

that a reversible addition of amine to aldehyde is favored by electron-attracting substituents while the subsequent dehydration step is accelerated by electron-repelling substituents. The balance between these two factors could result in a maximum in over-all rate. This explanation is even consistent with the observation that the rate of semicarbazone formation increases steadily with sigma for a series of acetophenones.¹⁶ Here the amino alcohol is tertiary and would dehydrate rapidly, eliminating the substituent effect at this stage of the reaction.

Quite a different explanation of maxima in equilibrium constants for semicarbazone is given by Branch and Calvin,¹⁷ who suggest that hemiacetal formation, which reduces the concentration of the aldehyde, is favored by electron-attracting substituents.

It would be deceptive to proceed further without

(16) R. P. Cross and P. Fugassi, *THIS JOURNAL*, **71**, 223 (1949).

(17) G. E. K. Branch and M. Calvin, "The Theory of Organic Chemistry," Prentice-Hall, Inc., New York, N. Y., 1941, p. 348. See also ref. 9, pp. 152, 249.

recognizing that the rate relationships discussed above are strongly temperature dependent. If A and E_a in Table IV do not vary with temperature,¹⁸ no maximum in rate for these four compounds will appear above 100°. The much larger variations in A and E_a given by Cross and Fugassi¹⁶ result in a positive value of ρ at 25°, negative ρ calculated for 50°, and a minimum in rate at 0°. (This minimum would not be present if A and E_a were exactly linear in σ . The slight deviations from linearity are responsible for its appearance.) The data of Tommila¹⁹ for the Cannizzaro reaction of substituted benzaldehydes show a deep minimum in E_a , but parallel values of A lead to a nearly linear $\log k$ - σ relationship.

Acknowledgment.—Part of this work was supported by the Office of Ordnance Research, U. S. Army.

(18) Some variation has been noted (ref. 2).

(19) E. Tommila, *Ann. Acad. Sci. Fennicae*, **A59**, No. 8, 3 (1942); *Chem. Zentr.*, **114**, II, 1527 (1943).

CHARLOTTESVILLE, VA.

[CONTRIBUTION FROM THE RESEARCH DEPARTMENT, UNION CARBIDE CHEMICALS CO.]

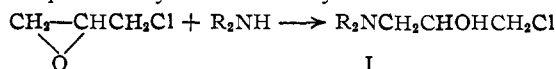
The Reaction of Epichlorohydrin with Secondary Amines

BY DONALD L. HEYWOOD AND BENJAMIN PHILLIPS

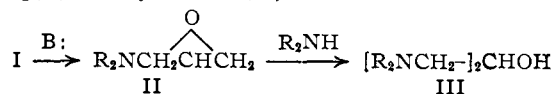
RECEIVED OCTOBER 5, 1957

Reaction of unsubstituted cyclic secondary amines and epichlorohydrin followed by treatment with alkali gave, when allowed to proceed to completion, 2,5-bis-(dialkylaminomethyl)-*p*-dioxanes. The structures were proved by independent synthesis and conditions were determined for directing the reactions to either the dioxanes or the N-(2,3-epoxypropyl)-dialkylamines as the major products.

The reaction between amines and epichlorohydrin has been studied extensively in the past, both from a point of view of investigating the nature of the reaction and of preparing polymers. The chemistry of epichlorohydrin in general was reviewed in 1949¹; work since then on the reaction between secondary amines and epichlorohydrin has been limited to uses of the reaction for preparative purposes²⁻⁶ and calculations of rate constants for reactions between several amines and epichlorohydrin.⁶ The reaction between secondary amines and epichlorohydrin is usually formulated as



Treatment of the chlorohydrin I with base (either excess amine¹ or alkali⁷) affords the N-(2,3-epoxypropyl) dialkylamine (II). When excess amine is



(1) "Epichlorohydrin," Technical Booklet SC: 49-35, Shell Chemical Corp., 1949.

