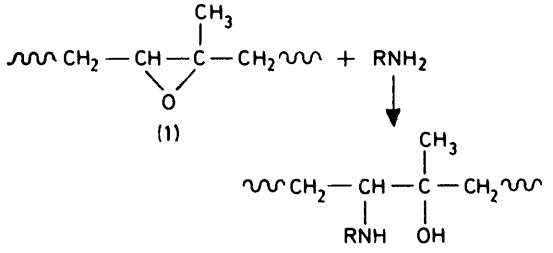
Reactions of a Mono- and a Tri-substituted Epoxide with Some Simple and β-Substituted Primary Amines; Novel Examples of Electrophilic Anchimeric Assistance

By **David R. Burfield, Seng-neon Gan,** and **Roger H. Smithers,*** Department of Chemistry, University of Malaya, Kuala Lumpur 22-11, West Malaysia

The reactions of a number of primary amines with a mono- and a tri-substituted epoxide have been examined. The results indicate that the presence of water has a strong reaction-accelerating effect for both heterocycles, and product studies have led to the isolation of secondary and tertiary amino-alcohols. Reactions of some amines possessing a weakly acidic group in the β-position proceeded anomalously rapidly, even under dry conditions, and it is suggested that these represent new examples of electrophilic anchimeric assistance.

IT has recently been conjectured [1,2] that non-oxidative cross-linking reactions occurring in natural rubber involve epoxide groups in the macromolecule. This proposal has been criticised [3] because a key step in the mechanism involves ring cleavage of the trisubstituted rubber epoxides (1) by amino-compounds, possibly amino-acids, as shown in Scheme 1. This objection



(1)

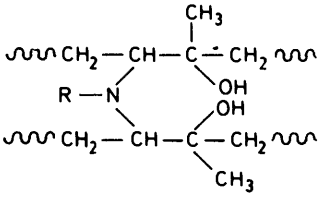
SCHEME 1

appears serious in view of the fact that Colclough *et al.*[4] have shown that the reaction of amines with the model epoxide 1-ethyl-2,2-dimethyloxiran under anhydrous conditions is extremely slow, even at 140 °C, let alone at the ambient temperatures under which natural rubber is known to undergo cross-linking.

In recent years, reactions of this type have assumed some industrial importance, *inter alia* in the curing of epoxide-based resins.[5] The prototype reaction, *i.e.* that between oxiran itself and ammonia, was first documented by Wurtz [6] in 1860; a more thorough later investigation by Knorr [7] revealed that the completely dry reagents did not react, but in the presence of a small amount of water the reaction took place readily to yield a mixture of amino ethanols. Similar findings have been substantiated in reactions between monosubstituted epoxides and primary and secondary amines,[4,5a] where the importance of solvent polarity and accelerating effects of weakly acidic compounds such as phenols have also been demonstrated.

Since induced cross-linking reactions in natural rubber occur under *aqueous* conditions,[8] it was important to discover whether similar activating effects occurred in the case of trisubstituted epoxides, which would perhaps facilitate the reaction under ambient conditions, a possibility which appears to have been largely overlooked in earlier work. In addition, it was of interest to find out if such reactions allowed the formation of amino-diols such as (2), or whether their formation would be precluded by steric considerations.

Model epoxides chosen for this study were methyloxiran and trimethyloxiran. Although trimethyloxiran is a better analogue for the natural rubber epoxide, the initial work utilised methyloxiran, which because of its relative simplicity yielded products that were easy to isolate and characterise; proficiency gained from this study was then applied to the trisubstituted case. The selection of some amines, *e.g.* cyclohexylamine and 2-aminoethanol, was influenced by their ability to promote cross-linking when added to latex in small amounts.[8]



(2)

Reactions were investigated by mixing the amine and epoxide at room temperature in various stoicheiometries under aqueous or dry conditions, and monitored, where appropriate, by following the ensuing temperature rise.

In cases where the heat of dissolution of the amine in water was significant, the system was allowed to equilibrate thermally before addition of the epoxide. Temperature rise *versus* time plots gave approximate rate measurements and reaction completion times. These

[1] D. R. Burfield, *Nature*, 1974, **249**, 29.
[2] D. R. Burfield and S. N. Gan, *J. Polymer Sci., Part A-1, Polymer Chem.* 1975, **13**, 2725.
[3] B. C. Sekhar, personal communication, 1975.
[4] T. Colclough, J. I. Cunneen, and C. G. Moore, *Tetrahedron*, 1961, **15**, 187.
[5] (*a*) L. Schechter, J. Wynstra, and R. P. Kurkjy, *Ind and Eng. Chem.*, 1956, **48**, 94; (*b*) W. Fisch, W. Hofmann, and J. Koskikallio, *J. Appl. Chem.*, 1956, **6**, 429: (*c*) L. A. O'Neill and C. P. Cole, *ibid.*, p. 356.
[6] A. Wurtz, *Annalen*, 1860, **114**, 51.
[7] L. Knorr, *Ber.*, 1897, **30**, 909.
[8] A. D. T. Gorton, *Rubber Ind.*, 1974, 41.

results must be viewed with some caution because the 'rates' are measured under non-isothermal conditions, and the maximum temperature attained does not indicate the precise completion of reaction, however they do allow some broad reactivity groupings to be made.

