Synthesis and Reactions of Quaternary Salts of Glycidyl Amines

D. M. BURNESS AND H. O. BAYER

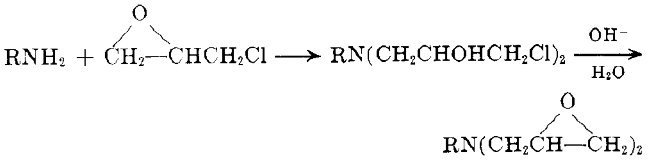
Contribution No. 2334 from the Kodak Research Laboratories, Eastman Kodak Company, Rochester, New York

Received December 26, 1962

The synthesis and properties of a variety of tertiary amines and quaternary ammonium salts containing one, two, or more glycidyl (*i.e.*, 2,3-epoxypropyl) groups are described. Reactions of N-(2,3-epoxypropyl)trimethylammonium *p*-tosylate (V) and other similar compounds with primary and secondary amines, mercaptans, hydrogen sulfide, and hydrogen bromide have been investigated.

The literature contains scant reference to quaternary salts of amino-substituted epoxides despite their potential utility as reactive intermediates for the introduction of highly polar quaternary ammonium functions into a large variety of nucleophilic substances. Ross[1] prepared the methiodide of N,N-bis(2,3-epoxypropyl)-*p*-anisidine which was found to have the highest chemical reactivity toward nucleophilic agents, such as thiosulfate ion, of any of a large variety of epoxides studied. In a few other cases[2] methiodides of other glycidyl amines have been prepared but chiefly for identification purposes.

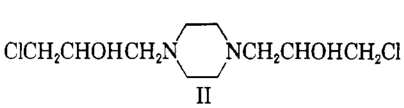
The published work on tertiary glycidyl amines, essential intermediates in the current study, is much broader in scope. The procedure developed by Gilman[3] for the simple glycidyl amine, 3-diethylamino-1,2-epoxypropane (I), was adapted to the diglycidyl amines[4] (see the following example).



$$RNH_2 + \overset{O}{CH_2\text{—}CH}CH_2Cl \longrightarrow RN(CH_2CHOHCH_2Cl)_2 \xrightarrow[H_2O]{OH^-} RN(CH_2\overset{O}{CH\text{—}CH_2})_2$$

Other workers have used less convenient techniques to prepare similar derivatives of substituted anilines,[5] cyclohexylamine,[2] and ammonia.[6]

With few exceptions, the reactions between epichlorohydrin and the various amines proceeded in reasonably good yield (50–70% for the two steps) to the tertiary glycidyl amines (Table I). In most cases the primary reaction proceeded satisfactorily without a solvent. With piperazine, however, a solvent (methanol) was required. With methylamine, it was found advantageous to use ether as a solvent in both steps; otherwise, the yield was impossibly low. Two stereoisomeric forms (*dl* and *meso*) of the bischlorohydrin (II) from piperazine were isolated, melting at 84 and 103°. As a result, the preparation of a crystalline 1,4-bis(2,3-epoxypropyl)piperazine (m.p. 63–64°) from the higher-melting isomer was facilitated.[7]

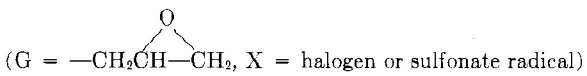


II

With few exceptions, the tertiary glycidyl amines, when pure, could be stored indefinitely at 0° with little or no deterioration. Samples of N-(2,3-epoxypropyl)-dimethylamine (III) proved to be less stable, presumably because of our inability to remove traces of epichlorohydrin in the distillation. The bisepoxide from ethanolamine underwent extensive decomposition during distillation and the pure distillate decomposed within a few days. N,N-Bis(2,3-epoxypropyl)methylamine was stored for three months at −20° without change, but another preparation, kept at 0°, had partially polymerized in a like period. Traces of moisture may have been responsible, for this is known[8] to promote polymerization of these bases.

Quaternization of the tertiary bases gives neutral compounds with a higher degree of stability toward undesired side reactions of the epoxide ring, in spite of their frequently hygroscopic nature.

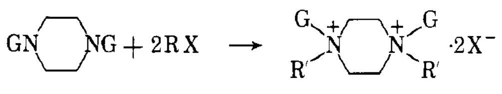
In this investigation, six distinct types of glycidyl amine quaternary salts were prepared; methods of synthesis from assorted free-base precursors are symbolized in the following equations.



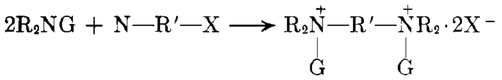
$$(G = \text{—}CH_2\overset{O}{CH\text{—}CH_2},\ X = \text{halogen or sulfonate radical})$$

$$R_2NG + R'X \longrightarrow R_2R'\overset{+}{N}G\cdot X^- \qquad (1)$$

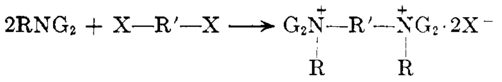
$$RNG_2 + R'X \longrightarrow RR'\overset{+}{N}G_2\cdot X^- \qquad (2)$$



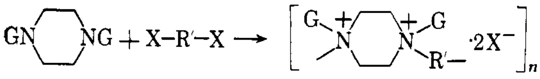
(3)



$$2R_2NG + N\text{—}R'\text{—}X \longrightarrow R_2\underset{G}{\overset{+}{N}}\text{—}R'\text{—}\underset{G}{\overset{+}{N}}R_2\cdot 2X^- \qquad (4)$$



$$2RNG_2 + X\text{—}R'\text{—}X \longrightarrow G_2\underset{R}{\overset{+}{N}}\text{—}R'\text{—}\underset{R}{\overset{+}{N}}G_2\cdot 2X^- \qquad (5)$$



(6)

---

[1] W. C. J. Ross, *J. Chem. Soc.*, 2257 (1950).

