELATED TO ETHYLENE GLYCOL[1]

By Nathan L. Drake and Ray M. Carter

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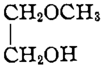
Certain derivatives of ethylene glycol, in particular its ethers and esters, have become important in industry by reason of their solvent power for the cellulose esters. It seems strange, therefore, that there appears in the published literature no information regarding either the preparation or the properties of the carbonates and the carbo-ethoxy derivatives of the mono ethers of ethylene glycol. Allpress[2] describes some carbonates and carbo-ethoxy derivatives of ethylene glycol, but the corresponding mono ethers have apparently not been made.

It was decided, therefore, to study certain of these substances, in the hope that they might prove of value in the lacquer industry as plasticizers. The raw materials were

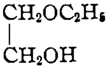
I



$$\begin{array}{l}CH_2OCH_3\\ |\\ CH_2OH\end{array}$$

Methylcellosolve

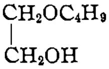
II



$$\begin{array}{l}CH_2OC_2H_5\\ |\\ CH_2OH\end{array}$$

Cellosolve

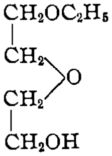
III



$$\begin{array}{l}CH_2OC_4H_9\\ |\\ CH_2OH\end{array}$$

Butylcellosolve

IV



$$\begin{array}{l}CH_2OC_2H_5\\ |\\ \left.\begin{array}{l}CH_2\\ CH_2\end{array}\right\rangle O\\ |\\ CH_2OH\end{array}$$

Carbitol

The carbonates were prepared by the reaction of phosgene and the glycol ether in a manner analogous to the preparation of alkyl carbonates. Phosgene was bubbled from a cylinder of the compressed gas into a weighed amount of the glycol ether in a tall narrow cylinder. The cylinder was immersed in a bucket of water in order that its temperature might be kept close to that of the laboratory, thus preventing the evolution of hydrogen chloride. At intervals the cylinder was removed and its increase in weight

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[1] From a thesis submitted to the Graduate School of the University of Maryland by Ray M. Carter in partial fulfilment of the requirements for the degree of Master of Science.

[2] Allpress, *J. Chem. Soc.*, **125**, 2259 (1924).

determined. When this increase indicated that the correct amount of phosgene had been introduced, the solution was heated, gently at first, then with increasing heat until boiling ensued.[3]

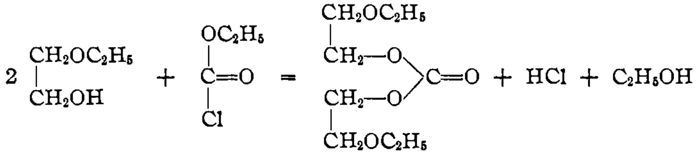
After the reaction was complete, the mixture was worked up in one of two ways: by washing with water, neutralizing with dilute sodium hydroxide, drying and fractionating, or by fractionating directly without preliminary neutralizing and drying.

In some cases this general method yielded unsatisfactory results. When methylcellosolve or carbitol were the starting materials, side reactions occurred between the hydrogen chloride and the ether, yielding halogen-containing products, among which was some alkyl chloride.

To obviate this difficulty, the glycol ether was first brought into reaction with metallic sodium and the resulting sodium glycolate treated with phosgene dissolved in benzene.

In preparing the carbo-ethoxy derivatives, ethyl chlorocarbonate was caused to react with the glycol ether. It was found early in the work, however, that a side reaction giving rise to considerable carbonate of the glycol ether occurred if the ether and chlorocarbonate were refluxed together.

Allpress[2] had noted earlier the formation of normal carbonate when ethylene glycol was heated with ethyl chlorocarbonate. In our case the reaction may be represented



$$2\begin{array}{l}CH_2OC_2H_5\\ |\\ CH_2OH\end{array} + \begin{array}{c}OC_2H_5\\ |\\ C{=}O\\ |\\ Cl\end{array} = \begin{array}{l}CH_2OC_2H_5\\ |\\ CH_2{-}O\\ \\ CH_2{-}O\\ |\\ CH_2OC_2H_5\end{array}\!\!\!\!>C{=}O + HCl + C_2H_5OH$$

It was found, furthermore, that this side reaction could be minimized if the glycol ether was added dropwise to the ethyl chlorocarbonate boiling under reflux.

Here, also, certain of the glycol ethers yielded halogen-containing byproducts, but in these cases the use of the sodium glycolate in benzene suspension obviated any difficulty.

