2-Dichloromethylene-*cis*-4,5-tetramethylene-1,3-dioxolane.—To a solution of 1.2 g. (0.031 g. atom) of freshly trimmed potassium metal in *ca.* 40 cc. of anhydrous *t*-butyl alcohol was added 2.96 g. (0.012 mole) of the acetal described above, and the mixture was refluxed for 80 minutes. Part of the *t*-butyl alcohol was removed by reduced pressure distillation, but the brown suspension bumped badly. The solution was diluted with anhydrous ether, but it could not be filtered through a sintered glass funnel. After the solution was distilled to dryness at reduced pressure and more ether was added, the brown suspension could be filtered through a fine sintered glass filter. The ether was removed from the clear filtrate by distillation, and *ca.* 10 cc. of petroleum ether was added to the residue. The mixture was cooled in Dry Ice and filtered to yield 1.20 g. (48%) of white crystals, m.p. 55.5–56.0°, m.p. 56.5–57.0° after two recrystallizations from petroleum ether. The sample was dried in a vacuum desiccator over paraffin and 85% potassium hydroxide.

Anal. Calcd. for $C_8H_{10}O_2Cl_2$: C, 45.96; H, 4.82. Found: C, 45.95; H, 4.87.

LOS ANGELES 24, CALIF.

[CONTRIBUTION FROM THE COBB CHEMICAL LABORATORY, UNIVERSITY OF VIRGINIA]

The Reaction of Aromatic Aldehydes with *n*-Butylamine. Acid Catalysis and Substituent Effects[1]

BY GEORGES M. SANTERRE, CHARLES J. HANSROTE, JR., AND THOMAS I. CROWELL

RECEIVED SEPTEMBER 23, 1957

General acid catalysis has been demonstrated for the reaction of substituted benzaldehydes with *n*-butylamine by employing acetic acid–lithium acetate buffers in methanol. The plot of log *k vs.* Hammett's σ-function, for the uncatalyzed reaction, is not linear but has a maximum near the point corresponding to benzaldehyde. Apparent energies and entropies of activation are given.

Recent studies of the kinetics of Schiff base formation[2] have been concerned with the second-order reaction which takes place in the absence of any acid catalyst other than the solvent.

$$RCHO + R'NH_2 \longrightarrow RCH{=}NR' + H_2O \quad (1)$$

The reaction of an aliphatic amine with an aromatic aldehyde, however, should be no exception to the rule that carbonyl addition reactions can be acid catalyzed; this paper describes the detection of acid catalysis and the effect of ring substituents on the rate.

The difficulties expected in determining the rate constant for an acid-catalyzed reaction of a base were described by Conant and Bartlett in their classical investigation of semicarbazone formation in aqueous solution.[3] Our acid-catalyzed reactions were run in methanol at 25°. For a thorough interpretation of the rate of reaction 1 in the presence of an acid, the dissociation constants of the acid (acetic) and *n*-butylamine (the only amine used in this investigation) must be known. The value of Kilpatrick and Eanes[4] for K_{HAc} in methanol containing 0.1 *M* lithium chloride is 2.19×10^{-9}. The dissociation constant, K_{HB^+}, of butylammonium ion in methanol is reported by Schaefgen, Newman and Verhoek[5] to be 1.78×10^{-12}. By their method we determined the value 2.57×10^{-12} in 0.1 *M* methanolic lithium chloride.

Experimental

Materials.—*p*-Chlorobenzaldehyde, benzaldehyde, *p*-methylbenzaldehyde and *p*-methoxybenzaldehyde were distilled at atmospheric pressure. The last three were handled in nitrogen. Piperonal was recrystallized from ethanol–water, the remaining aldehydes from water. Glacial acetic acid was dried by azeotropic distillation from benzene.

The following Schiff bases were prepared according to Campbell and co-workers[6]: *p*-methoxybenzal-*n*-butylamine, b.p. 164–165° (20 mm.); *p*-methylbenzal-*n*-butylamine, b.p. 138° (19 mm.); benzal-*n*-butylamine, b.p. 129–131° (25 mm.); *m*-nitrobenzal-*n*-butylamine, b.p. 193–194° (25 mm.).