(2) W. Davies and W. E. Savage, *J. Chem. Soc.*, 850 (1950).

(3) R. Rothstein and K. Binovic, *Compt. rend.*, **236**, 1050 (1953); R. Rothstein, *et al.*, *ibid.*, **239**, 284 (1954); K. Binovic, *Bull. soc. chim. France*, 167 (1957).

(4) W. Dale, U. S. Patent 2,520,093, Aug. 22, 1950.

(5) G. Benoit and A. Funke, *Bull. soc. chim. France*, 946 (1955).

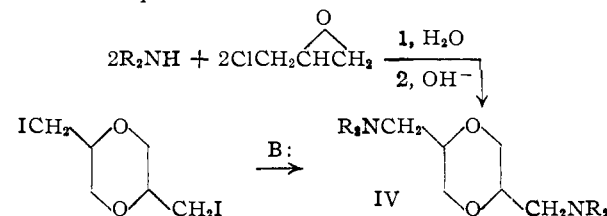
(6) J. Hansson, *Svensk. Kem. Tidskr.*, **66**, 287, 351 (1954); **67**, 245, 256, 263 (1955).

(7) H. Gilman, *et al.*, *THIS JOURNAL*, **68**, 1291 (1946).

used the 1,3-bis-(dialkylamino)-propanol-2 (III) can be isolated.^{3,5,8}

We had occasion to prepare a series of N-(2,3-epoxypropyl)-dialkylamines. Reaction of aqueous morpholine with epichlorohydrin followed by treatment with alkali gave a crystalline product (C₁₄H₂₆O₄N₂) in 65% yield. This compound was suspected of being 2,5-bis-(4-morpholinylmethyl)-*p*-dioxane [IV, R₂ = O(CH₂CH₂)₂] on the basis of amine titration by perchloric acid, infrared absorption spectrum, and a report in the literature⁹ on the isolation from similar reactions of compounds for which similar structures were proposed. The yields were not stated, however, and no proof of structure was presented.

That the C₁₄-product was indeed 2,5-bis-(4-morpholinylmethyl)-*p*-dioxane was shown by its independent synthesis by reaction of morpholine and *trans*-2,5-bis-(iodomethyl)-*p*-dioxane,⁹ in which excess morpholine served as the base.

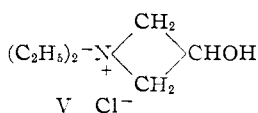


(8) C. K. Ingold and E. Rothstein, *J. Chem. Soc.*, 1666 (1931).

(9) R. K. Summerbell and J. R. Stephens, *THIS JOURNAL*, **76**, 6401 (1954).

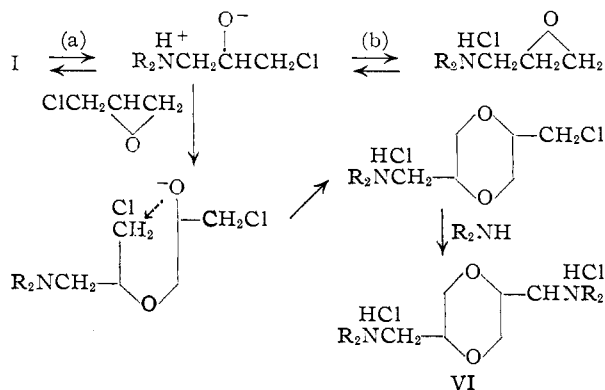
The reactions with some other secondary amines and epichlorohydrin were then investigated; the dioxane-forming reaction was significant only for three unsubstituted cyclic amines: pyrrolidine, piperidine and morpholine (see Experimental). It occurred to the extent of about 3% with diethylamine, and failed completely in the cases of two substituted morpholines: 2-phenylmorpholine and 2,6-dimethylmorpholine. In the latter case, conditions were the same as those that gave the dioxane product IV in 65% yield with morpholine, but only the "normal" product, 4-(2,3-epoxypropyl)-2,6-dimethylmorpholine [II, $R_2 = O-(CH(CH_3)CH_2-)_2$], could be isolated (77% yield). Dipropylamine also gave only the expected product (II, $R = n-C_3H_7$) in 63% yield.