[2] J. B. McKelvey, B. G. Webre, and R. R. Benarito, *J. Org. Chem.*, **25**, 1424 (1960).

[3] H. Gilman and L. Fullhart, *J. Am. Chem. Soc.*, **71**, 1478 (1949).

[4] Similar conditions have since been reported in two patents: (a) Farbenfabriken Bayer A.-G., British Patent 772,830 (1957); *Chem. Abstr.*, **51**, 14799 (1957); (b) VEB Filmfabrik Agfa Wolfen, Belgian Patent 597,295 (1960).

[5] (a) R. F. Homer, *J. Chem. Soc.*, 3690 (1950); (b) W. Davis, J. H. Everett, and W. C. J. Ross, *ibid.*, 133 (1950).

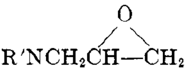
[6] J. B. McKelvey, B. G. Webre, and E. Klein, *J. Org. Chem.*, **24**, 614 (1959).

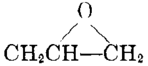
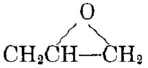
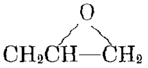
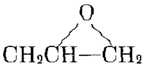
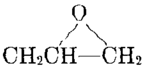
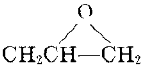
[7] This proved to be a dihydrate of the bisepoxide. The same reaction, run in ethanol, by K. Gerzon, J. E. Cochran, L. A. White, R. Monahan, E. V. Krumkalns, R. E. Scroggs, and J. Mills [*J. Med. Pharm. Chem.*, **1**, 233 (1959); *Chem. Abstr.*, **54**, 6733 (1960)] has been reported to yield, without isolation of the intermediate chlorohydrin, two isomers with m.p. 42–43° and 62–63°, tentatively identified as *dl* and *meso*, respectively. A bischlorohydrin of reported m.p. 125–127° was isolated from the first reaction step; the reason for the discrepancy in melting points is unknown.

[8] R. Wegler, *Angew. Chem.*, **67**, 582 (1955).

TABLE I

GLYCIDYL AMINES

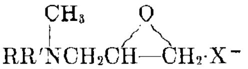

$RR'NCH_2CH{-}CH_2$ (with O bridging CH and CH_2)

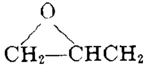
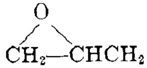
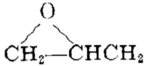
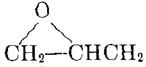
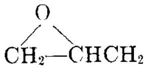
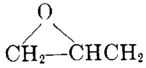
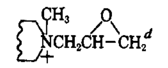
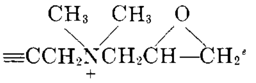
						Analysis					
						Calcd.			Found		
R	R'	Yield, %	B.p., °C. (mm.)	$n^{25}D$	Formula	C	H	N	C	H	N
CH_3	CH_3	48	65 (110)	1.4180	$C_5H_{11}NO$	59.4	11.0	13.8	59.1	10.9	13.4
C_2H_5	C_2H_5	60	67 (31)[d]	1.4306[d]	$C_7H_{15}NO$						
CH_3	n-$C_{14}H_{29}$	37[b]	126 (0.2)	1.4512	$C_{18}H_{37}NO$	76.3	12.8	4.9	76.6	12.9	5.2
CH_3		45	77.5 (2.5)[e]	1.4538	$C_7H_{13}NO_2$	58.6	9.1	9.8	59.0	9.4	10.0
C_2H_5		56	80 (3.5)[f]	1.4551	$C_8H_{15}NO_2$	61.2	9.7	8.9	61.0	9.8	9.2
C_3H_7		51	102.5 (6)[g]	1.4536	$C_9H_{17}NO_2$	63.2	10.0	8.2	62.9	9.7	8.1
C_4H_9		67	90 (0.3)[h]	1.4542	$C_{10}H_{19}NO_2$	64.8	10.4	7.6	64.8	10.6	7.8
HOC_2H_4		8.3[c]	115 (0.3)	1.4833	$C_8H_{15}NO_3$	55.6	8.8	8.1	55.5	8.5	8.1
p-$CH_3OC_6H_4$[a]		87	120–140 (0.5)	1.5570	$C_{13}H_{17}NO_3$						
From piperazine			M.p. 63–64° (dihydrate)		$C_{10}H_{22}N_2O_4$	51.2	9.4	12.0	50.9	9.6	12.0

[a] Intermediate chlorohydrin isolated in 57% yield; m.p. 113–116°; J. L. Everett and W. C. J. Ross, *J. Chem. Soc.*, 1982 (1949), report 109–111°. Ring closure by method of Davis, *et al.*,[5b] who report b.p. 228–229° (9 mm.). [b] Reaction between amine and epichlorohydrin, 5 hr. at 40–45°. [c] Largely decomposed on distillation. Pure product decomposed in few days at 0°. [d] Ref. 3 values: b.p. 69° (32 mm.); $n^{20}D$ 1.4362. [e] Ref. 4a reports 96–98° (12 mm.). [f] Ref. 4b reports 87–92° (3 mm.). [g] Ref. 4a reports 113–115° (12 mm.). [h] Ref. 4a reports 79–81° (0.3 mm.).