After work-up, which in the case of most aqueous systems involved extraction with chloroform or ether, drying, and removal of solvent, the products were subjected to (i) titration analysis for amine type content,[9] the results for which could be cross-checked in some cases against an n.m.r. analysis, and (ii) fractional distillation wherever expedient. The results are summarised in Table 1, Figures 1 and 2, and Scheme 2.

The elucidation of product structures, particularly from n.m.r. spectra was rendered more difficult by hydrogen bonding of the amino- and alcoholic protons; conversion into lithium alcoholates followed by *O*-methylation gave the ethers (5) (Scheme 2) and eased this problem in some cases. Where diastereoisomeric products are possible, *e.g.* (4a), n.m.r. spectra indicated the formation of only one isomer. Mass spectra, where taken, firmly support the assigned product constitutions, which indicate that, consistent with other results,[10] ring opening is regiospecific and occurs *via* exclusive attack of the amine at the least substituted carbon atom. The reaction of thiols with epoxides is well known to furnish

TABLE 1

Product distribution from the reactions of methyl- (A) and trimethyl-oxiran (B) with amines

Run no.	Epoxide	Amine	Conditions [c]	Products;[a,b] mole % of total amine: Primary	Secondary	Tertiary	Remarks
1 [d]	(A)	$PhCH_2{\cdot}NH_2$	Aqueous	32.1	49.0	18.9	Complete [e] in 12 min
2 [f]	(A)	$PhCH_2{\cdot}NH_2$	Aqueous	25.7	2.9	71.4	Complete in 13.5 min
3	(A)	$PhCH_2{\cdot}NH_2$	Dry	49.3	50.6	~0.1	Analysis after 48 h
4	(A)	$PhCH_2{\cdot}NH_2$	Dry	43.5	47.8	8.7	Analysis after 96 h
5	(A)	$PhCH_2{\cdot}NH{\cdot}CH_2{\cdot}CH(OH)Me$	Dry		47.1	52.9	Analysis after 24 h
6	(A)	Cyclohexylamine	Aqueous	2.0	81.6	16.3	Analysis after 17 h
7 [i]	(A)	$NH_2{\cdot}CH_2{\cdot}CO_2H$	Aqueous	*g*	38.1	16.9	Analysis after 17 h
8 [h,k]	(B)	$PhCH_2{\cdot}NH_2$	Aqueous	81.6	13.2	5.2	Analysis after 17 h
9	(B)	Cyclohexylamine	Aqueous	2.2	63.6	34.1	Analysis after 17 h
10 [h,i]	(B)	$NH_2{\cdot}CH_2{\cdot}CO_2H$	Aqueous alkaline (pH 9.1)	67.2	32.8	0	Analysis after 96 h
11	(A)	$HO{\cdot}CH_2{\cdot}CH_2{\cdot}NH_2$	Dry	23.5	50.6	25.9	Complete in 20 min
12	(A)	$HS_2CH_2{\cdot}CH_2{\cdot}NH_2$	Aqueous	0	98.5	1.5	Complete in 0.5 min
13	(B)	$HO{\cdot}CH_2{\cdot}CH_2{\cdot}NH_2$	Dry	2.8	79.9	17.2	Analysis after 48 h
14	(B)	$HS{\cdot}CH_2{\cdot}CH_2{\cdot}NH_2$	Aqueous	3.0	94.0	3.0	Complete in 21 min
15	(A)	$MeS{\cdot}CH_2{\cdot}CH_2{\cdot}NH_2$	Dry	89.9	10.0	0	Analysis after 24 h
16	(A)	$PhCH_2{\cdot}NH_2$	Ethanol solvent		Undetermined		No apparent reaction in 30 min
17	(A)	$PhCH_2{\cdot}NH_2$	Butanethiol solvent		Undetermined		No apparent reaction in 30 min

[a] Percentage totals obtained for aqueous systems differ from 100% owing mainly to the high solubility of the primary amines in water. [b] Satisfactory elemental and spectroscopic analyses were obtained for all new isolated compounds; see Experimental section. [c] All reactions were initiated at room temperature and, except where otherwise stated, equimolar stoicheiometries of reactants were used. [d] Both products isolated. [e] As indicated by the time taken to reach maximum reaction temperature. [f] 1 : 2 Molar ratio of amine to epoxide. [g] Unchanged glycine precipitated out after concentration of the reaction mixture and was removed prior to analysis. [h] Secondary amine isolated. [i] The corresponding diols were also formed (20—30%) in these reactions. [j] No detectable temperature rise in the first 120 min. [k] Virtually no reaction under dry conditions.