Baker and Adamson reagent lithium chloride was treated with hydrochloric acid and heated until dry; assay 99.8% of theoretical chloride. Lithium acetate was prepared by dissolving Eimer and Amend C.P. lithium carbonate in acetic acid and evaporating. The fused mass was pulverized, dried at 160°, and thereafter handled in a dry-box.

The solvent for the kinetic runs and spectral measurements was reagent grade methanol. This solvent was distilled from magnesium methoxide for the determination of K_{HB^+}.

Procedure.—The kinetic runs were made as previously described.[7] Samples were withdrawn and diluted with methanolic hydrochloric acid to convert the Schiff base to its conjugate acid and any unreacted aldehyde to the acetal. The Schiff base concentration then was obtained easily from the optical density at the ultraviolet absorption peak, using the last two columns of Table I. The measured absorption of the acetal at the wave length of the Schiff base conjugate acid was usually negligible (for example, ϵ_{320} 0.02×10^4 for an acidified solution of *p*-methoxybenzaldehyde). In the

TABLE I

SPECTRA OF ALDEHYDES AND SCHIFF BASES IN METHANOL

	$\lambda_{\max}$, mμ			
RCHO[a]	RCHO	RCH=NBu	RCH=NBu·HCl	$\epsilon_{\max} \times 10^{-4}$
p-$(CH_3)_2N$	340	329[b]	393[b]	4.92
p-CH_3O	275	268	320	2.89
3,4-CH_2O_2	310	305[c]	348[c]	1.73
p-CH_3	256	254	288	2.14
m-OH	254	250[b]	283[b]	1.52
H	246	246	275	1.71
p-Cl	255	253[b]	286	1.82
m-NO_2	257	235	250	1.31
p-NO_2	265	281[b]	261[b]	1.14

[a] Substituted benzaldehydes. [b] Observed in a solution of aldehyde and *n*-butylamine after complete reaction. [c] Ref. 7.

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(1) Presented before the Division of Organic Chemistry of the American Chemical Society, Miami, Fla., April 9, 1957. Taken in part from the dissertation of Georges M. Santerre, University of Virginia, 1956.

(2) R. L. Hill and T. I. Crowell, THIS JOURNAL, **78**, 2284, 6425 (1956).

(3) J. B. Conant and P. D. Bartlett, *ibid.*, **54**, 2881 (1932).

(4) M. Kilpatrick and R. D. Eanes, *ibid.*, **75**, 586 (1953).

(5) J. R. Schaefgen, M. S. Newman and F. H. Verhoek, *ibid.*, **66**, 1847 (1944).

(6) K. N. Campbell, *et al.*, *ibid.*, **70**, 3868 (1948).

(7) T. I. Crowell and D. W. Peck, *ibid.*, **75**, 1075 (1953).

case of *m*-hydroxybenzaldehyde, the absorption of both species had to be taken into account (ϵ_{283} 0.23 × 10^4 for the acidified aldehyde solution). The spectra of the nitrobenzaldehydes were such that the best differentiation of reactants and products could be made without acidification of the sample.

The final measurements indicated 100% reaction so closely for four aldehydes that the spectra of the Schiff bases were obtained from the remaining four aldehydes without isolating the pure compounds. Complete reaction was indicated, however, by the insensitivity of the calculated ϵ to variations up to fivefold in the amine concentration.

The value of K_{HB^+} at 0.1 *M* electrolyte concentration was determined using bromcresol purple as the indicator.[5] The absorption maximum was at 594 mμ and the value of the indicator constant, K_{HI^+}, was assumed to be 8.9×10^{-11} in this medium.[8] Four solutions, 0.004 *M* in *n*-butylamine and 0.016 to 0.030 *M* in *n*-butylammonium benzenesulfonate gave an average value of 0.0289 ± 0.0006 for K_{HB^+}/K_{HI^+}; then $K_{HB^+} = 2.57 \times 10^{-12}$.