TABLE II

MONO- AND DIGLYCIDYL AMMONIUM SALTS

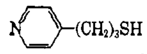

$RR'\overset{CH_3}{\underset{+}{N}}CH_2CH{-}CH_2 \cdot X^-$ (with O bridging CH and CH_2)

						Analysis					
						Calcd.			Found		
R	R'	X^-	Yield, %	M.p.,[a] °C.	Formula	C	H	N	C	H	N
CH_3	CH_3	$C_7H_7SO_3$	85	120–121[g]	$C_{13}H_{21}NO_4S$	54.3	7.3	4.9	54.2	7.5	4.5
CH_3	CH_3	ClO_4[f]	86	132.5–133.5[l]	$C_6H_{14}ClNO_5$[n]	33.4	6.5	6.5	33.7	6.2	6.9
C_2H_5	C_2H_5	$C_7H_7SO_3$	77	73.5–74.5[h]	$C_{15}H_{25}NO_4S$	57.1	8.0	4.4	56.6	7.7	4.2
CH_3[b]	n-$C_{14}H_{29}$	ClO_4	52	58–112[i]	$C_{19}H_{40}ClNO_5$	57.3	10.1	3.5	57.4	10.1	4.0
CH_3		$C_7H_7SO_2$	88	48–54	$C_{15}H_{23}NO_5S$[m]	54.7	7.0	4.3	54.4	7.2	4.1
C_2H_5		$C_7H_7SO_3$		Noncryst.	$C_{16}H_{25}NO_5S$			(Not isolated)			
C_2H_5		$(C_6H_5)_4B$	50	209–211[b]	$C_{33}H_{38}BNO_2$	80.7	7.7	2.9	80.2	7.7	3.0
n-C_3H_7		$C_7H_7SO_3$		Noncryst.	$C_{17}H_{27}NO_5S$			(Not isolated)			
n-C_4H_9		$C_7H_7SO_3$		Noncryst.	$C_{18}H_{29}NO_5S$			(Not isolated)			
p-$CH_3OC_6H_4$[c]		$C_7H_7SO_3$	66	135.5–137.5[h]	$C_{21}H_{27}NO_6S$	59.9	6.4	3.3	59.7	6.4	3.1
 [d]		$C_7H_7SO_3$	9	240.5–241.5[j]	$C_{26}H_{38}N_2O_8S_2$	54.7	6.7	4.9	54.4	6.7	5.0
 [e]		ClO_4	38	123.5–125[k]	$C_{14}H_{26}Cl_2N_2O_{10}$	37.1	5.7	6.2	36.8	6.0	6.5

[a] Melting points in all tables are corrected. [b] Reaction in benzene for 18 hr. at 25°, then 1 hr. at reflux. [c] Reaction with no solvent for 5 hr. at 100°. [d] Piperazine bis compound. Reaction in methanol for 1 hr. at reflux and 2 days at 25°. No attempt to work up sizable second crops. [e] Bis compound from 1,4-bis(methanesulfonoxy)-2-butyne and III in benzene; 1 hr. at reflux and 18 hr. at 25°. [f] By treatment of tosylate with sodium perchlorate in acetonitrile. [g] From acetone. [h] From 2-butanone. [i] From n-butyl alcohol. [j] From ethanol. [k] From acetonitrile-ethyl acetate. [l] From methanol. [m] *Anal.* Calcd. for epoxy O: 9.7. Found: 9.0; after 4 months at 0°, 8.1. [n] *Anal.* Calcd. for Cl: 16.5. Found: 16.5.

TABLE III

QUATERNARY SALTS, $YCH_2CHOHCH_2\overset{+}{N}(CH_3)_3 \cdot C_7H_7SO_3^-$, FROM REACTION OF 2,3-EPOXYPROPYLTRIMETHYLAMMONIUM p-TOSYLATE WITH AMINES AND MERCAPTANS

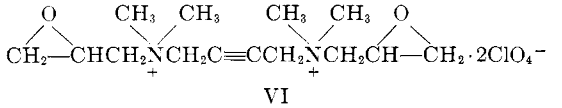
Reactant[a] YH	Yield,[d] %	M.p., °C.	Formula	Analysis Calcd. C	H	N	Found C	H	N
$C_6H_{13}NH_2$	69	117.5–120	$C_{19}H_{36}N_2O_4S$	58.8	9.3	7.2	58.5	9.2	7.5
$C_8H_{17}NH_2$	60	114.5–115.5	$C_{21}H_{40}N_2O_4S$	60.6	9.6	6.7	60.2	9.5	6.8
$C_{10}H_{21}NH_2$	77	113–130	$C_{23}H_{44}N_2O_4S$	62.1	9.9	6.3	61.9	9.8	6.4
$C_{12}H_{25}NH_2$	73	106–167	$C_{25}H_{48}N_2O_4S$	63.6	10.2	5.9	63.7	10.1	5.8
$C_{14}H_{29}NH_2$	66	111–181	$C_{27}H_{52}N_2O_4S$	64.8	10.5	5.6	64.3	10.4	5.5
$C_{14}H_{29}NHCH_3$	72	100–124[e]	$C_{28}H_{54}N_2O_4S$	65.4	10.6	5.4	65.0	10.1	5.3
 [b]	71	194–197	$C_{30}H_{52}N_4O_8S_2$	54.5	7.9	8.5	53.9	7.9	8.3
$C_6H_{13}SH$[c]	87	120–121[f]	$C_{19}H_{35}NO_4S_2$	56.3	8.6	3.5	56.3	8.7	3.5
$C_8H_{17}SH$	88	87–91	$C_{21}H_{39}NO_4S_2$	58.2	9.0	3.2	58.7	9.5	3.1
$C_{10}H_{21}SH$	79	94–120	$C_{23}H_{43}NO_4S_2$	59.9	9.3	3.0	59.3	9.7	3.0
$C_{12}H_{25}SH$	74	89–155	$C_{25}H_{47}NO_4S_2$	61.3	9.6	2.9	60.8	9.3	2.8
$C_{16}H_{33}SH$	88	78–190	$C_{29}H_{55}NO_4S_2$	63.8	10.1	2.6	63.5	10.5	2.6
	61	79–79.5[g]	$C_{21}H_{34}N_2O_5S_2$	55.0	7.4	6.1	54.9	7.7	5.9
$HS(CH_2)_{10}SH$[b]	84	107–121[h]	$C_{36}H_{64}N_2O_8S_4 \cdot 2H_2O$	52.8	8.3	3.4	52.7	8.5	3.5
$(HSCH_2CH_2)_2S$[b]	81	138–148	$C_{30}H_{52}N_2O_8S_5$	49.4	7.1	3.8	49.3	7.4	3.8

[a] All alkyl chains are normal. [b] Giving the bis compound. [c] Also prepared by alternate methods: (1) a 4.6-g. sample of XV (Table IV) and 4.1 g. of methyl p-tosylate refluxed in benzene for 1 hr. gave 88% yield and (2) from XVI—see Experimental. Products from three sources were found to be identical by infrared spectra and mixture melting points. [d] Yields are for purified products; most crude yields were nearly quantitative. Except where noted, recrystallization solvent was either acetone or acetonitrile. [e] From ethyl acetate. [f] Hydrate of m.p. 92–95° from acetone was dehydrated over phosphorus pentoxide. [g] From acetone; compound is monohydrate. [h] From ethanol.