Products.—A neglected aspect of other, related investigations has been product study; in this work we have isolated and characterised some of the products.

As in the prototype case, the reactions of these heterocycles with a primary amine would be expected to yield a mixture of amino-alcohol, the primary product, and amino-diol formed in a secondary reaction; this was found to be the case (see Table 1).

[9] The established titration method of Siggia *et al.* was used: see (*a*) S. Siggia, 'Quantitative Organic Analysis via Functional Groups,' Wiley, New York, 3rd edn., 1963; (*b*) S. Siggia, J. G. Hanna, and I. R. Kervenski, *Analyt. Chem.*, 1950, **22**, 1295.

[10] For selected references concerning epoxide chemistry see (*a*) J. G. Buchanan and H. Z. Sable, 'Selective Organic Transformations,' vol. 2, ed. B. S. Thygarajan, Wiley, New York, 1972; (*b*) L. A. Paquette, 'Principles of Modern Heterocyclic Chemistry,' Benjamin, New York, 1968; (*c*) R. J. Gritter in 'Chemistry of the Ether Linkage,' ed. S. Patai, Wiley, New York, 1967; (*d*) M. S. Malinovskii, 'Epoxides and Their Derivatives,' Sivan Press, Jerusalem, 1965; (*e*) 'Heterocyclic Compounds,' Part 1, ed. A. Weissberger, Wiley, New York, 1964.

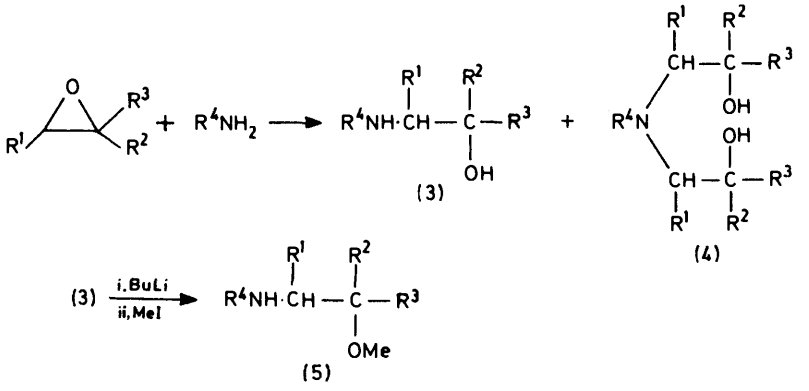
the corresponding alkylthio-alcohols;[10e] thus the reaction of 2-aminoethanethiol with these substrates can conceivably occur *via* attack of either heteroatom on the ring. That it is only the amine moiety which functions as the nucleophile was demonstrated by the following evidence for the structure (3e): (i) amine analysis indicated 98.5% secondary amine; (ii) both 2-aminoethanethiol and (3e) (but not methyl 2-aminoethyl sulphide) gave positive results in qualitative analytical tests for thiol groups with silver nitrate[9a] and lead acetate;[11] (iii) the i.r. spectrum of (3e) contains a weak band at 2 350 cm^{-1} which may be plausibly assigned[12] to S–H stretching.

Reactivity Trends.—Comparison of runs 1—4 in Table 1 shows the expected accelerating effect of water

[11] D. J. Pasto and C. R. Johnson, 'Organic Structure Determination,' Prentice-Hall, Englewood Cliffs, New Jersey, 1969.

[12] L. J. Bellamy, 'The Infra-red Spectra of Complex Molecules,' Methuen, London, 1966, p. 351.

for the monosubstituted epoxide, and, surprisingly, the readiness of the secondary reaction even under conditions of equimolar stoicheiometry. Runs 8 and 9 establish that essentially similar conclusions can be drawn for the trisubstituted epoxide; significantly, tertiary amine formation again competes with secondary and water has a rate-enhancing effect, although not unexpectedly reactions are generally slower than with methyloxiran and product distribution is influenced by both epoxide and amine structure. Presumably, for steric reasons, the differential in the rates of the primary and secondary reactions becomes diminished for the trisubstituted epoxide, thus allowing the formation of tertiary amine to compete more effectively with secondary (*cf.* runs 6 and 9). More nucleophilic amines also appear to produce larger amounts of tertiary amine (*cf.* runs 8 and 9).



