[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY, DUKE UNIVERSITY]

ortho Substitution Rearrangement *vs.* β-Elimination of Quaternary Ammonium Ion–Alcohols and Methyl Ether with Excess Sodium Amide[1]

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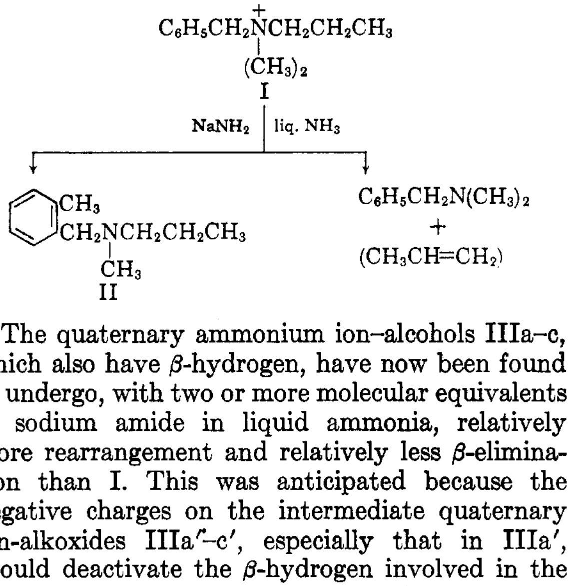
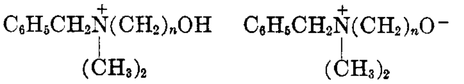
The benzyl-2-hydroxyethyldimethylammonium ion underwent exclusively the *ortho* substitution rearrangement with two or more molecular equivalents of sodium amide in liquid ammonia, whereas the corresponding methyl ether exhibited exclusively β-elimination with this reagent. The benzyl-3-hydroxypropyl- and the benzyl-6-hydroxyhexyldimethylammonium ions underwent mainly rearrangement and some β-elimination. Further rearrangements around the aromatic ring and certain other reactions were observed. The rearrangement of a quaternary ammonium ion–dialcohol was realized. These reactions involved the intermediate formations of the corresponding quaternary ion–alkoxides, the reactive intermediates being di- or trianions.

Although the benzyltrimethylammonium ion undergoes exclusively the *ortho* substitution rearrangement with sodium amide in liquid ammonia,[2] certain related quaternary ammonium ions having β-hydrogen have previously been observed to exhibit much β-elimination with this reagent. For example, the benzyl-*n*-propyldimethylammonium ion (I) has afforded the rearranged amine II and the β-elimination product, benzyldimethylamine, in yields of 52 and 40%, respectively (Scheme A).[3]

SCHEME A

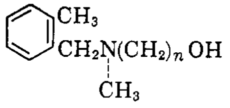


The quaternary ammonium ion–alcohols IIIa–c, which also have β-hydrogen, have now been found to undergo, with two or more molecular equivalents of sodium amide in liquid ammonia, relatively more rearrangement and relatively less β-elimination than I. This was anticipated because the negative charges on the intermediate quaternary ion-alkoxides IIIa′–c′, especially that in IIIa′, should deactivate the β-hydrogen involved in the elimination but not the methyl hydrogen ionized in the rearrangement. Actually IIIa afforded almost exclusively[4] the rearranged amino alcohol IVa, while IIIb and IIIc produced largely the corresponding rearranged amino alcohols IVb–c, though an appreciable amount (12%) of benzyldimethylamine was also obtained from IIIc. These and other results are summarized in Table I.



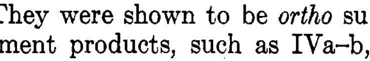
$$C_6H_5CH_2\overset{+}{N}(CH_2)_nOH \quad C_6H_5CH_2\overset{+}{N}(CH_2)_nO^-$$
$$(CH_3)_2 \qquad\qquad (CH_3)_2$$

IIIa. $n = 2$ IIIa′. $n = 2$
IIIb. $n = 3$ IIIb′. $n = 3$
IIIc. $n = 6$ IIIc′. $n = 6$



IVa. $n = 2$
IVb. $n = 3$
IVc. $n = 6$

The rearranged amino alcohols from quaternary ion–alcohols IIIa and IIIb were indicated by vapor phase chromatography to be pure substances. They were shown to be *ortho* substitution rearrangement products, such as IVa–b, by their oxidations to *o*-toluic acid (Equation 1) and by their infrared spectra, which gave strong bands in the 770–730 cm.$^{-1}$ region characteristic of four adjacent aromatic hydrogens.[5]



(1)

Had the amino alcohols been the possible Stevens 1,2-shift products, their oxidations should have given benzoic acid, and their infrared spectra should have shown bands in the 710–690- and 770–730-cm.$^{-1}$ regions characteristic of five adjacent aromatic hydrogens.[6] Neither of these properties was observed.

Structures IVa and IVb were confirmed by independent syntheses of their methyl bromide derivatives from *o*-xylyl bromide; IVa itself was inde-

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[1] Supported by the National Institutes of Health Grant.

[2] S. W. Kantor and C. R. Hauser, *J. Am. Chem. Soc.*, **73**, 4122 (1951).

[3] C. R. Hauser and A. J. Weinheimer, *J. Am. Chem. Soc.*, **76**, 1264 (1954).

[4] Although no benzyldimethylamine was isolated by distillation, a trace of this amine was indicated by a vapor phase chromatogram to be present in the crude reaction product (see Table I).

[5] See L. J. Bellamy, *The Infrared Spectra of Complex Molecules*, 2nd ed., John Wiley and Sons, New York, 1958, p. 77.

[6] See ref. 5, page 76.