The question may arise as to why some of these compounds were not synthesized by the more direct route, namely, the reaction of epichlorohydrin with the appropriate tertiary amines. Such a route was tried in a few cases and led to spurious results. This work will be described in a future publication.

Quaternization of the bases in equations 1, 2, and 3 with methyl p-tosylate was effected under mild conditions in benzene solution. The monoepoxy salts (equation 1, Table II) were obtained in crystalline form in good yield. With the exception of N,N-bis(2,3-epoxypropyl)dimethylammonium p-tosylate (IV), diglycidyl monoquaternary salts (equation 2, Table II) could not be crystallized except by conversion to tetraphenylboride salts by aqueous sodium tetraphenylboron. Their intractability is largely due to stereoisomeric mixtures. Some of the concentrated, neutral aqueous solutions of the tosylate salts proved surprisingly stable when stored near 0°. A 30% solution of a typical preparation of N,N-bis(2,3-epoxypropyl)ethylmethyl ammonium p-tosylate, for example, had lost only 6% of its epoxide content after six months at 0–5° and 52% after three and a half years. On the other hand, a 37% solution of its next lower homolog (IV) showed a 13% loss in epoxy content during a similar three-month period; meanwhile, however, the pure, hygroscopic, crystalline solid had not decomposed noticeably after seven months at 0°. Crystalline monoepoxide salts, *e.g.*, N-(2,3-epoxypropyl)trimethylammonium p-tosylate (V), could be stored indefinitely in closed containers at 25°.

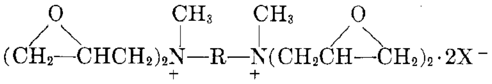
A salt (VI), prepared according to equation 4 from the active 1,4-bis(methanesulfonoxy)-2-butyne, could be isolated in crystalline form as the perchlorate; however, the less active 1,5-bis(methanesulfonoxy)pentane gave incomplete quaternization. Attempts to isolate the product led to hydrolytic cleavage of the epoxide ring, a reaction catalyzed by the incompletely quaternized free base.



$$\overbrace{CH_2-CH}^{O}CH_2\underset{+}{\overset{CH_3\ CH_3}{N}}CH_2C\equiv CCH_2\underset{+}{\overset{CH_3\ CH_3}{N}}CH_2\overbrace{CH-CH_2}^{O}\cdot 2ClO_4^-$$

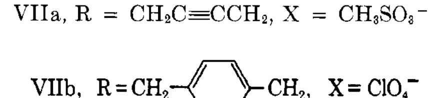
VI

Similar reactions utilizing diglycidyl amines have produced tetraglycidyl salts (VIIa, VIIb) and a polymeric analog (VIII) (equations 5 and 6).

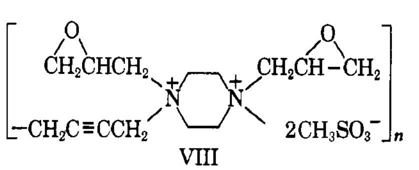


$$(\overbrace{CH_2-CH}^{O}CH_2)_2\underset{+}{\overset{CH_3}{N}}-R-\underset{+}{\overset{CH_3}{N}}(CH_2\overbrace{CH-CH_2}^{O})_2\cdot 2X^-$$

VIIa, R = $CH_2C\equiv CCH_2$, X = $CH_3SO_3^-$



VIIb, R = CH_2–, –CH_2, X = ClO_4^-

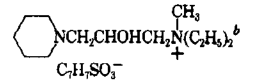


VIII

A brief study of simple reactions of the glycidyl amines and particularly the quaternary salts was undertaken with a few of the lower representatives of this series of compounds. Although no effort was made to study the reactivities of the compounds in ring-opening reactions, they appeared to be in agreement with the observations of Ross,[1] who noted that electronegative substituents (such as $R_3\overset{+}{N}CH_2$-) facilitated ring opening with anions but greatly decreased the rate in acid-catalyzed reactions. Accordingly, the quaternary salt, V, reacted readily with amines and mercaptans under moderate conditions (40–65°, methanol) to give nearly quantitative yields of essentially pure, crude products (Table III, equations 8 and 10). On the other hand, the acid-catalyzed hydrolysis of V had failed to occur

TABLE IV

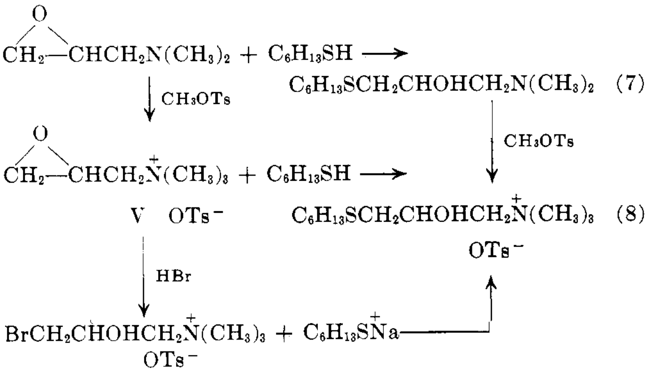
MISCELLANEOUS PRODUCTS DERIVED FROM EPOXIDES WITH AMINE FUNCTIONS

Compound	Structure	Yield, %	B.p., °C.	$n^{25}D$	Formula	Analysis Calcd. C	Calcd. H	Calcd. N	Found C	Found H	Found N
		85	62–65 (0.06 mm.)	1.4673	$C_{12}H_{26}N_2O$	67.3	12.1		67.7	12.0	
		93	100–102[f]		$C_{20}H_{36}N_2O_4S$	60.0	9.0	7.0	60.0	9.2	7.0
											