a; $R^1 = R^2 = H$, $R^3 = Me$, $R^4 = PhCH_2$
b; $R^1 = R^2 = R^3 = Me$, $R^4 = PhCH_2$
c; $R^1 = R^2 = H$, $R^3 = Me$, $R^4 = CH_2CO_2H$
d; $R^1 = R^2 = R^3 = Me$, $R^4 = CH_2CO_2H$
e, $R^1 = R^2 = H$, $R^3 = Me$, $R^4 = HS\cdot CH_2\cdot CH_2$

SCHEME 2 Isolated products

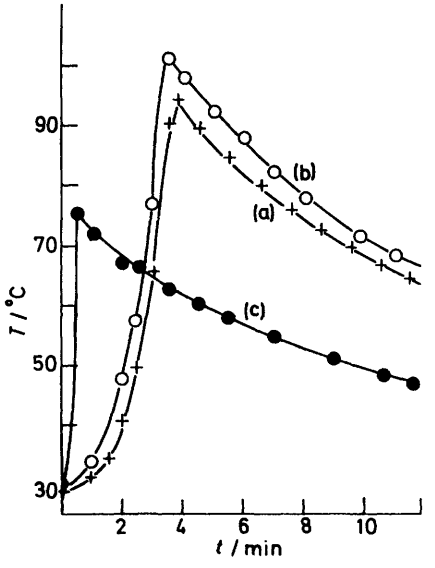


FIGURE 1 Temperature of reaction mixture *versus* time; solvent water; (a) 0.1 mol $NH_2\cdot CH_2\cdot CH_2\cdot NH_2$ + 0.1 mol methyloxiran; (b) 0.1 mol $NH_2\cdot CH_2\cdot CH_2\cdot OH$ + 0.1 mol methyloxiran; (c) 0.05 mol $NH_2\cdot CH_2\cdot CH_2\cdot SH$ + 0.05 mol methyloxiran

Anhydrous reactions of methyloxiran (runs 3 and 4) are relatively very slow, and are curious in that the rate of formation of secondary amine appears to tail off after 48 h, while that of formation of tertiary amine shows an

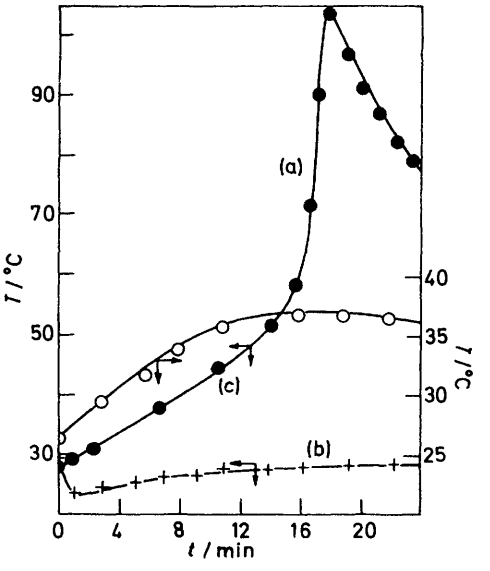
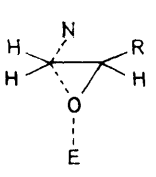


FIGURE 2 Temperature of reaction mixture *versus* time; (a) 0.1 mol $NH_2\cdot CH_2\cdot CH_2\cdot OH$ + 0.1 mol methyloxiran (no solvent); (b) 0.1 mol $NH_2\cdot CH_2\cdot CH_2\cdot NH_2$ + 0.1 mol methyloxiran (no solvent); (c) 0.05 mol $NH_2\cdot CH_2\cdot CH_2\cdot SH$ + 0.05 mol trimethyloxiran (solvent water)

increase. Tailing can be ascribed to a normal concentration effect, but the increase implies the presence of some other activating feature not present in the initial reactants and which emerges more clearly as the rate of the initial process slackens. Specifically, perhaps the β-hydroxy group generated as a result of the primary process influences the facility of the secondary. Run 5 demonstrates directly that this is the case: although this is stereochemically a much less favourable reaction than run 3, only half the time is required to reach the first approximate half-life point. In order to probe this β-effect more closely, reactions with other 2-hetero-substituted amines were examined. In Figure 2 the reactivities of 2-aminoethanol and ethylenediamine are compared; carefully dried 2-aminoethanol and methyloxiran reacted vigorously, whereas no significant reaction was observed with the diamine. In order to compare these two amines with 2-aminoethanethiol the reactions had to be conducted in water, because of solubility problems with the solid sulphur analogue. Figure 1 demonstrates the superior reactivity of the mercaptoamine: reaction was virtually instantaneous. The heightened reactivity of these β-substituted amines was also apparent on a reduced scale with trimethyloxiran, as shown in Figure 2 and the Table (runs 13 and 14). Alkylation of the β-grouping, as in run 15, resulted in a complete loss of the activating effect. It seemed likely that the accelerating effects could be duplicated by incorporating the activating groups into the solvent; runs 16 and 17 demonstrate that this is not the case.