The buffer solutions for acid-catalyzed reactions were prepared by calculating the acetate ion concentration necessary to give the desired *n*-butylamine concentration for a given concentration of acetic acid, using the equilibrium expression 2.

$$\frac{[\mathrm{BuNH_3}^+][\mathrm{Ac}^-]}{[\mathrm{BuNH_2}][\mathrm{HAc}]} = \frac{K_{\mathrm{HAc}}}{K_{\mathrm{BH}^+}} = 852 \qquad (2)$$

The electrolyte concentration, $[\mathrm{BuNH_3}^+] + [\mathrm{Li}^+]$, was adjusted to 0.1 *M* with lithium chloride.

Results

The reaction of all nine aldehydes with *n*-butylamine, in the absence of acid, showed second-order kinetics as previously observed.[2,7] Neither 0.1 *M* sodium acetate nor 0.1 *M* lithium chloride affected the rate constant, k_0, for piperonal. The absence of catalysis by bases or by traces of acid was demonstrated by adding sodium methoxide to many of the reaction mixtures.

The results of the acid-catalyzed run shown in Table II are typical except that most runs were carried further, but not more than 40%, toward completion. The second-order rate function in the third column is calculated from x, the concentration of Schiff base, a, the initial concentration of piperonal, and b, the initial, stoichiometric amine concentration. This function is linear in the time with slope k'_2, showing that the reaction appears to follow a second-order course if the ionization of the amine is neglected. The reason for this will be discussed in a later paragraph.

TABLE II

ACID-CATALYZED SCHIFF BASE FORMATION

Stoichiometric concentrations: piperonal, 0.01745 *M*; $\mathrm{BuNH_2}$, 0.01992 *M*; HAc, 0.02735 *M*; LiAc, 0.01320 *M*; LiCl, 0.06698 *M*. Calculated initial concentrations: $\mathrm{BuNH_2}$, 0.000102 *M*; HAc, 0.02755 *M*; H^+, 5×10^{-10} *M*; Ac^-, 0.03302 *M*

t, sec.	x, mole/l.	$\frac{1}{b-a} \ln \frac{a(b-x)}{b(a-x)}$ l./mole
165	0.00018	0.48
650	.00046	1.36
1700	.00103	3.12
2745	.00156	4.87
4050	.00215	6.98
5070	.00259	8.65

The initial rate is $k_2'ab$. (Although we chose to evaluate it from a second-order plot, the initial rate would be independent of our choice of reaction order. The same result is obtained by measuring the limiting slope of a plot of x *vs.* t.) If we define a new rate constant, k_2, so that $dx/dt = k_2(a - x)[\mathrm{BuNH_2}]$, involving the true rather than the stoichiometric concentration of *n*-butylamine, then $k_2 = k_2'b/[\mathrm{BuNH_2}]_{\mathrm{init}}$. Since $[\mathrm{BuNH_2}]_{\mathrm{init}}$ can be calculated from equation 2, k_2 can be evaluated for various acetic acid concentrations. For example, the slope, k_2', obtained from the data in Table II is 0.00165 l./mole-sec. and since $b/[\mathrm{BuNH_2}]_{\mathrm{init}} = 0.01992/0.000102 = 195$, $k_2 = 0.322$ l./mole-sec.

Figure 1 is a graph of k_2 *vs.* acetic acid concentration, each point the result of a kinetic run. The *p*H of the solutions, determined by the ratio $[\mathrm{Ac}^-]/[\mathrm{HAc}]$, are shown in the figure. It is evident that k_2 is linear in acetic acid concentration, the slope being k_{HAc}, the catalytic constant of acetic acid. Although the intercept does not yield an accurate value for the uncatalyzed rate, k_0 has been determined separately as described and may be incorporated in the final rate equation

