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ETHER AMINO ALCOHOLS. II

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The reaction between epichlorohydrin (1,2-epoxy-3-chloropropane) and the lower alcohols in the presence of sulfuric acid as a catalyst has been reported recently by Flores-Gallardo and Pollard (1) who have ascertained optimum conditions for the reaction reported independently by Fourneau and Ribas (2) and by Kharasch and Nudenberg (3). Kirstahler (4) has been granted a patent for the preparation of high molecular weight ethers by mixing an aliphatic alcohol having more than eight carbon atoms with a 1,2-propylene oxide with or without the presence of a catalyst.

The method described by Flores-Gallardo and Pollard (1) has been used in this investigation for the condensation of heptanol-1, octanol-1, and decanol-1 with epichlorohydrin. The condensation products obtained from the above alcohols and epichlorohydrin were used to synthesize the corresponding epoxy ethers by dehydrohalogenation with solid, finely powdered sodium hydroxide.

Ten new disubstituted ether amino alcohols of the type $ROCH_2CH(OH)CH_2NHCH_2CH_2NHCH_2CH(OH)CH_2OR$ were prepared by reaction of the corresponding 1,2-epoxy-3-alkoxypropane with ethylenediamine (1,2-diaminoethane).

These compounds have been tested for certain physiological activities:[1] *In vitro* amebic activity became demonstrable when R is greater than ethyl. The activity increased as R increases with the optimum inhibition being noted when R is *n*-octyl. The *n*-decyl compound was considerably less active than the *n*-octyl. A study of the *in vivo* activity proved the *n*-octyl compound to have little effect in the rat at maximum tolerated doses. These compounds were also ineffective against flu, rabies, St. Louis encephalitis, mumps, cowpox, Meningo pneumonitis, equine encephalitis, and typhus.

EXPERIMENTAL

Synthesis of 1-chloro-2-hydroxy-3-n-heptoxypropane. In a 2-liter, 3-necked, round-bottomed flask fitted with a stirrer, reflux condenser, and dropping-funnel were placed 9.0 moles (1045.8 g., 1272 ml.) of heptanol-1, and 3.0 moles (278 g., 235 ml.) of epichlorohydrin. To this mixture, 6.7 ml. of sulfuric acid (*d.* 1.84) was added dropwise. The mixture was refluxed for six hours, allowed to cool, and an excess of barium carbonate (30 g.) was added. The mixture was stirred for one hour and then was filtered through a charcoal mat. The filtrate was distilled at 20 mm., and 1-chloro-2-hydroxy-3-*n*-heptoxypropane was collected at 145.4–146.4°.

Extension of this synthesis to include octanol-1 and decanol-1 yielded the corresponding 1-chloro-2-hydroxy-3-alkoxypropanes. The data for these compounds are shown in Table I.

Synthesis of 1,2-epoxy-3-n-heptoxypropane. In the usual apparatus was placed 500 ml. of ether and 0.5 mole (104.36 g.) of 1-chloro-2-hydroxy-3-*n*-heptoxypropane. The flask was

[1] The authors express their sincere appreciation to Dr. Paul E. Thompson of Parke, Davis & Company for the amebiasis experiments.

provided with an ice-water cooling bath, and 0.75 mole (30 g.) of finely divided sodium hydroxide was added with rapid agitation of the mixture. The water-bath was allowed to reach room temperature, and the stirring was continued for eight hours. Then 150 ml. of water

TABLE I

DATA CONCERNING CHLORO-HYDROXY-ETHERS OF THE TYPE RO—$CH_2CH(OH)CH_2$—Cl

R	YIELD, %	B.P.		d_4^{25}	n_D^{25}	MOLAR REFRACTION	
		°C.	MM.			Observed	Calc'd
n-Heptyl	21.3	145.4–146.4	20	0.9862	1.4482	56.68	56.42
n-Octyl	31.4	133.4–136.4	7	.9311	1.4438	63.52	61.03
n-Decyl	27.9	167.8–168.8	10	.9568	1.4523	70.75	70.27

TABLE II

DATA CONCERNING EPOXY ETHERS OF THE TYPE RO—CH_2CH(O)CH_2

R	YIELD, %	B.P.	d_4^{25}	n_D^{25}	MOLAR REFRACTION		
		°C. AT 20 MM.			Observed	Calculated (Not including Epoxy Oxygen)	Refractive Equivalent of Epoxy Oxygen
n-Heptyl	77.2	115.7–116.2	0.8879	1.4299	50.107	47.823	2.284
n-Octyl	63.3	130.0–130.2	.8860	1.4317	54.505	52.441	2.064
n-Decyl	77.4	156.0–156.5	.8804	1.4377	63.873	61.667	2.206

TABLE III

DATA CONCERNING ETHER AMINO ALCOHOLS OF THE TYPE

RO—$CH_2CH(OH)CH_2NHCH_2CH_2NHCH_2CH(OH)CH_2$—OR

R	YIELD, % (Pure Product)	M.P., °C. (CORR.)	NITROGEN	
			Found	Calculated
Methyl	12.7	137.9–138.9	11.61	11.85
Ethyl	17.6	131.4–131.9	10.30	10.59
n-Propyl	12.0	130.4–130.9	9.46	9.58
Isobutyl	13.9	125.9–126.4	8.75	8.74
n-Pentyl	11.5	114.8–115.3	7.97	8.04
3-Methyl-*n*-butyl	13.5	107.9–108.9	8.08	8.04
n-Hexyl	21.2	113.8–114.8	7.26	7.44
n-Heptyl	9.9	112.8–113.8	6.85	6.92
n-Octyl	16.1	107.9–108.9	6.37	6.47
n-Decyl	22.9	105.9–107.9	5.67	5.73

was added and the layers separated. The aqueous layer was extracted three times with ether, the ether extracts were combined, and the ether was evaporated on the steam-bath. The residue was distilled, and 1,2-epoxy-3-*n*-heptoxypropane was collected at 115.7–116.2° at 20 mm.

In Table II are shown the results obtained when this synthesis was extended to include 1-chloro-2-hydroxy-3-*n*-octoxypropane and 1-chloro-2-hydroxy-3-*n*-decoxypropane.

Synthesis of N,N'-bis(2-hydroxy-3-n-heptoxypropyl)ethylenediamine. To 0.15 mole (16.5 g. of 69.9%) of boiling ethylenediamine hydrate in the usual apparatus was added dropwise 0.15 mole (25.4 g.) of 1,2-epoxy-3-*n*-heptoxypropane. The mixture was stirred and refluxed for six hours and then poured into a beaker to solidify. Excess liquid was removed by drying between clay plates, and the resulting crude product was recrystallized from ethyl acetate.

Table III shows the constants for this compound and the results obtained when other 1,2-epoxy-3-alkoxypropanes were used in the synthesis.

SUMMARY

The synthesis of chloro-hydroxy ethers by reaction between epichlorohydrin (1,2-epoxy-3-chloropropane) and heptanol-1, octanol-1, and decanol-1 is reported. Dehydrochlorination of these compounds to the corresponding epoxy ethers is described. The reaction between ethylenediamine (1,2-diaminoethane) and each of several epoxy ethers to produce disubstituted ether amino alcohols is outlined.

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