	·$2C_7H_7SO_3^-$ salt	70	120–123[f]		$C_{28}H_{48}N_2O_7S_2$	57.3	7.8	10.9	57.2	7.8	10.7
	·$2(C_6H_5)_4B^-$ salt		192–194[f]		$C_{62}H_{72}B_2N_2O$	84.3	8.2	3.2	84.2	7.9	3.0
XIII	$C_6H_{13}NHCH_2CHOHCH_2N(CH_3)_2$[d]	50	100–102 (3 mm.)	1.4527	$C_{11}H_{26}N_2O$	65.3	12.9	13.9	66.2	12.7	13.6
XIV	$C_6H_{13}N[CH_2CHOHCH_2N(CH_3)_2]_2$[d]	20	132–135 (0.07 mm.)	1.4635	$C_{16}H_{37}N_3O_2$	63.4	12.2	13.8	63.9	11.8	13.3
XV	$C_6H_{13}SCH_2CHOHCH_2N(CH_3)_2$[e]	70	82–84 (0.06 mm.)	1.4747	$C_{11}H_{25}NOS$	60.2	11.4		60.4	11.5	
XVI	$BrCH_2CHOHCH_2\overset{+}{N}(CH_3)_3$ $C_7H_7SO_3^-$	67	112–114[f]		$C_{13}H_{22}BrNO_4S$	42.2	6.0	21.7	42.8	6.1	21.4
VII	$(CH_3)_3\overset{+}{N}CH_2CHOHCH_2OH$ ClO_4^-	75	111.5–113.5[f]		$C_6H_{16}ClNO_6$	30.8	6.85	15.2[g]	30.9	6.9	15.5[g]
IX	$(C_2H_5)_2NCH_2CHOHCH_2SH$	63	64–65 (1 mm.)	1.4796	$C_7H_{17}NOS$	(SH, 20.9)		8.6	(SH, 21.0)		8.7
X	$C_2H_5N(CH_2CHOHCH_2SH)_2$	44	147–159 (0.11–0.45 mm.)	1.5345	$C_8H_{19}NO_2S_2$	42.7	8.5	6.2	43.2	8.1	6.3

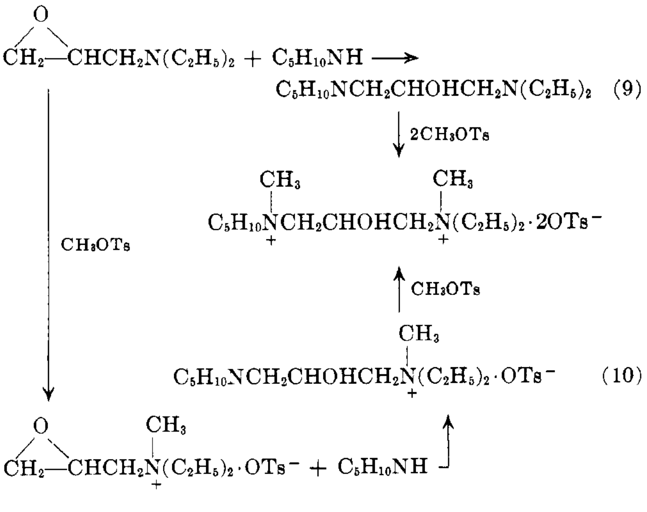
[a] From I and piperidine in methanol for 18 hr. at 45°; yield, 85%. [b] From N-(2,3-epoxypropyl)diethylmethylammonium *p*-tosylate and piperidine by the usual procedure in 93% yield. Recrystallized ethyl acetate. [c] Method 1: mixture of 6.4 g. of XI and 12 g. of methyl *p*-tosylate in ethyl acetate heated at reflux for 2 hr; recrystallized from acetone for 70% yield. Method 2: mixture of 4.0 g. of XII and 2.0 g. of methyl *p*-tosylate under same conditions gave 72% yield. Products were identical as shown by infrared spectra and mixture melting points of both the tosylates and the tetraphenylborides. [d] From 6 g. (0.06 mole) of III and 12 g. (0.12 mole) of *n*-hexylamine in methanol for 16 hr. at 45°; distillation produced 50% yield of XIII and 20% of XIV. [e] From 6 g. of III and 7.2 g. of *n*-hexanethiol in methanol; reaction exothermic. Refluxed for 1.5 hr. and distilled; yield, 70%. [f] Melting point. [g] Cl value.

after three days at 30°, steam-bath temperature being required. The highly exothermic nature of the reaction between the free base, III, and *n*-hexyl mercaptan is probably due to initial salt formation with subsequent vigorous attack by the highly nucleophilic mercaptide ion on the epoxide ring. In earlier work,[3] employing alkali metal mercaptides with the homologous glycidyl amine, I, the reaction required considerably more drastic conditions.

There was no reason to doubt that the products of these reactions would have the structures shown in the equations rather than those of the alternate primary alcohols (*e.g.*, $RSCH(CH_2OH)CH_2\overset{+}{N}R_3\cdot X^-$), which would result from ring opening at the secondary carbon atom. Studies with other unsymmetrical epoxides have shown that under neutral or basic conditions the so-called "normal products" (equations 7 and 9) are formed almost exclusively with epoxides bearing electron-withdrawing substituents.[3,9] It was shown that



quaternization does not affect the direction of ring opening by either mercaptans or amines when the same product resulted by either route in the reaction sequences preceding and following.