TABLE I

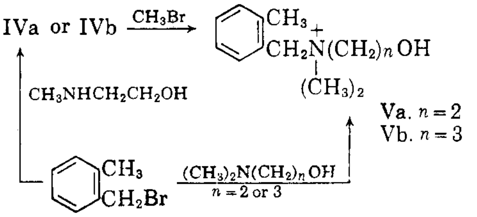
REARRANGEMENT *vs.* β-ELIMINATION OF IIIa–c TO FORM IVa–c OR BENZYLDIMETHYLAMINE BY SODIUM AMIDE IN LIQUID AMMONIA

Quaternary Ion-Alcohol	$NaNH_2$, Mol. Equiv.	Time, Hr.	Rear. Amine	Yield, %	Benzyl-dimethylamine, Yield, %
IIIa	1.0[a]	3.25	IVa	0[b]	0
IIIa	1.0	3.25	IVa	4	0
IIIa	2.0	1.0[c]	IVa	58[d]	0
IIIa	3.0	0.8	IVa	67	0
IIIa	2.0[e]	1.0	IVa	65	0
IIIa	3.0[e]	1.0	IVa	67	Trace[f]
IIIb	3.0	1.0	IVb	36	—
IIIb	3.0	1.5	IVb	55	1.0
IIIb	3.75	3.5	IVb	71	0.9
IIIc	4.0	7.0	IVc	52[g]	12.0[h]

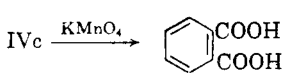
[a] Inverse addition procedure was employed. [b] IIIa (87%) was recovered as its picrate. [c] A 3.25-hr. reaction period afforded about same yield. [d] An estimated 32% of IIIa was recovered as its picrate. [e] Potassium amide was used. [f] Indicated by vapor phase chromatography, see note 4. [g] Contained 5–10% impurity. [h] 5-Hexene-1-ol was also isolated in 11% yield.

pendently synthesized (Scheme B). Because the methyl bromide derivative of IVa was hygroscopic, the quaternary ion was isolated as its picrate.

SCHEME B



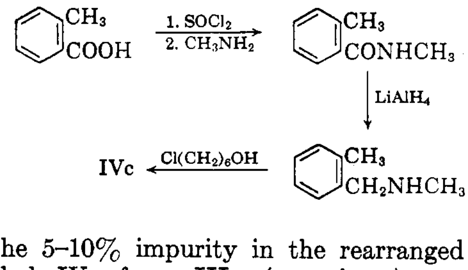
The rearranged amino alcohol from quaternary ion–alcohol IIIc was indicated by vapor phase chromatography to consist mainly (90–95%) of one substance and partly (5–10%) of two other substances. The main compound was shown to be an *ortho* substitution rearrangement product, such as IVc, by its oxidation to phthalic acid (Equation 2) and by its infrared spectrum, which gave a strong band in the 770–730-cm.$^{-1}$ region for four adjacent aromatic hydrogens.[5]



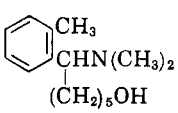
(2)

Structure IVc was confirmed by an independent synthesis from *o*-toluic acid (Scheme C).

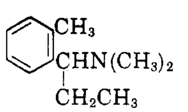
SCHEME C



The 5–10% impurity in the rearranged amino alcohol IVc from IIIc (see above) may have consisted partly of VI, which would be the other possible *ortho* substitution rearrangement product, and partly of a Stevens 1,2-shift product. The presence of the latter appeared to be indicated by the infrared spectrum of the crude amino alcohol from IIIc, which showed a faint band in the 710–690-cm.$^{-1}$ region characteristic of five adjacent aromatic hydrogens.[6] The rearranged amine II, obtained earlier[3] from quaternary ion I, has now been indicated by vapor phase chromatography to contain a small amount (8–12%) of an impurity, presumably the other possible *ortho* substitution rearrangement product VII.

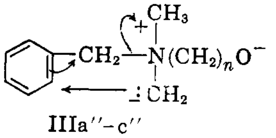


VI

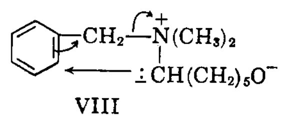


VII

These *ortho* substitution rearrangements of quaternary ion–alcohols IIIa–c to form amino alcohols IVa–c involved the intermediate formation of not only the monoanions IIIa′–c′ but also the dianions IIIa″–c″. They appear to be the first definite examples involving such dianion intermediates. In the reaction of IIIc, dianion VIII may also have been an intermediate leading to VI (see above). The methyl carbanions in dianions IIIa″–c″ and the methylene carbanion in VIII would presumably be in equilibrium with the benzyl carbanions, which cannot undergo the *ortho* substitution rearrangement. The intermediate formation of such carbanions was indicated by the production of transient colors (see Experimental).



IIIa″–c″



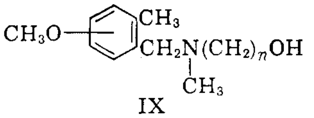
VIII

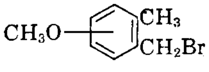
Incidentally the intermediate monoanion IIIa′ did not undergo either of the possible intramolecular types of displacement to form ethylene oxide (and benzyldimethylamine) or benzyl β-dimethylaminoethyl ether; these reactions would have involved three- and five-membered ring mechanisms, respectively. Thus, when the reagent was added to a molecular equivalent of the quaternary ion–alcohol IIIa (inverse addition procedure) and the resulting suspension of IIIa′ stirred for 3.25 hours, most (87%) of IIIa was recovered as its picrate (see Table I) and no amine was isolated. A little (4%) of the rearranged amino alcohol IVa was obtained when IIIa was added to the reagent in the usual manner, but excess reagent was then present during the initial stages of the addition.