Much has been written regarding the ring cleavage of epoxides.[10] Ring opening can occur by nucleophilic substitution, which may be electrophilically assisted, or with very strong bases *via* an epoxide anion to produce enolate [10a] or carbenoid [13] intermediates. Both from the structure of the products and from our conditions, it seems that the present case involves straightforward nucleophilic ring opening, and both the rate-enhancing effect of water and the β-effect can be accommodated by the presently accepted interpretation of such reactions, the so called ' push–pull ' mechanism. According to this concept, the major factors involved in such processes are



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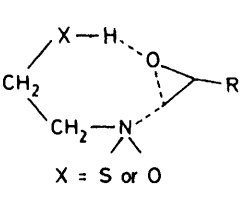


(7)

approach of the nucleophilic reagent (N), rupture of the C–O bond, and the effect of the electrophilic reagent (E; the solvent in these reactions) as represented in the transition state (6). Thus, besides being a proton-transfer reagent, water acts to some extent as a weak electrophile, and the relative reactivities of the β-groups, *i.e.* SH > OH > NH parallel their known acidities. This, taken together with the complete loss of the activating effect on removal of the acidic X–H bond by methylation, points to the β-groups as playing a key role as electrophiles. Significantly, glycine, which also possesses an acidic grouping on the β-carbon atom, is less reactive than a simple amine like benzylamine (*cf.* runs 1 and 7) and the relative pK_b values (Table 2) enable

TABLE 2

Basicities of β-substituted amines

Amine	pK_b
$NH_2{\cdot}CH_2{\cdot}CH_2{\cdot}NH_2$	4.0
$HO{\cdot}CH_2{\cdot}CH_2{\cdot}NH_2$	4.5
$HS{\cdot}CH_2{\cdot}CH_2{\cdot}NH_2$	5.4 [a]
$HO_2C{\cdot}CH_2{\cdot}NH_2$	11.7

[a] J. W. Haefele and R. W. Broge, *Kosmetik-Parfum-Drogen Rundschau*, 1961, **8**, 1 (*Chem. Abs.*, 1962, **56**, 4591).

reactivities to be put on a more quantitative basis. Reactivity is seen to increase with decreasing basicity, reaching a maximum at 2-aminoethanethiol before a sharp decrease at glycine. In other words, reactivity appears to be a fine balance between an enhancing effect, which increases with β-group acidity, and a deactivating effect resulting from partial * or complete internal protonation of the base, as typified by the zwitterionic structure of amino-acids. Consistently, although the reaction of neutral glycine with trimethyloxiran was too slow to be detectable under our conditions, a smooth reaction proceeded with its conjugate base (run 10, Table 1).

The β-Effect.—Our results show the β-effect to be an important new phenomenon (see below), yet evidence from earlier investigations also pointed to its existence. Thus, a rate-enhancing effect of hydroxy-groups generated in the reaction of 2,3-epoxypropyl phenyl ether with 2,2′-iminodiethanol was postulated to explain the inflection in the corresponding kinetic plots.[5a] Most recently, the more rapid reaction of 2-aminoethanol than of ethylenediamine with a monosubstituted epoxide has also been noted,[15] but no rationale was advanced.

The failure of epoxide and amine to produce any significant reaction in ethanol and butanethiol solvents suggests that the β-effect involves a unique intramolecular ' push–pull ' process involving a seven-membered transition state (7). Although this transition state is similar to others which have been formulated for neighbouring group participations,[16] it is unlike most examples in that it is not a cationic transition state, but rather represents another novel example of *electrophilic* anchimeric

* 2-Aminoethanethiol itself is purportedly 60% zwitterionic at pH 10.[14]

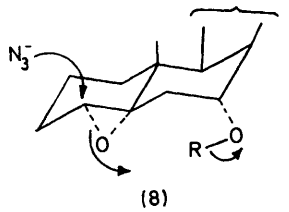
[13] See for example R. N. McDonald, R. N. Steppel, and R. C. Cousins, *J. Org. Chem.*, 1975, **40**, 1694.

[14] H. Tanaka, H. Sakurai, and A. Yokoyama, *Chem. and Pharm. Bull. (Japan)*, 1970, **18**, 1015.