Although primary amines can react with two equivalents of an epoxide to give bis compounds, no difficulty was experienced in obtaining good yields (60–77%) of the pure mono salts, $RNHCH_2CHOHCH_2\overset{+}{N}(CH_3)_3\cdot OTs^-$, using 100% excess of amine with V. In contrast, reaction of the unquaternized amine (III) with *n*-hexylamine under similar conditions gave a mixture consisting of a 50% yield of the mono adduct and 20% of the bis adduct. Diquaternary salts are readily prepared by reaction of V with dimercaptans or disecondary diamines (Table III).

---

(9) R. E. Parker and N. S. Isaacs, *Chem. Rev.*, **59**, 737 (1959).

The reaction of epoxy quaternary ammonium salts with primary or secondary amines has proved to be a convenient way of preparing compounds containing both quaternary ammonium and secondary or tertiary amino groups. In addition, the reaction serves to confer a degree of solubility on long-chain and other water-insoluble amines (and mercaptans) in polar solvents. Some of these products appear to have detergent properties.

Reaction of tertiary mono- and diglycidyl amines with hydrogen sulfide to form mercaptans IX and X (see Table IV) proceeded in reasonably good yield (63% and 44%, respectively) considering the opportunity for, and actually observed, formation of higher-boiling by-products. Such compounds are of a type being studied as radiation prophylactics.

Experimental

I. **Glycidyl Amines.**—Both mono- and diglycidyl amines (Table I) were prepared from the appropriate secondary or primary amine and epichlorohydrin by known procedures[8] or adaptations of them. Significant variations are noted herewith and in footnotes of Table I.

A. **2,3-Epoxypropyldimethylamine (III).**—Anhydrous dimethylamine (103 g., 2.3 moles) was placed in a precooled 1-l., three-necked flask equipped with a centrifugal stirrer, thermometer, dropping funnel, and Dry-Ice condenser. Cooling was accomplished by an acetone–Dry-Ice bath held at −10 to −20°. With good stirring, 6 ml. of water was added, followed by dropwise addition of 210 g. (2.27 moles) of epichlorohydrin. The latter was added at a rate of about 2–3 drops per second, at an initial temperature of 10°, but it soon reached 14 to 18°; this temperature was held rigidly throughout the addition. The temperature was held at 16–20° under close attention for about 1.5 hr. after the addition and then carefully allowed to rise to 24°. When it was apparent that reaction was complete (*ca.* 1 hr.), the solution was cooled in an ice–salt bath to 15° and a cold solution of 105 g. of sodium hydroxide in 175 ml. of water was added in a fine stream during 10 min., the temperature being kept below 24°. After another 10 min. at 24°, the upper oily layer was separated and the aqueous layer containing undissolved salt was extracted with three 100-ml. portions of ether. The extracts were combined with the oil and dried in the cold for about 0.5 hr. over 100 g. of potassium hydroxide pellets. The ether solution was decanted from the drying agent and aqueous phase and placed over fresh alkali overnight at 0°. It was filtered and rapidly distilled through a 6-in. packed column ($^3/_{16}$-in. helices) using a steam bath. This product, stored at 0°, slowly developed a cloudy appearance owing to salt formation with traces of unreacted epichlorohydrin, and eventually a dark sediment formed, necessitating redistillation. Nevertheless, recovery was good, even after 3 months' storage at 0°.

B. **Bis(2,3-epoxypropyl)methylamine.**—Apparatus and procedure resembled that used in part A, but with the following variations. To a solution of 33 g. of anhydrous methylamine in 400 ml. of ether was added 6 ml. of water, followed by gradual addition of 195 g. of epichlorohydrin at a reaction temperature of about 15°. The mixture was warmed at 27–29° for 6 hr., left for 18 hr. at 0°, then heated under reflux for 1.5 hr. It was then cooled and held at 22° during the 10-min. addition of a solution of 88 g. of sodium hydroxide in 140 ml. of water and for 1.75 hr. thereafter. The ether layer was separated, the aqueous layer extracted with ether, and the combined ether solutions were dried and distilled as already described.

C. **1,4-Bis(2,3-epoxypropyl)piperazine.** 1. **1,4-Bis(3-chloro-2-hydroxypropyl)piperazine (II).**—To 223 g. (2.42 moles) of epichlorohydrin containing 3 g. of water was added, dropwise, a solution of 102 g. (1.18 moles) of piperazine in 100 ml. of methanol. The temperature was maintained below 20° during the addition and at 20–30° for an additional 3 hr. During this time the product began to separate and an additional 200 ml. of methanol was added to facilitate stirring. The mixture was cooled, filtered, and the white crystalline solid washed with ligroin. Rapid recrystallization from 1200 ml. of boiling ethyl acetate, using charcoal, produced 106 g. of isomer A, m.p. 101.5–103°. On cooling the filtrate to −60°, 16 g. of isomer B, m.p. 82–84°, was obtained.

Anal. Calcd. for $C_{10}H_{20}Cl_2N_2O_2$: C, 44.3; H, 7.5; N, 10.4. Found (A): C, 43.8; H, 7.7; N, 10.2. Found (B): C, 44.7; N, 7.6; N, 10.2.

2. **1,4-Bis(2,3-epoxypropyl)piperazine.**—Chlorohydrin A (45 g.) was added to a stirred solution of 120 g. of sodium hydroxide in 200 ml. of water at 50°. Benzene was added, stirring was continued for 0.5 hr., and the benzene layer was then separated and filtered. This procedure was repeated with another portion of benzene and the combined benzene solutions were concentrated to dryness at reduced pressure. Recrystallization from 30 ml. of ether produced 22.5 g. of a partially hydrated product, m.p. 43–58°. Further recrystallization from ether produced the pure dihydrate of m.p. 63–64°.