Table I shows that the yield of rearranged amino alcohol IVa from quaternary ion–alcohol IIIa with two molecular equivalents of sodium amide was 58% and that much (32%) unchanged IIIa remained in the reaction mixture. A longer reaction period failed to improve the yield, but the use of three molecular equivalents of sodium amide or two or three of potassium amide increased the yield somewhat. Apparently more complete reaction was hindered by coating of the monoalkali salt of IIIa, which was relatively insoluble in the liquid ammonia.

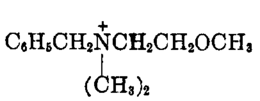
Table I further shows that the best yields of rearranged amino alcohols IVb and IVc from IIIb and IIIc were 71 and 52%, respectively. The latter experiment was carried out only once because the chloride IIIc was hygroscopic and was not prepared in pure condition. The monoalkali salts of IIIb and IIIc appeared to be quite insoluble in the medium. In the experiment with IIIc, both of the β-elimination products, benzyldimethylamine and 5-hexene-1-ol, were isolated in approximately equal yields (11–12%).

Although amino alcohols IVa–c may be prepared readily, as indicated in Schemes B and C, certain of their ring substituted derivatives could probably be synthesized more conveniently employing the *ortho* substitution rearrangement. For example, the 3- or 5-methoxy amino alcohols IX might be obtained more easily through the rearrangement of the appropriate 2- or 4-methoxy quaternary ion–alcohol[7] than from the 3- or 5-methoxy benzyl bromide X or from the corresponding substituted *o*-toluic acid. Such substituted benzyl bromides or toluic acids appear not to be readily available.


IX

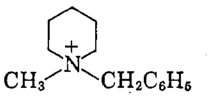

X

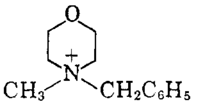
In contrast to quaternary ammonium ion–alcohol IIIa, the methyl ether of this compound (XI) gave, with sodium amide in liquid ammonia, benzyldimethylamine in yields of 22 and 47% in 1.2 and 4.0 hours, respectively. Much unchanged quaternary ion XI appeared to remain. No rearranged amine was detected.


$C_6H_5CH_2\underset{(CH_3)_2}{\overset{+}{N}}CH_2CH_2OCH_3$

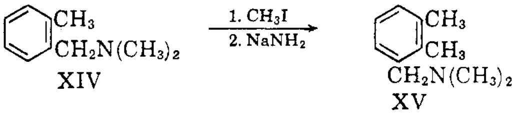
XI

The benzyldimethylamine appears best accounted for by the usual type of β-elimination of a quaternary ammonium ion, in which the other product would be vinyl methyl ether. This result is not surprising, since the β-hydrogen of XI would presumably be activated by the oxygen of the ether. Such an activation of β-hydrogen by an ether group has been observed recently by Fery and van Hove,[8] who showed that, whereas the quaternary ion XII undergoes mainly rearrangement with sodium amide in liquid ammonia, the related ether XIII exhibits only β-elimination.

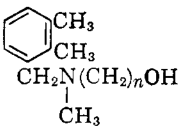

XII

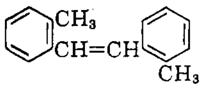

XIII

Further rearrangements around the aromatic ring and other reactions. It has previously been shown[2] that the rearranged 2-methylbenzyldimethylamine (XIV) obtained in 96% yield from the benzyltrimethylammonium ion can be rearranged further through its methiodide to form 2,3-dimethylbenzyldimethylamine (XV) in 64% yield (Equation 3). Still further rearrangements around the aromatic ring were likewise realized.[2]


XIV XV (3)

Similarly the present rearranged amino alcohols IVa and IVb were further rearranged through their methylation products Va–b (see Scheme B) to afford amino alcohols XVIa and XVIb in yields of 2 and 25%, respectively. These reactions produced much high-boiling neutral material, from which was isolated 2,2′-dimethylstilbene (XVII) in yields of 23 and 14%, respectively. This dimeric olefin was obtained as by-product in the reaction represented by Equation 3, but the yield was only 6% under similar conditions.[2]


XVIa. $n = 2$
XVIb. $n = 3$


XVII

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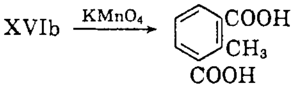
[7] For the similar usage of 2- and 4-substituted benzyltrimethylammonium ions for the synthesis of certain substituted benzyldimethylamines see W. Q. Beard and C. R. Hauser, *J. Org. Chem.*, **25**, 334 (1960).

[8] L. P. A. Fery and L. van Hove, *Bull. soc. chim. Belges*, **68**, 65 (1959); *Bull. soc. chim. Belges*, **69**, 79 (1960).

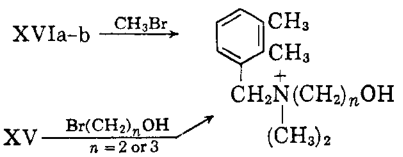
That the rearranged amino alcohols from Va and Vb were *ortho* substitution products was supported by their infrared spectra, which showed a strong band at 772 cm.$^{-1}$ and one of medium intensity at 725 cm.$^{-1}$, characteristic of three adjacent aromatic hydrogens.[9] Also, XVIb was oxidized to 2-methylisophthalic acid (Equation 4).



(4)

The structures of rearranged amino alcohols XVIa–b were confirmed by independent syntheses of their methyl bromide derivatives from amine XV and the appropriate bromo alcohols (Scheme D).

SCHEME D

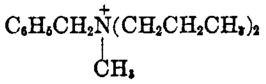


XVIIIa. $n = 2$
XVIIIb. $n = 3$

The dimeric olefin XVII from Va–b might have arisen through self-alkylation followed by β-elimination as proposed previously for the production of XVII from XIV[2] or by an elimination involving the 2-methyl hydrogen of Va–b through the intermediate formation of *o*-xylylene as suggested recently.[10]

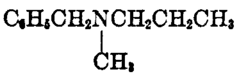
The reasons for the lower ratios of rearranged amine to hydrocarbon material from quaternary ion–alcohols Va–b than from the quaternary ion of XIV are not entirely clear at the present time. Perhaps the apparently greater insolubility of the intermediate quaternary ion–alkoxides from Va–b favored the formation of the hydrocarbon material.