All the compounds prepared had high boiling points, and preliminary experiments showed that it would be necessary to use a column that would maintain a high reflux ratio if good fractionation was to be accomplished. Two columns were used. One was 81 cm. from bottom outlet to side arm, the other 46 cm. Both were 2.5 cm. in internal diameter, the longer having a bottom outlet of 12 mm. internal diameter, and the shorter a bottom outlet of 19 mm. internal diameter. The longer of the two operated satisfactorily up to 225°, but above that point the lower outlet

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[3] Except in the case of diethylene glycol ether, IV, where the boiling point was very high.

was too small for the amount of liquid refluxing, and the column flooded. The shorter column was therefore made, provided with a wider outlet. It operated satisfactorily up to 300° at a distillation rate of 120 drops per minute and an estimated reflux ratio of 20:1. Both columns were heavily lagged with asbestos, corks were covered with tin foil, and short pieces of glass tubing were used to pack the columns. It was found unnecessary to use water in the dephlegmator; while distilling the lower-boiling liquids, air was blown through the dephlegmator, but for the higher-boiling substances the air current was not necessary.

The solvent action of the different preparations on three different cellulose esters was examined. The cellulose esters used were (1) 20–30 second R. S. nitrocotton, (2) 15 sec. A. S. nitrocotton, (3) cellulose acetate, 0.4 poise viscosity. These tests showed that both the carbonates and carbo-ethoxy derivatives of cellosolve, methylcellosolve and carbitol had high solvent power for both the A. S. and R. S. nitrocotton. The corresponding derivatives of the butyl ether were not such good solvents, the carbo-ethoxy derivative being somewhat better than the carbonate.

The only compounds which would dissolve cellulose acetate were the carbonate and carbo-ethoxy derivative of methylcellosolve. The other preparations merely swelled the cellulose acetate.

The high boiling points of some of these materials, particularly the derivatives of diethylene glycol, make them of interest as possible lacquer plasticizers.

Table I summarizes some of the properties of the compounds prepared. The percentage of ester was determined by saponification in a pressure bottle with *N*/2 alcoholic sodium hydroxide. The only change in the standard procedure was the addition of 100 cc. of water and 50 cc. of 10% barium hydroxide to the contents of the bottle before back titration with *N*/2 acid. Specific gravity was determined by means of a pycnometer. The boiling point was obtained by applying the proper stem and calibration correction to the temperature read during the fractionation. Refractive index was determined using an Abbé refractometer calibrated against distilled water.

TABLE I

PROPERTIES OF THE ESTERS

Carbonate	B. p., °C.	Mm.	% ester	Sp. gr.$^{25}_{4}$	n^{25}_{D}	Solvent action on R. S. nitrocotton	A. S. nitrocotton	Cellulose acetate
Ethyl (β-methoxyethyl)	182.1–183.1	760.4	99	1.0424	1.4036	Sol.	Sol.	Sol.
Di(β-methoxyethyl)	230.2–232.1	760.4	95	1.0936	1.4193	Sol.	Sol.	Sol.
Ethyl (β-ethoxyethyl)	194–194.9	762.7	97	1.0115	1.5064	Sol.	Sol.	Swells
Di(β-ethoxyethyl)	245.1–246.1	758.8	102	1.0635	1.4239	Sol.	Sol.	Swells
Ethyl (β-butoxyethyl)	223.9–224.4	759.0	95	0.9756	1.4143	Sl. sol. +	Sl. sol. +	Swells
Di(β-butoxyethyl)	297.2–298.2	761.7	95	0.9766	1.4279	Sl. sol.	Sl. sol.	Swells
Ethylcarbitol	242.7–244.2	764.4	101	1.0485	1.4203	Sol.	Sol.	Swells
Dicarbitol	231.9–234.9	55	95	1.0636	1.4353	Sol.	Sol.	Swells

Experimental

Di(β-methoxyethyl) Carbonate.—Seventy-nine and five-tenths grams of clean sodium was added to a solution of 300 g. of the monomethyl ether of ethylene glycol in 300 g. of benzene and a water-bath was used to bring the reaction to completion. To this mixture was added a benzene solution of phosgene, while the whole was kept cool in ice water. Phosgene was added until a distinct odor of it remained after shaking the reaction flask. Approximately 180 g. of phosgene was required. The salt which separated was dissolved by adding water and, after separation of the aqueous layer, the remaining oil was washed twice with 100-cc. portions of water. The product was dried over calcium chloride and distilled.

Ethyl (β-Methoxyethyl) Carbonate.—Five hundred grams of the glycol ether was added dropwise to 827 g. of ethyl chlorocarbonate boiling under reflux. After all of the ether had been added, boiling was continued for an hour. The crude was fractionated without a water wash or any further treatment.