Rothstein and Binovic³ postulated the existence of a "cyclaminium" ion (V) as a precursor of the dioxane product in the diethylamine-epichlorohydrin reaction. Their evidence was (a) the non-



identity of the ionic chloride-containing entity with the hydrochloride of the major product (N-(2,3-epoxypropyl)-diethylamine), and (b) the increase in concentration of ionic chloride on standing in solution. This latter effect was observed previously.¹⁰

An alternative mode of formation of the dioxane product is



Support for the above mechanism is gained from our observation that when the reactants are mixed rapidly in the presence of a small amount of water and worked up immediately after the initial reaction has subsided, the epoxyamine II is the major product. If, instead, the reactants are mixed slowly and allowed to stand overnight, the dioxane IV is the major product. Furthermore, when pure 4-(2,3-epoxypropyl)-morpholine was allowed to react with 1 mole of aqueous HCl and then treated with alkali, the dioxane IV was isolated, thus demonstrating the reversibility of step b. The ionic chloride-containing products in the previous work may have been simply the dihydrochlorides of the dioxane products VI. The difference in reactivity between the unsubstituted cyclic

amines on the one hand, and the acyclic and substituted cyclic amines on the other, is probably a manifestation of the low and high steric requirements¹¹ of the two types of amines of comparable basicity. The higher steric requirements will result in additional F-strain in step c of the mechanism formulated above. The effect of substituent groups on the carbon beta to the amine function in the cyclic amines is perhaps more subtle.

A third possible mode of formation of the dioxane products is through a type intermediate suggested by Culvenor and co-workers,¹² who also observed the formation of dioxane derivatives on treatment of epichlorohydrin with basic reagents.

Although *trans*-2,5-bis-(iodomethyl)-*p*-dioxane was used in the alternate syntheses of the amino-methyl dioxanes, this is not taken as evidence that the dioxane product from the amine-epichlorohydrin reaction was exclusively the *trans* isomer. In fact, it is indicated by the following observation that a mixture of *cis* and *trans* isomers was formed in the latter reaction: the crude 2,5-bis-(4-morpholinylmethyl)-*p*-dioxane [IV, $R_2 = O(CH_2CH_2-)_2$] exhibited the theoretical neutralization equivalent and melted 14° below the final constant m.p. (108–110°).¹³ The stereochemistry of the products was not investigated further.

Experimental¹⁴

2,5-Bis-(4-morpholinylmethyl)-*p*-dioxane (I). A. From Morpholine and Epichlorohydrin.—Epichlorohydrin (277.5 g., 3.0 moles) was added all at once and with vigorous stirring to morpholine (261.4 g., 3.0 moles) containing 9 g. of water. The temperature of the ensuing vigorous reaction was maintained between 18 and 35° by occasional cooling with solid carbon dioxide in acetone for 2 hours, after which the solution was allowed to stand for 48 hours at room temperature. The reaction mixture, which had partially crystallized, was then heated to 75° and treated during 15 minutes with 365 g. of aqueous sodium hydroxide (38.4%). The cooled solution was filtered to give 131 g. of crude product, m.p. 94–96°. Continuous extraction of the filtrate with ether gave, after removal of the ether, an additional 159 g. of product, m.p. 94–102°; total yield 290 g. (66%), b.p. 175–180° (1.5 mm.), m.p. 108–110° (ethanol).

Anal. Calcd. for $C_{14}H_{26}O_4N_2$: C, 58.72; H, 9.15; N, 9.78; mol. wt., 286; neut. equiv., 143. Found: C, 59.31; H, 9.28; N, 9.54; mol. wt., 294; neut. equiv., 143.

The dihydrochloride was prepared. After being recrystallized from methanol-ethanol, it decomposed without melting at 245–260°.