Rearrangement of a quaternary ion–dialcohol. The benzyldi - *n* - propylmethylammonium ion (XIX) has previously been shown[3] to undergo largely β-elimination with sodium amide in liquid ammonia to form benzyl-*n*-propylmethylamine (XX) (70%) and presumably propylene.



$C_6H_5CH_2\underset{CH_3}{\overset{+}{N}}(CH_2CH_2CH_3)_2$

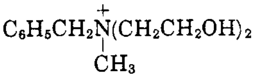
XIX



$C_6H_5CH_2\underset{CH_3}{N}CH_2CH_2CH_3$

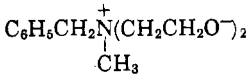
XX

The benzylbis(2-hydroxyethyl)methylammonium ion (XXI), which has the same number of β-hydrogens as XIX, has now been found to undergo mainly the ortho substitution rearrangement with excess potassium amide in liquid ammonia–tetrahydrofuran, though no rearrangement was observed with excess sodium amide in liquid ammonia under the usual conditions. The rearranged amine XXII and the β-elimination product XXIII were obtained in yields of 53 and 8%, respectively. The latter product might possibly have arisen through an intramolecular displacement to give ethylene oxide.



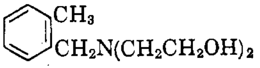
$C_6H_5CH_2\underset{CH_3}{\overset{+}{N}}(CH_2CH_2OH)_2$

XXI

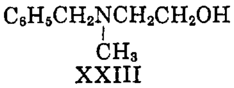


$C_6H_5CH_2\underset{CH_3}{\overset{+}{N}}(CH_2CH_2O^-)_2$

XXI′



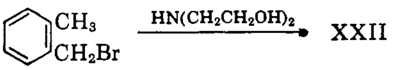
XXII



$C_6H_5CH_2\underset{CH_3}{N}CH_2CH_2OH$

XXIII

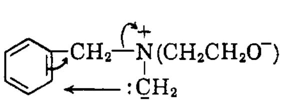
That the main product was XXII was supported by its oxidation to form phthalic acid (see Equation 2) and by its infrared spectrum, which showed a strong band at 740 cm.$^{-1}$ for four adjacent aromatic hydrogens.[5] This spectrum also showed a very weak band at 700 cm.$^{-1}$ for five adjacent aromatic hydrogens[6] as in XXIII, a trace of which was indicated to be present by vapor phase chromatography. Structure XXII was confirmed by an independent synthesis (Equation 5).



(5)

The structure of the second compound isolated was indicated to be XXIII by its vapor phase chromatogram and by mixed melting point of its methobromide salt IIIa (see Experimental). A vapor phase chromatogram indicated the presence of a small amount of an unidentified third compound, the boiling point of which was between those of XXII and XXIII.

The greater tendency of dialcohol XXI to rearrange than XIX was anticipated because negative charges on the intermediate dialkoxide ion XXI′ should deactivate the β-hydrogens thereby minimizing β-elimination. The failure of XXI to rearrange under the usual conditions appeared to be due to the insolubility of the intermediate quaternary ion–alkoxides. Interestingly, the reactive intermediate in the rearrangement of the dialkoxide ion XXI′ was presumably the trianion XXI″.



XXI″

EXPERIMENTAL[11]

Benzyl-2-hydroxyethyldimethylammonium bromide (IIIa). To a stirred solution of 102.0 g. (0.60 mole) of benzyl bromide

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[9] See ref. 5, p. 78.

[10] C. R. Hauser, W. Q. Beard, and F. N. Jones, *J. Org. Chem.*, **26**, 4790 (1961).

[11] Analyses are by Galbraith Microanalytical Laboratories, Knoxville, Tenn. All melting points and boiling points are uncorrected. All vapor phase chromatography was carried out on a Perkin-Elmer Model 154-C Vapor Fractometer. Infrared spectra were produced on either a Perkin-Elmer Model 21 spectrophotometer or a Perkin-Elmer Infracord.

in 200 ml. of acetonitrile was added dropwise, during 20 min., 55.0 g. (0.62 mole) of 2-dimethylaminoethanol in 200 ml. of acetonitrile. The exothermic reaction caused the mixture to reflux. After 6 hr. the solution was cooled in an ice bath, and 400 ml. of anhydrous ether was slowly added with stirring. The resulting white precipitate was collected on a suction funnel, washed with dry ether, and dried in a vacuum oven for 10 hr. at 40° to give 152.0 g. (98%) of bromide IIIa, m.p. 130–131°.

Anal. Calcd. for $C_{11}H_{18}BrNO$: C, 50.78; H, 6.97; N, 5.38. Found: C, 50.87; H, 7.13; N, 5.46.

The picrate recrystallized once from 95% ethanol, melted at 99.0–99.5.°

Anal. Calcd. for $C_{17}H_{20}N_4O_8$: N, 13.72. Found: N, 13.57.