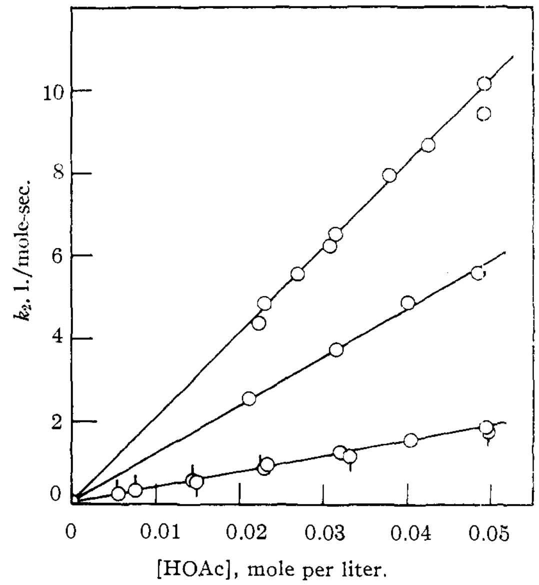

Fig. 1.—Rate as a function of equilibrium concentration of acetic acid: upper curve, benzaldehyde; middle curve, *p*-tolualdehyde; lower curve, piperonal; ○, *p*H 8.7; ♀, *p*H 9.0; ȯ, *p*H 9.3.

$$\text{rate} = (k_0 + k_{\mathrm{HAc}}[\mathrm{HAc}])[\mathrm{RCHO}][\mathrm{BuNH_2}] \qquad (3)$$

Table III lists the values of k_0 for all the aldehydes studied and k_{HAc} for the three studied in buffer solutions. Each k_0 given is the mean of from four to seven runs; the average deviation from the mean is 2–3% except for *m*- and *p*-nitrobenzaldehyde where it is 6%, due essentially to the constant, high absorbance of the nitro group.

The Arrhenius parameters A and E_a, where $\log k_0 = A - E_a/2.3RT$, are given in Table IV for four aldehydes studied at 0° as well as 25°. Apparent entropies of activation are calculated for a standard state of 1 mole per liter, assuming $\Delta H^{\ddagger} = E_a - RT$.

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(8) I. M. Kolthoff and L. S. Guss, THIS JOURNAL, **61**, 330 (1939).

TABLE III

RATE CONSTANTS FOR SUBSTITUTED BENZALDEHYDES

Substituent	σ	k_0, l./mole-sec.	k_{HAc}, l.^{2}/mole^2-sec.
p-$(CH_3)_2N$	−0.600	0.0158	
p-CH_3O	− .268	.0465	
3,4-CH_2O_2	− .159	.0337[a]	37.5
p-CH_3	− .11[b]	.0852	127
m-OH	− .002	.090[c]	
H	.000	.104	198
p-Cl	+ .226	.0795	
m-NO_2	.710	.0352	
p-NO_2	.778	.0328	

[a] Ref. 2. [b] H. Kloosterziel and H. J. Backer, THIS JOURNAL, **74**, 5806 (1952). [c] In 0.189 M $NaOCH_3$, the observed k_0 was 0.080 ± 0.003 l./mole-sec. The effect of the charged substituent, m-O^-, on this reaction requires further study.

TABLE IV

RCHO	10^2k_0 (0°), l./mole-sec.	Ea, kcal.	A	$\Delta S^\ddagger$, e.u.
p-$(CH_3)_2N$	0.46	10.0	4.05	−41.9
3,4-CH_2O_2	1.15	7.3	3.66	−43.0
p-Cl	2.58	7.0	4.25	−41.3
p-NO_2	0.70	8.0	5.85	−33.7

Discussion

Equation 3 indicates general acid catalysis and one of the corresponding mechanisms.[9] Although Fig. 1 shows a very slight variation of k_2 with pH for piperonal, it is due either to a systematic error or to a difference in the salt effects of chloride and acetate ions. Oxonium-ion catalysis could hardly be observed in these slightly alkaline solutions. Kresze and Manthey[10] report specific catalysis as well as uncatalyzed reaction for the formation of an aromatic Schiff base. Semicarbazone formation is general acid catalyzed,[3] as is the hydrolysis of Schiff bases.[11]