Anal. Calcd. for $C_{14}H_{26}O_4N_2 \cdot 2HCl$: C, 46.80; H, 7.85; Cl, 19.8. Found: C, 47.16; H, 8.20; Cl, 19.7.

In other preparations of 2,5-bis-(4-morpholinylmethyl)-*p*-dioxane, the morpholine in excess water was fed continuously into the epichlorohydrin while the temperature was maintained at 25–40° with ice-water cooling. The remainder of the work-up was the same as above, and yields were comparable.

B. From *trans*-2,5-Bis-(iodomethyl)-*p*-dioxane and Morpholine.—A solution of 7.36 g. (0.02 mole) of *trans*-2,5-bis-

(11) H. C. Brown, *Rec. Chem. Progr. Kresge-Hooker Sci. Lib.*, **14**, 83 (1933).

(12) An analogy suggested by a referee; see: C. C. J. Culvenor, W. Davies and W. E. Savidge, *J. Chem. Soc.*, 2198 (1949); C. C. J. Culvenor, W. Davies and F. G. Haley, *ibid.*, 3123 (1950).

(13) As pointed out by a referee, there is no evidence to exclude the possibility that the lowering of the melting point is due to the presence of 2,6-isomers.

(14) Melting points are uncorrected; mol. wts. were ebullioscopic and amine neut. equivs. were by titration with perchloric acid in glacial acetic acid (S. Siggia, "Quantitative Organic Analysis via Functional Groups," 2nd ed., John Wiley and Sons, Inc., New York, N. Y., 1954, p. 105).

(10) N. S. Drozdov and O. M. Cherutzov, *J. Gen. Chem. (U.S.S.R.)*, **4**, 669 (1934); *C. A.*, **29**, 2148⁷ (1935).

(iodomethyl)-*p*-dioxane⁹ in 49.5 g. (0.57 mole) of morpholine was refluxed for 1 hour. On cooling to -8° , 10 g. of light tan solid (morpholine hydroiodide) precipitated and was removed by filtration. Concentration of the filtrate at 50 mm. left 7 g. of dark crystalline 2,5-bis-(4-morpholinylmethyl)-*p*-dioxane which, after recrystallization from ethanol, exhibited a m.p. and mixed m.p. with the product from A (above) of 109.5–111.5 $^{\circ}$.

C. From 4-(2,3-Epoxypropyl)-morpholine and HCl.—Hydrochloric acid (42 ml. of 10 *N* solution) was added with stirring and cooling to 4-(2,3-epoxypropyl)-morpholine during 20 minutes. The solution was then allowed to stand at room temp. for 3 days, after which sodium hydroxide (56 g. of 30% soln.) was added. The white precipitate which formed (20 g., 34%) was recrystallized from ethanol to give 2,5-bis-(4-morpholinylmethyl)-*p*-dioxane, m.p. and mixed m.p. with the product from A (above), 107–110 $^{\circ}$.

4-(2,3-Epoxypropyl)-morpholine.—The reaction was performed exactly as in method A for the preparation of 2,5-bis-(4-morpholinylmethyl)-*p*-dioxane above, except that the sodium hydroxide solution was added at 30 $^{\circ}$ 1 hour after the initial exothermic reaction subsided. Fractionation of the residue after removal of the ether gave 231 g. (54%) of 4-(2,3-epoxypropyl)-morpholine, b.p. 93–95 $^{\circ}$ (12 mm.), n_{D}^{20} 1.4651, lit.⁵ b.p. 95–97 $^{\circ}$ (12 mm.).

Anal. Calcd. for $C_7H_{13}O_2N$: C, 58.72; H, 9.15; mol. wt., 143; neut. equiv., 143. Found: C, 59.33; H, 9.53; mol. wt., 148; neut. equiv., 143.

A crystalline residue of 43 g. (10%) of 2,5-bis-(4-morpholinylmethyl)-*p*-dioxane remained after the distillation.