Rearrangement of bromide IIIa *to form* IVa. To a stirred suspension of 0.20 mole of sodium amide in 500 ml. of commercial, anhydrous liquid ammonia[12] was added, during 5 min., 26.0 g. (0.10 mole) of bromide IIIa. The resulting bright yellow-green reaction mixture soon became green, then olive. More (200 ml.) liquid ammonia was added to facilitate stirring of the thick suspension. After 1 hr., 10.7 g. (0.20 mole) of solid ammonium chloride was added, and the liquid ammonia was evaporated as 400 ml. of anhydrous ether was added. The resulting ethereal suspension was filtered to remove the salt material, and the filtrate was extracted with three 200-ml. portions of cold 2 *N* hydrochloric acid. Evaporation of the dried ether solution left no appreciable residue. The acid extracts were combined and made basic with an aqueous solution of 50.0 g. of sodium hydroxide (cooled and stirred). The resulting mixture was extracted with three 150-ml. portions of ether, and the combined ethereal extracts dried over anhydrous magnesium sulfate. The solvent was removed, and the residue distilled to give 10.3 g. (58%) of *o*-xylyl-2-hydroxyethylmethylamine (IVa), b.p. 147–149° at 17 mm., $n^{24.5}D$ 1.5243, $n^{21.5}D$ 1.5259, leaving 0.5 g. of pot residue. No benzyldimethylamine was found.

The salt material left on the funnel on filtering the ethereal suspension of the reaction product was washed with dry ether, and dried in a vacuum desiccator for 3 days; weight 24.5 g.[13] A 1.0-g. sample of this material was dissolved in water, and the small amount of residue was removed by filtration. To the solution was added a saturated aqueous picric acid solution to precipitate 0.30 g. of the picrate of quaternary ion IIIa, m.p. 95–99°. Recrystallization from 95% ethanol gave 0.25 g. (15%) of the picrate, m.p. and mixed m.p. 98.5–99.5°. On the assumption that repetition of the process would precipitate an additional 17% of the picrate (see next section), the estimated recovery of the essentially pure quaternary ion IIIa as its picrate would be 32%. This corresponds fairly well to the amount (28%) of unchanged salt IIIa estimated to be present in the salt material (see ref. 13).

A vapor phase chromatogram of the distilled rearranged amino alcohol IVa showed a single peak.[14]

Anal. Calcd. for $C_{11}H_{17}NO$: C, 73.70; H, 9.56; N, 7.81. Found: C, 73.57; H, 9.33; N, 7.98.

Oxidation of 2.0 g. of this product (IVa) was effected by addition of 5.8 g. of potassium permanganate to a stirred mixture of IVa and 100 ml. of 0.5 *N* sodium hydroxide solution at room temperature (25–30°), followed by 2.0-g. portions of the permanganate at 0.5 hr. intervals until a total of 11.8 g. had been added. The resulting mixture was filtered through a Supercel mat, and the filtrate acidified with concd. hydrochloric acid to give 0.83 g. (55%) of *o*-toluic acid, m.p. 105–106°. This melting point was not depressed on admixture with an authentic sample of *o*-toluic acid.

Independent synthesis of rearranged amino alcohol IVa was achieved by slowly adding a solution of 7.4 g. (0.04 mole) of *o*-xylyl bromide in 50 ml. of dry benzene to a stirred solution of 12.0 g. (0.16 mole) of 2-methylaminoethanol in 50 ml. of dry benzene. After 3 days at room temperature the reaction mixture was extracted with 100 ml. of 4 *N* hydrochloric acid. The extract was made basic with concd. sodium hydroxide solution, and the resulting mixture was extracted three times with ether. The combined ether extract was dried over anhydrous magnesium sulfate and the solvent distilled. The residue was distilled to give 5.4 g. (75%) of *o*-xylyl-2-hydroxyethylmethylamine (IVa), b.p. 146.5–147.5° at 17 mm., $n^{21.5}D$ 1.5261. The infrared spectrum of a sample of this product was identical with that of a sample of IVa obtained from rearrangement of quaternary salt IIIa.

Methylation of 1.8 g. (0.01 mole) of rearranged amino alcohol IVa was effected with 1.9 g. (0.02 mole) of methyl bromide in 10 ml. of acetonitrile at room temperature. After 26 hr., anhydrous ether was added with cooling to precipitate an oily quaternary salt. Water (35 ml.) was added and the mixture shaken. The two layers were separated. Evaporation of the dried ether layer left no residue. To the aqueous layer was added a saturated aqueous solution of picric acid to precipitate an oily picrate, which crystallized on scraping the sides of the flask with a glass rod. After removing the crystals, that aqueous solution was treated twice more with picric acid to give a total of 3.4 g. 81%) of the picrate of the methyl derivative of IVa, m.p. 99–100° and at 99.5–100.5° after recrystallization from 95% ethanol.

Anal. Calcd. for $C_{18}H_{22}N_4O_8$: C, 51.18; H, 5.25; N, 13.27. Found: C, 51.22; H, 5.14; N, 13.15.

Independent synthesis of this picrate was achieved by allowing a solution of 2.0 g. (0.01 mole) of *o*-xylyl bromide and 1.0 g. (0.01 mole) of 2-dimethylaminoethanol in 10 ml. of acetonitrile to stand at room temperature for 7 hr. The reaction solution was then cooled in an ice bath, and anhydrous ether added slowly with stirring to precipitate *o*-xylyl-2-hydroxyethyldimethylammonium bromide as an oil, which crystallized on further cooling. This quaternary salt was collected, washed with dry ether, and kept in a vacuum desiccator; yield 2.3 g. (78%). The salt was too hygroscopic for a consistent melting point.

To an aqueous solution of a sample of this product was added a saturated aqueous solution of picric acid resulting in the precipitation of an oily picrate, which crystallized on being cooled. The picrate melted at 98–99° and at 99.5–100.5° after recrystallization from 95% ethanol. This melting point was not depressed on admixture with a sample of the picrate of the methyl bromide derivative of IVa obtained from the rearrangement of IIIa. The infrared spectra of the two samples of the picrate were identical.