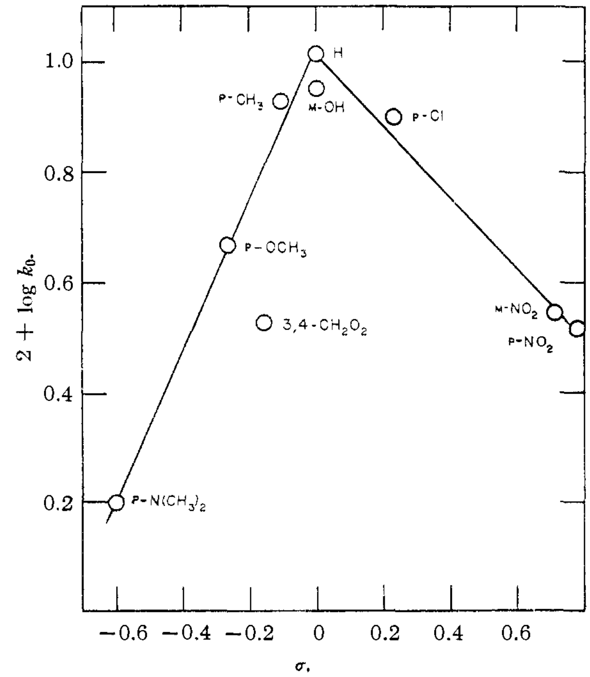

Fig. 2.—Log k_0, for uncatalyzed Schiff base formation, plotted against Hammett's σ-function.

Two aspects of the kinetics require further comment. The equilibrium constant[2] of 3000 requires reaction 1 (RCHO = piperonal) to go practically to completion in methanol. At a hydrogen-ion concentration of 5×10^{-10}, however, the amine concentration (Table II) is only 0.5% of the stoichiometric concentration; the proportion of the Schiff base which is ionized must be much less (aliphatic amines can be distinguished from their Schiff bases by titration[2,12]). It is easily shown that at the concentrations of our experiments, a few parts per thousand of water may shift the equilibrium well toward the left. Fortunately for the consistency of our data, this was observed experimentally.

The second-order course of the acid-catalyzed reaction must also be justified. Good buffering has been achieved throughout the semicarbazone reaction by utilizing an excess of the buffer system[3,13a] or of the semicarbazide.[13b] Our aldehyde, amine and acetate concentrations were all of the same order of magnitude, however, and the consumption of amine, which must decrease the pH, might be expected to destroy the pseudo-second-order relation observed with complete buffering. The increased ionization of the amine is balanced by increased acetic acid concentration, however; by equation 3, since k_0 is negligible, the kinetics remain approximately second order.

More exactly, third-order kinetics can be predicted. Combining (2) and (3)

$$\text{rate} = \frac{dx}{dt} = \frac{k_{HAc}K_{BH^+}}{K_{HAc}} [BuNH_3^+][Ac^-][RCHO] \quad (4)$$

Since the amine is almost completely ionized, $[BuNH_3^+] = b - x$ nearly; also $[Ac^-] = [Li^+] + [BuNH_3^+]$ since $[H^+]$ is small; equation 4 then becomes

$$\frac{dx}{dt} = \frac{k_{HAc}K_{BH^+}}{K_{HAc}} (b - x)([Li^+] + b - x)(a - x) \quad (5)$$

Our results satisfy the integrated form of (5) from which k_{HAc} may be calculated directly. The rather high value of 0.1 M for $[Li^+] + b$ renders the term $[Li^+] + (b - x)$ nearly constant, allowing second-order kinetics.

The remainder of this discussion deals with structural effects in the uncatalyzed reaction, given by k_0 in Table III and plotted in Fig. 2. (The three values of k_{HAc} parallel the corresponding k_0's.) The chief point of interest is the maximum in k_0 with respect to Hammett's σ-function near the point for benzaldehyde. The phenomenon has been observed before in Schiff base formation[14] and hydrolysis,[11b] and in semicarbazone formation.[15] A possible mechanistic interpretation is

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(9) J. Hine, "Physical Organic Chemistry," McGraw-Hill Book Co., Inc., New York, N. Y., 1956, p. 246.