II. **Mono- and Diglycidyl Ammonium Salts.**—Except as indicated in footnotes of Table II and in other examples described, the reactions of the free bases with methyl *p*-toluenesulfonate were carried out in benzene at 25° for periods ranging from 3 to 18 hr., followed by isolation and recrystallization from the appropriate solvent. Conversions of the tosylates to perchlorates or tetraphenylborides were usually effected in aqueous solution with the sodium salts of these anions.

A. **N,N-Bis(2,3-epoxypropyl)dimethylammonium *p*-Tosylate (IV).**—A solution of 71.5 g. of N,N-bis(2,3-epoxypropyl)methylamine and 93 g. of methyl *p*-toluenesulfonate in 150 ml. of dry benzene was held at 25–30° for 19 hr. The benzene was decanted; the sirupy residue was washed several times with benzene and then heated at 40° (0.1 mm.) for 1 hr. on a rotating evaporator. The residue, still containing about 10% benzene, weighed 156 g. and gradually crystallized. The colorless, very hygroscopic crystals were washed with ether; m.p. 48–54°. The perchlorate, formed in acetone with sodium perchlorate, could not be induced to crystallize.

B. **2-Butynylenebis[N,N-bis(2,3-epoxypropyl)-N-methylammonium Mesylate] (VIIa).**—A solution of 8.5 g. of 1,4-bis(methanesulfonoxy)-2-butyne[10] and 10.7 g. of N,N-bis(2,3-epoxypropyl)methylamine in 25 ml. of acetonitrile was stirred at 25–33° for 17 hr. Ether was then added, the precipitated gum washed several times with warm ether and dissolved in 250 ml. of acetonitrile. After drying over magnesium sulfate, decolorization with charcoal, and reprecipitation with cold ether, most of the residual solvent was removed *in vacuo* to give 17 g. of a colorless, hygroscopic, plastic mass.

Anal. Calcd. for $C_{20}H_{36}N_2O_{10}S_2$: C, 45.4; H, 6.8; N, 5.3; epoxy O, 12.1. Found: C, 43.3, 43.1; H, 6.6, 6.6; N, 5.6; epoxy O, 10.5.

C. ***p*-Xylylenebis[N,N-bis(2,3-epoxypropyl)-N-methylammonium Perchlorate] (VIIb).**—A mixture of 9.3 g. of *p*-xylylene dibromide and 10.8 g. of N,N-bis(2,3-epoxypropyl)methylamine in 175 ml. of acetonitrile was heated gradually to 50° and held there for 2 hr. The mixture was cooled, the solvent decanted, and the residue washed with warm acetonitrile. It was then dissolved in 20 ml. of water, washed with benzene, and the aqueous solution treated with a concentrated aqueous solution containing 10 g. of sodium perchlorate. The resulting gummy precipitate was crystallized from dilute ethanol to give 11.1 g. of a crude product of m.p. 200–207°. Further recrystallization from dilute ethanol and acetonitrile–ethyl acetate gave colorless, granular crystals of m.p. 209–214°.

Anal. Calcd. for $C_{22}H_{34}Cl_2N_2O_{12}$: C, 44.8; H, 5.8; Cl, 12.05. Found: C, 44.8; H, 5.8; Cl, 12.2.

D. **Poly[2-butynylene-N,N'-bis(2,3-epoxypropyl)piperazinium Dimesylate] (VIII).**—A solution of 12.0 g. of 1,4-bis(methanesulfonoxy)-2-butyne and 9.8 g. of 1,4-bis(2,3-epoxypropyl)piperazine in 55 ml. of acetonitrile was stirred for 14 hr. at 25–30° and then heated at reflux for 0.5 hr. The mixture was cooled, poured into 250 ml. of ether, and the precipitated, colorless gum washed with ether and the solvent removed *in vacuo;* yield 22.2 g.

Anal. Calcd. for $C_{16}H_{28}N_2O_8S_2$: C, 43.7; H, 6.4; N, 6.4; S, 14.5; epoxy O, 7.3. Found: C, 42.9, 42.9; H, 6.5, 6.7; N, 6.3; S, 13.9; epoxy O, 8.0.

III. **Reactions of 2,3-Epoxypropyltrimethylammonium *p*-Tosylate (V). A. With Amines and Mercaptans.**—For monoalkylation of primary amines, a solution of the salt in methanol was added to a methanolic solution of two equivalents of the

---

[10] We are indebted to Dr. D. D. Reynolds, of these laboratories, for this compound.

amine held at 45°. After 18 hr. at this temperature, the solvent was removed and the crystalline residue washed with ether and recrystallized. In the cases of secondary amines and mercaptans, approximately equivalent amounts of reactants were used and the methanol solutions heated at reflux for about 3 hr. Pertinent data are listed in Table III.

B. With Hydrogen Bromide.—To a solution of 14.4 g. (0.05 mole) of V in 75 ml. of methanol at 5° was added a solution of 4 g. (0.05 mole) of hydrogen bromide in 40 ml. of methanol. After 2 hr. at 25°, the solution was heated at reflux for 18 hr., neutralized with 0.1 g. of sodium bicarbonate, evaporated to dryness, and the residue recrystallized twice from acetone. The structure of the product (XVI) was confirmed by conversion to the known $C_6H_{13}SH$ adduct of V (see Table III) as follows: A solution of 1.4 g. of sodium *n*-hexylmercaptide and 3.7 g. of XVI in 75 ml. of methanol was heated at reflux for 7 hr. and left at 30° for 2 days. Then 2.7 g. of silver *p*-tosylate was added, the solution was boiled, filtered, and the filtrate evaporated to dryness. Recrystallization of the residue from acetone, using charcoal, gave an 86% yield of N-(2-hydroxy-4-thiadecyl)trimethylammonium *p*-tosylate; m.p. 119–121°. Its identity with the products prepared as indicated in Table III was confirmed by mixture melting points and infrared spectra.