Rearrangement of bromide IIIa (0.10 mole) was also effected with three molecular equivalents of sodium amide and two and three molecular equivalents of potassium amide. In the first two of these experiments, after replacing the ammonia by ether water was added to the ethereal suspension to dissolve the salts, and the amino alcohol IVa was isolated from the ether layer by extraction with acid. In the experiment with three equivalents of potassium amide, after replacing the ammonia with ether the ethereal suspension was filtered and the filtrate dried over anhydrous magnesium sulfate. The solvent was removed and a sample of the crude residue was subjected to vapor phase chromatography. The chromatogram obtained by using a column packed as described in note 14 indicated the presence of a trace of benzyldimethylamine besides the amino alcohol IVa. The crude product was then distilled to give IVa in 67% yield, b.p. 108.5–110.0° at 1.73 mm. The yields from the various experiments are given in Table I.

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[12] See C. R. Hauser, F. W. Swamer, and J. T. Adams, *Org. Reactions*, VIII, 122 (1954).

[13] Based on the yield of amino alcohol IVa, there should have been present 17.3 g. of inorganic salts, leaving 7.2 g. (28%) presumably to be unchanged bromide IIIa.

[14] Several columns were used the best of which seemed to be one packed with one part Union Carbide polypropylene glycol on four parts of Johns-Manville Chromasorb W (30–60 mesh) by weight.

Treatment of bromide IIIa *with one equivalent of sodium amide.* To a stirred suspension of 26.0 g. (0.10 mole) of bromide IIIa in 250 ml. of liquid ammonia was added through a stopcock attached to the bottom of a flask 0.10 mole of a suspension of sodium amide in 250 ml. of liquid ammonia (inverse addition procedure). No distinct color change was observed. The gray reaction mixture was treated, after 3.25 hr., with 5.4 g. (0.10 mole) of solid ammonium chloride, and the ammonia was replaced by ether. The resulting ethereal suspension was filtered. Evaporation of the ether filtrate left no basic or neutral material. The salt material on the funnel was dissolved in water, and the solution treated with Norit. After filtering, the clear filtrate was treated with saturated picric acid solution to precipitate the quaternary ammonium picrate. The mixture was heated on the steam bath until solution was achieved, and the picrate then allowed to crystallize. The crystals were removed by filtration to give 17.0 g. of the picrate of quaternary ion IIIa, m.p. 99.5–100.0°. The filtrate was again treated with aqueous picric acid to give 12.7 g. of the picrate, m.p. 98.5–99.5°. A third treatment gave 6.0 g. of the picrate, m.p. 98.5–99.5°; but a fourth treatment afforded only picric acid. The melting point of each of these fractions was not depressed on admixture with an authentic sample of the picrate of IIIa. The total recovery of IIIa as the essentially pure picrate amounted to 35.7 g. (87%).

When 0.10 mole of bromide IIIa was added to 0.10 mole of sodium amide in liquid ammonia in the usual manner, a bright yellow-green color was produced immediately but this color disappeared when all of the salt was added. There was obtained 0.7 g. (4%) of amino alcohol IVa, the methiodide of which Va was identified by the mixture melting point method.

Benzyl-3-hydroxypropyldimethylammonium bromide (IIIb). This salt was prepared from 51.4 g. (0.30 mole) of benzyl bromide, 30.9 g. (0.30 mole) of 3-dimethylaminopropanol-1 in 500 ml. of acetonitrile essentially as described above for salt IIIa. After 19 hr., 500 ml. of dry ether was added to precipitate 79.2 g. (96%) of IIIb, m.p. 100–101°. This melting point was not changed on recrystallization from ethanol–hexane. The salt was somewhat hygroscopic.

Anal. Calcd. for $C_{12}H_{20}BrNO$: C, 52.56; H, 7.35; N, 5.11. Found: C, 52.37; H, 7.15; N, 5.37.

Rearrangement of bromide IIIb *to form* IVb. To a stirred suspension of 0.30 mole of sodium amide in 500 ml. of liquid ammonia under a Dry Ice–acetone condenser was added, during 5 min., 27.4 g. (0.10 mole) of bromide IIIb. The initial bright yellow color was discharged within 1 hr. during which time a heavy precipitate formed. After 1.5 hr., 16.1 g. (0.30 mole) of solid ammonium chloride was added, and the liquid ammonia was replaced by ether. The resulting ethereal suspension was filtered to remove the salts.[15] The ethereal filtrate was extracted with hydrochloric acid and the amine product isolated as described above for the product from IIIa. There was obtained on distillation at 15–16 mm. 0.13 g. (1%) of benzyldimethylamine, b.p. 65–70°; 0.20 g. of a mid-fraction, b.p. 70–159°; and 10.54 g. (55%) of *o*-xylyl-3-hydroxypropylmethylamine (IVb), b.p. 159–160°. No residue was left on evaporation of the ether solution after extraction with acid.

The benzyldimethylamine was identified by comparison of its infrared spectrum with that of an authentic sample of this amine and by conversion to its methiodide[16] and picrate,[17] which were identified by the mixture melting point method.

The distilled rearranged amino alcohol IVb gave a vapor phase chromatogram that showed a single peak.[14]

Anal. Calcd. for $C_{12}H_{19}NO$: C, 74.57; H, 9.91; N, 7.25. Found: C, 74.55; H, 10.06; N, 7.21.

Oxidation of 2.0 g. of amino alcohol IVb was effected with 13.7 g. of potassium permanganate and 100 ml. of 0.5 *N* sodium hydroxide solution essentially as described above for IVa to give 1.10 g. (81%) of *o*-toluic acid, m.p. 106-106.5°, which was identified by the mixture melting point method.

Methylation of 1.0 g. (0.005 mole) of amino alcohol IVb was effected with 1.0 g. (0.011 mole) of methyl bromide in 10 ml. of acetonitrile at room temperature. After 2 hr., the resulting precipitate was collected on a funnel and dried to give 1.5 g. (100%) of *o*-xylyl-3-hydroxypropyldimethylammonium bromide (Vb). m.p. 127–128° and at 128–129° after one recrystallization from ethanol–hexane.