[15] J. Kalal, F. Svec, and V. Marousek, *J. Polymer. Sci., Part C*, 1974, **47**, 155.

[16] For a review, see B. Capon, *Quart. Rev.*, 1964, **18**, 45.

assistance. One more recently reported example [17] involves participation by a 7α-hydroxy-group in the ring-opening of a 4α,5α-epoxycholestane by azide ion as shown in (8a). Here, as in our example, use of the methyl ether derivative (8b) resulted in much lower reactivity.



(8)

a; R = H
b; R = Me

As stated,[17] such examples are as yet rare in the literature, and the present case is unique in that one cyclic transition state involving electrophile, nucleophile, and the rupturing bond best accommodates the results. In other neighbouring group participations, seven-membered examples are relatively disfavoured on strain and entropy grounds.[16] However, the present case may be exceptional because the ring contains three heteroatoms, and models suggest that, particularly for the thia-analogue, strain is reduced on account of the non-equivalent bond lengths and angles thereby introduced. Although little appears to be known concerning the geometry and conformational properties of seven-membered and larger ring compounds containing heteroatoms,[18] the available evidence indicates that their inclusion can facilitate the formation of otherwise unfavourable medium-sized rings from acyclic precursors.[19]

In conclusion, this work has shown that, under aqueous conditions, a trisubstituted epoxide reacts smoothly with primary amines of varying structure at room temperature to give both secondary and tertiary amines, a result of considerable significance to the question [20] of the role of epoxides in cross-linking reactions in natural rubber. Even allowing for the enhancing effect of water, these results are in marked contrast to those reported earlier.[4] It is surprising that butylamine should not react with 1-ethyl-2,2-dimethyloxiran at 140 °C; however, an explanation may lie in the experimental conditions employed. These processes presumably have large negative entropies of activation and thus an increase in reaction temperature will lead to an adverse increase in the free energy of reaction which, if this influence predominates, may outweigh any kinetic advantage thereby gained.

EXPERIMENTAL

^{1}H N.m.r. spectra were recorded at 60 MHz with a Hitachi–Perkin-Elmer R-20B instrument (tetramethylsilane as internal standard; solvent $CDCl_3$ unless stated otherwise). I.r. spectra were obtained with a Beckmann IR 4240 instrument for liquid film samples. Mass spectra were recorded at 70 eV with an A.E.I. MS 9 spectrometer. Elemental analyses were performed by the Australian Microanalytical Service, University of Melbourne, Australia.

Materials.—Methyloxiran and most commercial grade amines were purified prior to use by distillation, and kept over molecular sieves; 2-aminoethanol was dried over potassium hydroxide pellets, and then purified in the same way. Commercial glycine was purified by recrystallisation from water–methanol.

Trimethyloxiran.—This was prepared from 2-methylbut-2-ene *via* two procedures.

(a) *Epoxidation.* Monoperoxyphthalic acid (*ca.* 1 mol) in ether (500 ml) was cooled in an acetone–solid CO_2 bath; when the temperaure fell below 5 °C, the olefin (80 g, 1.143 mol) was added dropwise with stirring, occasional cooling then being applied to keep the temperature between 0 and 5 °C. Stirring was continued for a further 2 h, at which point an iodide titration indicated that the reaction was complete. Distillation (Vigreux column) then removed the ether, followed by the epoxide (17.5 g, 20%; b.p. 76—79°), which was stored over molecular sieves.

(b) *Bromohydrin method.* The standard procedure outlined above gave consistently poor yields, and was tedious in that monoperoxyphthalic acid had first to be freshly prepared. A more straightforward method, particularly for large-scale runs, was the following adaptation of an older procedure.[21]

A stock solution of potassium bromide (178.5 g, 1.50 mol in 3 l of water) (200 ml) was saturated with bromine and added slowly to a stirred suspension of the olefin (100 g, 1.43 mol) in water (300 ml), whereupon complete decolourisation occurred. The process was repeated with further 200 ml portions until the emulsion acquired a permanent faint yellow tinge (total volume added *ca.* 2.5 l). The bromohydrin layer was separated, potassium hydroxide (70 g, 1.25 mol) in water (300 ml) was added all at once, and the mixture was distilled. The fraction boiling at 72—82°, dried ($MgSO_4$) and redistilled, yielded trimethyloxiran (57 g, 46%), b.p. 74—78° (Found: C, 69.5; H, 11.9; O, 19.0. Calc. for $C_5H_{10}O$: C, 69.7; H, 11.7; O, 18.6%).