C. With Water.—A solution of 5 g. of V in 15 ml. of water, heated at reflux for 18 hr., showed incomplete reaction. A similar solution containing 1 drop of 72% aqueous perchloric acid and allowed to stand for 3 days at 30° gave nearly complete recovery of V. When this latter solution was heated at reflux for 20 hr., evaporated to dryness, and converted to the perchlorate in acetonitrile solution with sodium perchlorate, 3.1 g. (75% yield) of diol XVII was obtained; m.p. 110–112.5° (from ethanol). A second recrystallization raised the melting point to 111.5–113.5°.

IV. Reactions of Tertiary Glycidyl Amines.—Most of the compounds prepared from the tertiary amines were involved in structure elucidations of the products derived from the quaternary salts. Reaction conditions and properties of the products are given in Table IV and in the following example.

3-Diethylamino-2-hydroxypropyl Mercaptan (IX).—A solution of 60 g. (1.5 moles) of sodium hydroxide in 500 ml. of water was saturated with hydrogen sulfide, with stirring and cooling in an ice bath. A slow stream of the gas was continued during the subsequent 2-hr. addition of 65 g. (0.5 mole) of 2,3-epoxypropyldiethylamine at a temperature of 4–10°. After 2 hr. at 10–20°, the solution was cooled to 5° and 123 ml. of concentrated (37.5%) hydrochloric acid added at less than 10°. The bulk of the water was removed on the steam bath at reduced pressure, and the residue extracted with 200-, 100-, and 100-ml. portions of ether. The combined ether solutions were dried over anhydrous magnesium sulfate and distilled through a 12-in. column packed with helices.

Essentially the same procedure was used to prepare XI from N,N-bis(2,3-epoxypropyl)ethylamine.

V. 3-(4-Pyridyl)propanethiol.—A solution of 346 g. (5.2 moles) of potassium hydroxide in 1600 ml. of 95% ethanol was treated with hydrogen sulfide until nydrogen sulfide was no longer absorbed. A slow stream of the gas was continued while the solution was heated to reflux and a solution of 288 g. (1.5 moles) of γ-3-chloropropylpyridine hydrochloride[11] in 400 ml. of ethanol was added during 0.5 hr. After an additional 2 hr. under reflux, the solution was cooled and the mercaptan liberated by the addition of 183 ml. (2.2 moles) of concentrated hydrochloric acid, *i.e.*, to the equivalence point of *ca.* pH 6.5. The solution was filtered, then concentrated to a volume of 700 ml., diluted with 500 ml. of brine, and the organic phase was extracted with chloroform. After drying over anhydrous magnesium sulfate, the solution was distilled rapidly through a short Vigreux column. The portion having a b.p. of 80–105° (0.1–0.3 mm.) was then fractionated to give 148 g. (65%) of colorless oil; b.p. 102–103.5° (1.2 mm.); $n^{25}\text{D}$ 1.5532.

Anal. Calcd. for $C_8H_{11}NS$: C, 62.8; H, 7.2; N, 9.15. Found: C, 62.8; H, 7.0; N, 8.9.

Acknowledgment.—The authors are indebted to Miss Thelma Davis for infrared spectra and to Miss Jane O. Fournier for preparation of a quantity of compound V.

[11] This was prepared according to the method of K. C. Kennard and D. M. Burness, *J. Org. Chem.*, **24**, 464 (1959). The crude hydrochloride was isolated after the reflux period by removing volatiles at reduced pressure, treating the residue with toluene and again stripping it at reduced pressure; the remaining hygroscopic solid was washed with ligroin (65–75°) and filtered.

Action of Base on Quaternary Salts of Nicotinamide[1-3]

DONALD C. DITTMER[4] AND J. M. KOLYER[5]

Department of Chemistry, University of Pennsylvania, Philadelphia 4, Pennsylvania

Received March 8, 1963

Treatment of 1-benzyl-3-carbamoylpyridinium chloride with sodium hydroxide in dilute ethanol yielded a new substance 11, believed to be a cyclic trimer. The structure of the new compound was based on its analysis, infrared spectrum, ultraviolet spectrum, fluorescence spectrum, proton magnetic resonance spectrum, molecular weight, and its chemical reactions. The compound is believed to have been formed by way of a pyridinium ylide. Several new pseudo base ethers of 1-substituted nicotinamide salts have been prepared.

Treatment of 1-substituted pyridinium salts and related compounds with hydroxide ions is reported to yield easily dissociated pseudo bases in which the hydroxide ion has become bound covalently to one of the carbon atoms of the heterocyclic ring.[6] In some cases the pyridinium ring is opened by alkali.[7]

This paper is about a new type of compound obtained by treatment of 1-benzyl-3-carbamoylpyridinium chloride with hydroxide ions or by treatment of pseudo base ethers with ethanol. Several new pseudo base ethers have been prepared also.

1

Results

When an aqueous solution of 1-benzyl-3-carbamoylpyridinium chloride was treated with sodium hydroxide in dilute ethanol, a white solid of empirical formula $(C_{13}H_{12}N_2O)_n$ precipitated; the empirical formula corresponds to the hypothetical ylide 1.

If the treatment with base was done in aqueous solution, the dimolecular ether 2 precipitated. The ether is formulated as a 1,4-dihydro structure on the basis of its having only one ultraviolet absorption maximum at 330–335 mμ in the nonpolar solvents,

---

[1] This work was supported in part by grant 7582 from the Nationa Science Foundation.

[2] For complete details see John M. Kolyer, Ph.D. thesis, University of Pennsylvania, 1960.

[3] Reported at the 139th National Meeting of the American Chemical Society, St. Louis, Mo., March, 1961.

[4] Department of Chemistry, Syracuse University, Syracuse 10, N. Y.

[5] Walter T. Taggart Memorial Fellow, 1959-1960.

[6] A. Hantzsch and M. Kalb, *Ber.*, **32**, 3109 (1899).

[7] Reviewed by H. S. Mosher in R. C. Elderfield, "Heterocyclic Compounds," Vol. I, John Wiley and Sons, Inc., New York, N. Y., 1950, pp. 424–433.