Anal. Calcd. for $C_{13}H_{22}BrNO$: C, 54.17; H, 7.70; N, 4.86. Found: C, 54.31; H, 7.84; N, 4.66.

Independent synthesis of this quaternary salt was achieved by allowing a solution of 2.8 g. (0.015 mole) of *o*-xylyl bromide and 1.50 g. (0.015 mole) of 3-dimethylaminopropanol-1 in 20 ml. of acetonitrile to stand at room temperature. After 4 hr., some precipitate was present, and slow addition of 30 ml. of dry ether produced more precipitate. The solid was collected on a funnel and dried to give 4.18 g. (100%) of *o*-xylyl-3-hydroxypropyldimethylammonium bromide (Vb), m.p. 128–129°, which was not changed by recrystallization from ethanol–hexane. This melting point was not depressed on admixture with a sample of the methyl bromide derivative of IVb obtained from the rearrangement of IIIb. The infrared spectra of the two samples were identical.

Rearrangement of bromide IIIb was also allowed to proceed for 1.0 and 3.5 hr. (see Table I). In these experiments, after replacing the ammonia by ether, the resulting ethereal suspension was shaken with water to dissolve the salts. The two layers were separated, and the amine products isolated from the ethereal layer.

Benzyl-6-hydroxyhexyldimethylammonium chloride (IIIc). A solution of 27.3 g. (0.20 mole) of hexamethylene chlorohydrin and 27.0 g. (0.20 mole) of benzyldimethylamine in 200 ml. of acetonitrile was refluxed for 15 min., and then allowed to stand overnight. To the solution was added sufficient ether (dried by distillation from lithium aluminum hydride) to produce cloudiness, which was discharged by heating on a steam bath. On cooling, the solution precipitated white crystals, which were collected on a funnel and washed well with dry ether. The crystals were dried in a vacuum desiccator to give 30.1 g. (55%) of the chloride of IIIc (hygroscopic), m.p. 80–120°. Attempts to recrystallize this salt from various solvents were unsatisfactory.

Rearrangement of chloride IIIc *to form* IVc. To a stirred suspension of 0.40 mole of sodum amide in 500 ml. of liquid ammonia (Dry Ice–acetone condenser) was added, during 5 min., 25.0 g. (0.092 mole) of crude chloride IIIc. The initial yellow-green color slowly changed to tan. After 7 hr., 21.4 g. (0.40 mole) of ammonium chloride was added, and the ammonia replaced by ether. After removing the salts by filtration,[18] the ethereal filtrate was extracted with hydrochloric acid and the amine product isolated as described above for the product from IIIa. There was obtained 1.50 g. (12%) of benzyldimethylamine, b.p. 67–69° at 14–15 mm. (identified as described above), 0.40 g. of a mid-fraction, b.p. 69–184° at 14–15 mm., and 11.2 g. (52%) of *o*-xylyl-6-hydroxyhexylmethylamine (IVc), b.p. 184–188° at 14–15 mm. and 143–146° at 0.60–0.75 mm. An analytical sample was taken at 145° to 0.75 mm.

Anal. Calcd. for $C_{15}H_{25}NO$: C, 76.54; H, 10.71; N, 5.95. Found: C, 76.70; H, 10.55; N, 6.14.

The rearranged amino alcohol, b.p. 145° at 0.75 mm., gave a vapor phase chromatogram that showed three peaks.[14] The main peak, apparently due to 90–95% of the fraction,

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(15) The dried salts weighed 27.4 g., which was estimated to contain 4.4 g. (16%) of unchanged bromide IIIb; see ref. 13.

(16) H. Emde, *Arch. Pharm.*, **247**, 353 (1909).

(17) J. von Braun, M. Kuhn, and O. Goll, *Ber.*, **59**, 2330 (1926).

(18) The dried salts weighed 28.6 g., which was estimated to contain about 2.1 g. (8%) of unchanged chloride IIIc; see note 13.

was shown to have arisen from amino alcohol IVc, since the addition of an independently synthesized sample of this compound only enhanced this peak.

The ether solution from which the amines were extracted was dried over anhydrous magnesium sulfate, and the solvent removed. The residue was distilled to give 1.05 g. (11.4%) of 5-hexene-1-ol, b.p. 66.0–66.5° at 13 mm., $n^{25.5}{}_D$ 1.4336, lit.[19] b.p. 57–58° at 15 mm., $n^{25}{}_D$ 1.4335, and lit.[20] b.p. 74° at 25 mm., $n^{23.5}{}_D$ 1.4341. The α-naphthylurethane melted at 63–64°, lit.[21] m.p. 62°.

Oxidation of 1.0 g. of rearranged amino alcohol IVc was effected with 9.85 g. of potassium permanganate and 100 ml. of 0.5 *N* sodium hydroxide solution essentially as described above for IVa. After stirring overnight, the mixture was filtered (Supercel mat) and solid sodium bisulfite added to the filtrate to discharge the purple color. The mixture was refiltered. Acidification with concd. hydrochloric acid and evaporation of part of the solution afforded on cooling, and recrystallization from water, 0.30 g. (42%) of phthalic acid, m.p. 209–210°. This melting point was not depressed on admixture with an authentic sample of phthalic acid. The product was converted to fluorescein and *o*-phthalanil, m.p. 210–212°, lit.[22] m.p. 210°.

Independent synthesis of rearranged amino alcohol IVc was achieved from *o*-toluic acid (100.0 g., 0.735 mole) through its acid chloride, which was treated with 100 g. of 40% aqueous methylamine to give, after recrystallization from chloroform–hexane, 76.1 g. (70%) of *N*-methyl-*o*-toluamide, m.p. 75°, lit.[23] m.p. 75°.