Although the standard titration procedure for the analysis of epoxides has been reported as not applying to a number of trisubstituted examples, excellent results were in fact obtained. Samples in benzene were titrated with standard hydrogen bromide in acetic acid to the blue-green end-point of Crystal Violet (assay 98 ±1.6%).

2-Aminoethyl Methyl Sulphide.—A solution of 2-aminoethanethiol (7.7 g, 0.10 mol) in dry methanol (20 ml) was added slowly to a cold (ice-bath) solution of sodium methoxide [sodium (2.53 g, 0.11 g atom) in methanol (30 ml)]. The solution was stirred, brought to room temperature, and concentrated to *ca.* 25 ml. Methyl iodide (15.6 g, 0.11 mol) in methanol (5 ml) was then added with stirring and cooling and the mixture stirred at room temperature for 2 h. As much of the methanol as possible was then removed by distillation, and water (10 ml) and sodium chloride (2.0 g) were added. After shaking thoroughly, extraction with dichloromethane (3 × 10 ml), drying ($MgSO_4$), and con-

[17] See Y. Houminer, *J.C.S. Perkin I*, 1975, 1663, and references cited therein.
[18] C. Romers, C. Altona, H. R. Buys, and E. Havinga, *Topics Stereochem.*, 1969, **4**, 91.
[19] J. Sicher, *Progr. Stereochem.*, 1962, **3**, 218.
[20] S. N. Gan, Ph.D. Thesis, University of Malaya, 1976.
[21] J. Read and W. G. Reid, *J. Chem. Soc.*, 1928, 1487.

centration, distillation through a short Vigreux column gave the amine (4.5 g, 49.5%), b.p. 62—63° at 32 mmHg, δ (neat) 1.38 (2 H, s), 2.03 (3 H, s), and 2.15—2.75 (4 H, m).

Reaction Procedure.—All reactions were carried out on a 100 mmol scale except those involving 2-aminoethanethiol, which were 50 mmol. The reaction of benzylamine with methyloxiran serves as an example.

Benzylamine (10.7 g, 100 mmol), methyloxiran (5.8 g 100 mmol), and water (25 ml) were mixed; stirring was begun immediately, and the temperature noted at intervals up to 20 min, when the reaction was judged complete. The mixture was then extracted with chloroform (3 × 20 ml) and the combined extracts were dried ($MgSO_4$) and evaporated at room temperature. The product was a thick viscous liquid (15.7 g).

Amine Analysis.[9]—End points were determined by plots of pH *versus* volume of acid, or, where no sharp inflections occurred, by use of screened Methyl Red indicator. Blank titrations were carried out to reduce errors.

Total amine content was determined by titration of accurately weighed samples (*ca.* 1 g) in propan-2-ol (50 ml) against standard hydrogen chloride in propan-2-ol (*ca.* 1.0M). Secondary and tertiary amine contents were determined by first removing primary amine by treatment of samples (*ca.* 2 g) with salicylaldehyde (5 ml) for 90 min before titration. Likewise, tertiary amine was determined by removal of primary and secondary amines from the sample (*ca.* 3 g) by acetylation with acetic anhydride (10 ml), followed by the usual acid titration. For results, see Table 1.

Fractional Distillation.—The reaction mixture described above was fractionally distilled in a semi-micro apparatus with a short Vigreux column. This led to isolation of the amino-alcohol (3a) (6.6 g, 40%) and the amino-diol (4a) (3.6 g, 33%) as viscous liquids. 1-Benzylaminopropan-2-ol (3a) had b.p. 102° at 2 mmHg; d_4^{28} 1.018; δ 1.05 (3 H, d, *J* 6.0 Hz), 2.4 (2 H, m), 3.05br (2 H, s), 3.65 (3 H, s, m), and 7.15 (5 H, s). *N-Benzyl-1,1'-iminodipropan-2-ol* (4a) had b.p. 159—162° at 2 mmHg; d_4^{28} 1.002 (Found: C, 70.15; H, 9.5; N, 5.95; O, 14.2. $C_{12}H_{19}NO_2$ requires C, 69.95; H, 9.4; N, 6.25; O, 14.5%); $\nu_{max.}$ 1 050, 1 125, 1 450, 1 490, and 3 360 cm^{-1}; δ 1.05 (6 H, d, *J* 6.0 Hz), 2.44 (4 H, m), 3.5—4.0 (6 H, m), and 7.25 (5 H, s).