4-(2,3-Epoxypropyl)-2,6-dimethylmorpholine was isolated in 71–77% yield when 2,6-dimethylmorpholine (b.p. 58 $^{\circ}$ (30 mm.), n_{D}^{20} 1.4414) was treated with epichlorohydrin in the manner described in method A for 2,5-bis-(4-morpholinylmethyl)-*p*-dioxane, and had the following properties: b.p. 71–73 $^{\circ}$ (3 mm.), n_{D}^{20} 1.4560.

Anal. Calcd. for $C_9H_{17}O_2N$: C, 63.13; H, 10.00; N, 8.19; neut. equiv., 171. Found: C, 62.94; H, 10.09; N, 8.48; neut. equiv., 170.8.

2,5-Bis-[4-(2,6-dimethylmorpholinyl)-methyl]-*p*-dioxane was prepared from *trans*-2,5-bis-(iodomethyl)-*p*-dioxane and 2,6-dimethylmorpholine in the manner described above for 2,5-bis-(4-morpholinylmethyl)-*p*-dioxane by method B; yield 74%, m.p. 108–111 $^{\circ}$ (recrystallized from diisopropyl ether). A mixed m.p. of this product and 2,5-bis-(4-morpholinylmethyl)-*p*-dioxane was 93–104 $^{\circ}$.

Anal. Calcd. for $C_{15}H_{34}O_4N_2$: C, 63.13; H, 10.00; mol. wt., 342; neut. equiv., 171. Found: C, 62.57; H, 9.89; mol. wt., 341; neut. equiv., 167.7.

2,5-Bis-(1-piperidinylmethyl)-*p*-dioxane was prepared from piperidine and epichlorohydrin as in method A for 2,5-bis-(4-morpholinylmethyl)-*p*-dioxane (42% yield), and from piperidine and 2,5-bis-(iodomethyl)-*p*-dioxane as in method B (44% yield); m.p.'s (ligroin) and mixed m.p. of

the two products were 101–104 $^{\circ}$. Binovic reported this compound as a viscous, non-distillable residue.³

Anal. Calcd. for $C_{16}H_{30}O_2N_2$: C, 68.04; H, 10.71; N, 9.93; mol. wt., 282; neut. equiv., 141. Found: C, 68.06; H, 10.87; N, 10.24; mol. wt., 296; neut. equiv., 139.6.

2,5-Bis-(1-pyrrolidinylmethyl)-*p*-dioxane was prepared in 28% yield from pyrrolidine and epichlorohydrin as in method A for the morpholine analog above. Attempts to prepare it from *trans*-2,5-bis-(iodomethyl)-*p*-dioxane and pyrrolidine were unsuccessful. The product had b.p. 131–138 $^{\circ}$ (2 mm.), m.p. 107.5–109.5 $^{\circ}$ (ligroin).

Anal. Calcd. for $C_{14}H_{26}O_2N_2$: C, 66.10; H, 10.30; N, 11.06; mol. wt., 254; equiv. wt., 127. Found: C, 67.23; H, 10.66; N, 10.06; mol. wt., 263; neut. equiv., 126.9.

Preparations of N-2,3-Epoxypropyldialkylamines.—The first two compounds listed in Table I were prepared by re-

TABLE I
PREPARATION OF N-2,3-EPOXYPROPYLDIALKYLAMINES,

R ₂	Formula	B.p.		n_{D}^{20}	Yield, %
		$^{\circ}C.$	mm.		
-(CH ₂) ₅ -	C ₈ H ₁₅ ON	77–78	12 ^a	1.4637	77
-(CH ₂) ₄ -	C ₇ H ₁₃ ON	63–64	12 ^b	1.4567	43
(C ₂ H ₅) ₂ =	C ₇ H ₁₅ ON	58–60	20 ^c	1.4277	20 ^e
(n-C ₃ H ₇) ₂ =	C ₉ H ₁₉ ON	75–76	12 ^d	1.4307	63

