[CONTRIBUTION FROM THE STERLING CHEMISTRY LABORATORY, YALE UNIVERSITY]

STUDIES OF GLYCIDOL. II. REACTIONS WITH SECONDARY AMINES[1]

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The writers have pointed out in a previous communication[2] that glycidol, I, should be particularly useful in synthetic work by reason of the activity of its ethylene oxide ring. This paper, the second in the series, deals specifically with the action of glycidol on secondary amines. Since the amino-alcohols which are thus formed are peculiarly suited as intermediates for the preparation of amino-esters related to those of the procaine

$$\underset{\text{I}}{CH_2\text{—}CHCH_2OH} + NHR_2 = \underset{\text{II}}{R_2NCH_2CHOHCH_2OH}$$

type, the reaction has been carefully studied and the method of procedure applied to the synthesis of several dialkylaminopropanediols, II.

Roth[3] has prepared two of these compounds by the interaction of glycerol-α-monochlorohydrin and secondary amines. His procedure requires heating the reactants in a bomb tube at 100° for five to six hours. While the evidence is not conclusive, the mechanism[4] of this reaction is believed by many to be as follows

$$HOCH_2CHOHCH_2Cl \xrightarrow{NHR_2} CH_2CHCH_2OH \xrightarrow{HNR_2} R_2NCH_2CHOHCH_2OH$$

While there are a few articles in the literature dealing with reactions of glycidol and similarly constituted compounds such as epichlorohydrin with basic amines, there is but one investigator who has prepared dialkylaminopropanediols by this method. Knorr[5] has treated dimethyl- and diethylamines with glycidol, obtaining in each case the same product that was given by the corresponding reactions with monochlorohydrin, thus substantiating in part the above-mentioned hypothesis. The reaction of Knorr is the more practicable since the free base rather than the hydrochloride is formed in the reaction and may be directly distilled or crystallized. Knorr's procedure requires mixing of the reactants and cooling of the reaction mixture during a period of twenty-four hours.

[1] Constructed from part of the thesis presented by T. H. Rider to the Faculty of the Graduate School of Yale University in candidacy for the degree of Doctor of Philosophy.

[2] Rider and Hill, THIS JOURNAL, **52**, 1521 (1930).

[3] Roth, *Ber.*, **15**, 1149 (1882).

[4] An interesting test of this theory lies in the reaction of glycerol-β-monochlorohydrin with secondary amines. If the products are identical, the theory is substantiated. An investigation of this reaction is being undertaken by one of us.

[5] Knorr, *Ber.*, **32**, 757 (1899).

While the method of Roth is the less satisfactory of the two, it may be greatly simplified. Instead of carrying out the reaction in a bomb tube, the writers have found it to proceed quite satisfactorily upon merely warming the chlorohydrin and amine for a short time under a reflux condenser. This same procedure suffices in the reaction between glycidol and secondary amines. In this case, however, there is a very important side reaction—that of the polymerization of the glycidol. Both the polymerization of glycidol by the amine, and the addition of the amine to glycidol proceed rapidly under the same general conditions. When diethylamine is added slowly to glycidol, during heating on a steam-bath, no diethylaminopropanediol can be isolated. If, on the other hand, glycidol is slowly added to boiling diethylamine, 90% yields of diethylaminopropanediol may be obtained. The presence of a sufficient excess of the amine in the reaction mixture may be insured, in most cases, by the slow addition of glycidol, in such fashion that there is at no time an appreciable amount of unreacted glycidol in the reaction mixture. We have found that the tendency to polymerize glycidol is much greater in the cases of diethyl- and dimethylamines, than with amines of higher molecular weight. In these latter cases, therefore, we have used a mole and a half of amine to one of glycidol. The yields are materially decreased if this excess of amine is not used. The greater tendency of amines of lower molecular weight to polymerize glycidol is also shown in the progressive increase in yields by the use of the higher amines.

Dimethylaminopropanediol forms a picrate and a quaternary ammonium salt with methyl iodide, both precipitating soon after alcoholic solutions of the reactants are mixed. These reactions have both been described by Knorr; our quaternary salt melting at 134–136° corresponds to that obtained by him. Our picrate, on the other hand, prepared by the same method melts at 126–128°, while Knorr gives a melting point of 160° for this substance. Although this investigator describes a picrate of the diethylaminopropanediol, the writers have been unable to prepare this compound. Furthermore, we have found it impossible to prepare either the picrate or the quaternary salts of the other higher aminodiols. This is possibly to be attributed to a rapid loss of basicity, or to steric influences attendant upon increase in size of the groups on nitrogen.

The action of acid chlorides and isocyanates on the dialkylaminopropanediols will be discussed in a subsequent paper.

Experimental Part

General Procedure for the Preparation of the 1-Dialkylamino-2,3-propanediols.—The secondary amine is heated to a temperature somewhat below its boiling point—or with the higher amines on a steam-bath—in a three-necked round-bottomed flask equipped with mercury-sealed

mechanical stirrer, a reflux condenser and a dropping funnel. During stirring, glycidol is slowly added from the dropping funnel, the rate of addition being so regulated that the amine does not reach its boiling point. In the case of dimethyl- and also diethylamine, one and one-half moles of amine are used to one mole of glycidol. In all other cases the reactants are used in 1:1 molar ratio. The glycidol should not be added through the condenser, since the traces of amine there encountered cause a relatively large amount of polymerization. The liquid products are distilled in vacuo. Piperidinopropanediol solidifies when the reaction mixture cools, and it is then recrystallized from acetone. The experimental data relating to the aminodiols are given in Table I.

TABLE I

DIALKYLAMINOPROPANEDIOLS

-Aminopropanediols	Formula	Nitrogen, % Calcd.	Found		Yield, %	B. p., °C.	Pressure mm.
Dimethyl-	$C_5H_{13}O_2N$	11.76	11.78	11.75	82	111	15[a]
Diethyl-	$C_7H_{17}O_2N$	9.52	9.58	9.61	90	106	3
Di-*n*-propyl-	$C_9H_{21}O_2N$	8.00	8.13	7.86	92	143	9
Di-isobutyl-	$C_{11}H_{25}O_2N$	6.90	6.96	6.96	94	122	2
Di-*n*-amyl-	$C_{13}H_{29}O_2N$	6.06	6.10	5.99	95	149	2
Piperidino-	$C_8H_{17}O_2N$	8.80	8.65	8.72	96.5	...	..[b]

[a] A 30% aqueous solution of dimethylamine was used in this reaction. [b] Piperidinopropanediol melts at 83°.

Picrate of Dimethylaminopropanediol.—The diol and picric acid are mixed in absolute alcohol solution and allowed to stand. The picrate precipitates from the solution and after filtration is purified by crystallization from absolute alcohol; m. p. 126–128°.

Anal. Calcd. for $C_{11}H_{16}O_9N_4$: N, 16.1. Found: N, 16.0, 16.0.

Summary

1. The reaction between glycidol and secondary amines has been studied.

2. A series of dialkylaminopropanediols has been prepared in yields which average over 90% of the theoretical.

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