Similarly isolated were *3-benzylamino-2-methylbutan-2-ol* (3b), b.p. 117—120° at 2 mmHg (Found: C, 74.75; H, 9.85; N, 7.0; O, 8.6. $C_{12}H_{19}NO$ requires C, 74.6; H, 9.85; N, 7.25; O, 8.3%); δ 1.04 (3 H, s), 1.05 (3 H, d, *J* 6.0 Hz), 1.18 (3 H, s), 2.25br (1 H, s), 2.45 (1 H, q, *J* 6.0 Hz), 3.45—3.80 (3 H, m), and 7.25 (5 H, s) (the geminal methyl groups are diastereotopic). Attempts to distil (4b) resulted in decomposition; (3c) could not be isolated. *NN-Bis-(2-hydroxypropyl)glycine* (4c) had b.p. 124—128° at 3 mmHg (Found: C, 50.3; H, 9.3; N, 7.55; O, 33.2. $C_8H_{17}NO_4$ requires C, 50.3; H, 8.9; N, 7.3; O, 33.5%); $\nu_{max.}$ 1 390, 1 640, 2 100, 2 600—3 100, and 3 350 cm^{-1}; *m/e* 146 (1%) 57 (6%), and 45 (100%).

N-(2-Hydroxy-1,2-dimethylpropyl)glycine (3d). After removal of water, a viscous solution containing a suspended white solid was obtained. Addition of methanol produced a granular precipitate, which was filtered off and dried (m.p. 200—203°). This was insoluble in propan-2-ol, so titration with standard hydrogen bromide in acetic acid was carried out. Slow recrystallisation from methanol (96 h) yielded the *amino-alcohol* (3d), m.p. 244—245° (Found: C, 51.8; H, 9.5; N, 8.75; O, 29.8. $C_7H_{15}NO_3$ requires C, 52.2; H, 9.3; N, 8.7; O, 29.8%); $\nu_{max.}$ 510, 1 390, 1 630, and 2 000—3 300 cm^{-1} (multiple bands); δ (D_2O) 1.25 (9 H, m), 3.15 (1 H, q, *J* 6.5 Hz), 3.60 (1 H, s), and 3.66 (1 H, s); *m/e* 162 (1%, *M* + H), 161 (0.1%), 160 (0.5%, *M* − H), 146 (20%), 102 (100%), 56 (85%), and 30.7 (*m**, 102 − HCO_2H).

3-(2-Mercaptoethylamino)propan-2-ol (3e). The aqueous reaction of 2-aminoethanethiol with methyloxiran was too vigorous for a preparative run at room temperature, but reaction at 0—5 °C gave quantitative yields. The product could not be distilled without decomposition, therefore the dried chloroform extract was passed through a pad of Kieselguhr, the solvent removed, and elemental analysis carried out directly (Found: C, 39.6; H, 8.2; N, 10.1; S, 26.6. Calc. for $C_5H_{13}NOS$: C, 44.45; H, 9.65; N, 10.35; S, 23.7%); $\nu_{max.}$ 725, 1 035, 1 070, 1 120, 2 375, and 3 320 cm^{-1}; δ 1.25 (3 H, d, *J* 6.0 Hz), 2.30—3.10 (9 H, m), and 3.88 (1 H, sextet).

The ethers (5a and b) were obtained by methylation of (3a and b) using the following general procedure. The amino-alcohol (3a) (3.30 g, 20 mmol) in absolute ether (10 ml) was stirred under nitrogen while butyl-lithium (9.5 ml of 2.35M-solution in hexane; 22.0 mmol) was slowly added from a syringe *via* a serum cap. After stirring for 5 min, methyl iodide (2.85 g, 20 mmol) in ether (5 ml) was added in the same way, and the mixture became warm. After stirring for 15 min, aqueous work-up followed by drying, removal of solvent, and distillation yielded *N-benzyl-2-methoxypropylamine* (5a) as an oil in near quantitative yield; b.p. 110—111° at 7 mmHg; d_4^{28} 0.983 (Found: C, 74.05; H, 9.65; N, 7.65; O, 9.3. $C_{13}H_{21}NO_2$ requires C, 73.75; H, 9.5; N, 7.8; O, 8.95%); δ 1.05 (3 H, d, *J* 6.0 Hz), 1.43 (1 H, s), 2.20 (3 H, s), 2.25 (1 H, d), 2.26 (1 H, d), 3.5 (2 H, d, *J* 6.0 Hz), 3.75 (1 H, m), and 7.2 (5 H, s). *N-Benzyl-2-methoxy-1,2-dimethylpropylamine* (5b) had b.p. 106—108° at 2 mmHg; $\nu_{max.}$ 1 120, 1 170, 1 470, 1 590, and 3 400 cm^{-1}; δ 1.04 (3 H, s), 1.05 (3 H, d), 1.15 (3 H, s), 2.45 (1 H m), 2.7br (4 H, s), 3.6—3.8 (2 H, m), and 7.24 (5 H, s).

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