(10) V. G. Kresze and H. Manthey, *Z. Elektrochem.*, **58**, 118 (1954).

(11) (a) B. A. Porai-Koshits, *et al.*, *J. Gen. Chem.* (*U.S.S.R.*), **17**, 1774 (1947); (b) A. V. Willi and R. E. Robertson, *Can. J. Chem.*, **31**, 361 (1953); A. V. Willi, *Helv. Chim. Acta*, **39**, 1193 (1956).

(12) S. K. Freeman, *Anal. Chem.*, **25**, 1750 (1953).

(13) (a) F. W. Westheimer, THIS JOURNAL, **56**, 1962 (1934); F. P. Price and L. P. Hammett, *ibid.*, **63**, 2387 (1941); (b) G. H. Stempel and G. S. Schaffel, *ibid.*, **66**, 1158 (1944).

(14) B. Oddo and F. Toguacchini, *Gazz. chim. ital.*, **52**, II, 347 (1922).

(15) D. S. Noyce, A. T. Bottini and S. G. Smith, *J. Org. Chem.*, **22**, in press (1957). Dr. Noyce kindly sent us their data before publication.

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 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 Fugassi[16] 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 Tommila[19] 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.

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[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.

[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

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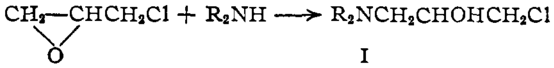
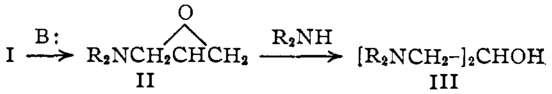
Reaction of unsubstituted cyclic secondary amines and epichlorohydrin followed by treatment with alkali gave, when allowed to proceed to completion, 2,5-bis-(dialkylaminomethyl)-*p*-dioxanes. The structures were proved by independent synthesis and conditions were determined for directing the reactions 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 1949[1]; work since then on the reaction between secondary amines and epichlorohydrin has been limited to uses of the reaction for preparative purposes[2-5] and calculations of rate constants for reactions between several amines and epichlorohydrin.[6] The reaction between secondary amines and epichlorohydrin is usually formulated as



$$\underset{\text{O}}{\text{CH}_2\text{—CHCH}_2\text{Cl}} + \text{R}_2\text{NH} \longrightarrow \underset{\text{I}}{\text{R}_2\text{NCH}_2\text{CHOHCH}_2\text{Cl}}$$

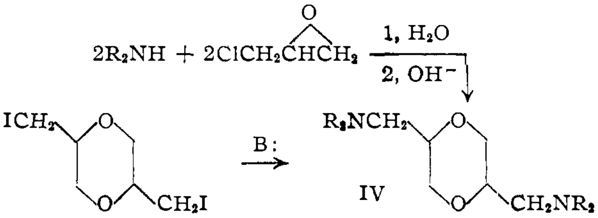
Treatment of the chlorohydrin I with base (either excess amine[1] or alkali[7]) affords the N-(2,3-epoxypropyl) dialkylamine (II). When excess amine is used the 1,3-bis-(dialkylamino)-propanol-2 (III) can be isolated.[3,5,8]



$$\text{I} \xrightarrow{\text{B:}} \underset{\text{II}}{\text{R}_2\text{NCH}_2\overset{\text{O}}{\text{CHCH}_2}} \xrightarrow{\text{R}_2\text{NH}} \underset{\text{III}}{[\text{R}_2\text{NCH}_2\text{–}]_2\text{CHOH}}$$

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 ($C_{14}H_{26}O_4N_2$) in 65% yield. This compound was suspected of being 2,5-bis-(4-morpholinylmethyl)-*p*-dioxane [IV, $R_2 = O(CH_2CH_2—)_2$] on the basis of amine titration by perchloric acid, infrared absorption spectrum, and a report in the literature[3] 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 C_{14}-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.



IV

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

[2] W. Davies and W. E. Savige, *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).

[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).