^a Reported: 86.5–88 $^{\circ}$ (15 mm.),¹⁰ 98–101 $^{\circ}$ (25 mm.),⁵ 85–86 $^{\circ}$ (19 mm.), n_{D}^{18} 1.4690.⁴ ^b Reported: 73–75 $^{\circ}$ (18 mm.),³ n_{D}^{20} 1.4620. This compound decomposed on standing and a satisfactory analysis could not be obtained; neut. equiv., 129.5, 128.9 (theor., 127). ^c Reported: 60–63 $^{\circ}$ (20 mm.),⁵ 62–65 $^{\circ}$ (20 mm.),⁷ 55–60 $^{\circ}$ (15 mm.),¹⁰ 42–43 $^{\circ}$ (7 mm.), n_{D}^{18} 1.4386.³ ^d Reported: 83 $^{\circ}$ (20 mm.), n_{D}^{18} 1.4375.³ ^e In some preparations a small amount (3%) of what was probably dioxane product (b.p. 110–112 $^{\circ}$ (1.5 mm.), 96–98 $^{\circ}$ (1 mm.), n_{D}^{20} 1.4548) was isolated. (Rothstein and Binovic³ reported b.p. 135–137 $^{\circ}$ (5 mm.), n_{D}^{20} 1.5850.) *Anal.* Calcd. for $C_{14}H_{30}O_2N_2$: C, 65.07; H, 11.70; N, 10.85; mol. wt., 258. Found: C, 65.63; H, 11.92; N, 9.51; mol. wt., 251. Another by-product (8%) was 1,3-bis-(diethylamino)-propanol-2, b.p. 104–108 $^{\circ}$ (9 mm.), n_{D}^{20} 1.4452, lit.⁸ b.p. 114 $^{\circ}$ (9 mm.).

action of the dialkylamine and epichlorohydrin in a manner similar to the preparation of 4-(2,3-epoxypropyl)-morpholine (above). The last two were prepared as described for 4-(2,3-epoxypropyl)-2,6-dimethylmorpholine; *i.e.*, a longer reaction time did not afford the dioxane product.

SOUTH CHARLESTON, W. VA.

COMMUNICATIONS TO THE EDITOR

POLY- β -BENZYL ASPARTATES: OPTICAL ROTATION AND THE SENSE OF THE HELIX¹

Sir:

The synthesis of high molecular weight polypeptides with asymmetric carbon atoms has stimulated both theoretical² and experimental³

(1) This paper is Polypeptides. XX. For the previous paper in this series see E. R. Blout and G. D. Fasman in "Recent Advances in Gelatin and Glue Research," Pergamon Press, London, 1957, p. 122.

(2) (a) D. D. Fitts and J. G. Kirkwood, *Proc. Nat. Acad. Sci.*, **42**, 33 (1956); (b) W. Moffitt, *J. Chem. Phys.*, **25**, 467 (1956); (c) W. Moffitt, *Proc. Nat. Acad. Sci.*, **42**, 736 (1956); (d) D. D. Fitts and J. G. Kirkwood, *This Journal*, **78**, 2650 (1956).

investigations of their optical activities. When in the helical configuration,⁴ these polypeptides do not obey a single-term Drude equation but, instead, may be fitted to a phenomenological equation proposed by Moffitt and Yang.^{3b} Although Moffitt's theoretical evaluation of certain parameters in

(3) (a) P. Doty and J. T. Yang, *ibid.*, **78**, 498 (1953); (b) W. Moffitt and J. T. Yang, *Proc. Nat. Acad. Sci.*, **42**, 596 (1956); (c) P. Doty, A. Wada, J. T. Yang and E. R. Blout, *J. Poly. Sci.*, **XXIII**, 851 (1957); (d) J. T. Yang and P. Doty, *This Journal*, **79**, 761 (1957).

(4) L. Pauling and R. B. Corey, *Proc. Nat. Acad. Sci.*, **37**, 235 (1951).