Di(β-ethoxyethyl) Carbonate.—Gaseous phosgene was bubbled into a water-cooled cylinder containing 679 g. of glycol mono-ethyl ether until the weight increase was 339 g. The resulting solution was refluxed for four and one-half hours, washed with water, dried over calcium chloride and fractionated.

Ethyl(β-Ethoxyethyl) Carbonate.—Five hundred grams of glycol monoethyl ether was added slowly to 604 g. of boiling ethyl chlorocarbonate. Refluxing was continued for three hours after the addition of ether was completed. The resulting crude was fractionated without washing or neutralizing.

Di(β-butoxyethyl) Carbonate.—Two hundred and seventy-four grams of phosgene was bubbled into 717 g. of cooled ethylene glycol monobutyl ether. The solution was then boiled gently under reflux for three hours. After a water wash, it was dried over calcium chloride and fractionated.

Ethyl (β-Butoxyethyl) Carbonate.—Five hundred grams of ethylene glycol monobutyl ether and 460 g. of ethyl chlorocarbonate were mixed and boiled under reflux for four hours. After washing and drying, the product was fractionated. A considerable amount of di(β-butoxy ethyl) carbonate was obtained, showing this method of preparation to be inferior to that in which the glycol ether is added to boiling chlorocarbonate.

Dicarbitol Carbonate.—Three hundred and fifty-four grams of phosgene was dissolved in 903 g. of cooled carbitol (IV) and the mixture allowed to stand for eighteen hours before heating. The solution was then heated for four hours at a temperature of about 200°. After a water wash, the washings were extracted with benzene and added to the main bulk of the product, whereupon all was dried over calcium chloride and fractionated *in vacuo*.

Ethylcarbitol Carbonate.—Fifty-eight and 8 tenths grams of sodium was brought into reaction with 300 g. of carbitol in 300 g. of benzene. Heating on a water-bath was necessary to complete the reaction. To this mixture was added a solution of 278 g. of ethyl chlorocarbonate in 300 g. of benzene. The salt which separated was dissolved in water and the water-insoluble layer washed with more water. After drying the product was fractionated.

Summary

1. The carbonates and carbo-ethoxy derivatives of the methyl, ethyl and butyl ethers of ethylene glycol, and of the ethyl ether of diethylene glycol, have been prepared and their boiling points, specific gravities and refractive indices determined.

2. All of the substances except those derived from the butyl ether of ethylene glycol have good solvent power for nitrocotton.

College Park, Maryland

[Contribution from the Department of Chemistry, Yale University]

THE SYNTHESIS OF THIAZOLE AMINES POSSESSING PHARMACOLOGICAL INTEREST. IV

By W. S. Hinegardner[1] and Treat B. Johnson

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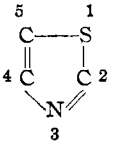
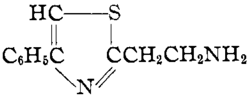
By bridging from carbon to carbon with a thiazole nucleus I in an aliphatic chain compound, it is theoretically possible to introduce structural features which make it practicable to study, from new points of view, the relationship between chemical constitution and physiological and pharmacological action. The thiazole nucleus I is chosen for such heterocyclic constructions because it contains both sulfur and nitrogen in cyclic linkage, and is a heterocycle which does not show high toxic effects when introduced into living organisms. Three distinct positions are available for carbon substitution in the ring (2,4,5), making it possible to obtain by synthesis interesting structural isomers for biological and clinical work. Furthermore, the thiazole cycle is a construction containing a stable molecular configuration with fixed positions for the cyclic double bonds and with no possibility of structural alterations corresponding to lactam $\rightleftarrows$ lactim or keto $\rightleftarrows$ enol tautomeric changes. These same considerations apply also to heterocyclic combinations containing oxygen and selenium substituted in place of the thiazole sulfur, which will finally be included in our research program.



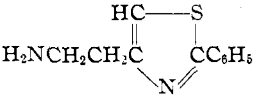
I

The organic constructions which are receiving our attention at present are the bridged thiazole derivatives of bases of the phenylethylamine type, II. It is a well-known fact that nucleus and side-chain substitutions in this base bring about pronounced physiological effects leading to products of therapeutic value. Our program calls for the study of compounds in which the aliphatic part is linked to the benzene nucleus by the thiazole ring, giving heterocyclic amines corresponding in structure to formulas III and IV. In this paper we shall report a practical procedure for preparing the new amine IV. In a later paper we shall describe a practical method for synthesizing the isomeric compound expressed by formula III.

$C_6H_5CH_2CH_2NH_2$ II



III



IV

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[1] Metz Research Fellow in Organic Chemistry, 1928–1929.