This amide (51.0 g., 0.5 mole) was reduced with 19 g. (0.5 mole) of 95% lithium aluminum hydride in 2 l. of dry ether to give 37.0 g. (80%) of *N*,*o*-dimethylbenzylamine, b.p. 84.0–84.5° at 9.8 mm., lit.[24] 100–102° at 11 mm. The picrate melted at 130–132°, lit.[24] m.p. 129°.

A solution of 13.5 g. (0.10 mole) of this amine and 13.6 g. (0.10 mole) of hexamethylene chlorohydrin in 100 ml. of acetonitrile was refluxed for 12 hr. After cooling and adding 100 ml. of ether, the solution was extracted with two 100-ml. portions of 3 *N* hydrochloric acid. The combined acid extract was made basic with 30.0 g. of sodium hydroxide in concd. aqueous solution. The resulting mixture was extracted three times with ether, and the combined ether extract was dried over anhydrous magnesium sulfate. The solvent was removed, and the residue distilled to give 5.0 g. (37%) of recovered *N*,*o*-dimethylbenzylamine, b.p. 70–73 at 1.8 mm. and 8.66 g. (37%) of amino alcohol IVc, b.p. 146.0–147.5° at 0.65–0.70 mm. The infrared spectrum of this product was identical with that of IVc obtained through the rearrangement of quaternary ion IIIc, except that the latter spectrum showed a very small absorption at 700 cm.$^{-1}$

Benzyl-2-methoxyethyldimethylammonium bromide (XI). To 91.3 g. (1.20 mole) of 2-methoxyethanol was added, during 3 hr., 100 g. (0.37 mole) of phosphorus tribromide, and the resulting solution stirred overnight. The material boiling up to 130° was collected, cooled, washed with cold water, and dried over calcium chloride. Distillation afforded 44.0 g. (29%) of 2-bromoethyl methyl ether, b.p. 109–111°, lit.[25] b.p. 110°.

To a stirred solution of 44.0 g. (0.32 mole) of this bromoether in 200 ml. of acetonitrile was added 42.7 g. (0.32 mole) of benzyldimethylamine in 100 ml. of acetonitrile. After stirring at room temperature for 2 days and refluxing for 1.5 hr., the reaction mixture was cooled and dry ether added slowly. The resulting precipitate was collected on a funnel, washed with dry ether, and dried in a vacuum desiccator to give 55.4 g. (64%) of bromide XI, m.p. 123–124.5° and at 124.0–124.5° after recrystallization from acetone–hexane.

Anal. Calcd. for $C_{12}H_{20}BrNO$: C, 52.56; H, 7.35; N, 5.11. Found: C, 52.74; H, 7.15; N, 4.90.

A second crop of 8.0 g. of bromide XI, m.p. 122.0–123.5° was obtained from the mother liquor.

Bromide XI, m.p. 124–125°, was prepared from 2-dimethylaminoethyl methyl ether and benzyl bromide in 77% yield. However, since the amino ether could be prepared in only 32% yield from 2-bromoethyl methyl ether, the over-all method was not as satisfactory as the one above. Admixture of a sample of the product with a sample of that obtained as described above showed no depression in melting point.

Reaction of bromide XI *with sodium amide. β-Elimination.* To a stirred suspension of 0.21 mole of sodium amide in 500 ml. of liquid ammonia (Dry Ice–acetone condenser) was added, during 5 min., 27.4 g. (0.10 mole) of bromide XI. Only a slight darkening of the gray sodium amide occurred. After 4 hr., 11.3 g. (0.21 mole) of ammonium chloride was added, and the liquid ammonia replaced by dry ether. After removing suspended salts by filtration,[26] the ethereal filtrate was extracted with hydrochloric acid and the amine product isolated as described above for the product from IIIa. There was obtained 6.4 g. (47%) of benzyldimethylamine, b.p. 68–70° at 16 mm. (identified as described above) and 0.1 g. of pot residue. No rearranged amine was found.

Evaporation of the ether solution after extraction with acid left no appreciable residue.

When the reaction was carried out with 0.10 mole of bromide XI and 0.11 mole of sodium amide in 500 ml. of liquid ammonia for 2 hr., the yield of benzyldimethylamine was 22%.

Further rearrangement around aromatic ring and other reactions. A. *Reactions of quaternary ion–alcohol* Va. Rearranged amino alcohol IVa (18.0 g., 0.10 mole) was methylated with 28.4 g. (0.20 mole) of methyl iodide in 100 ml. of acetonitrile (solution stirred 3 days). The resulting precipitate was collected, washed with dry ether, and dried to give 32.0 g. (99%) of *o*-xylyl-2-hydroxyethyldimethylammonium iodide (Va), m.p. 118–119° and at 120.5–121.0° after one recrystallization from absolute ethanol–hexane.

Anal. Calcd. for $C_{12}H_{20}INO$: C, 44.87; H, 6.28; N, 4.36. Found: C, 45.08; H, 6.33; N, 4.44.

This quaternary salt (32.1 g., 0.10 mole) was added, during 5 min., to a stirred suspension of 0.30 mole of sodium amide in 500 ml. of liquid ammonia under a Dry Ice–acetone condenser. After 7 hr., the thick reaction mixture (bright blue) was neutralized with 16.1 g. (0.30 mole) of ammonium chloride, and the ammonia was replaced by 500 ml. of ether. The suspended salts were dissolved in 500 ml. of water (stirred), and the layers were separated. The ether layer was extracted twice with 3 *N* hydrochloric acid, then dried, and the solvent removed. The residue was distilled to give 2.7 g. of material, b.p. 160–170° at 3.4 mm., which solidified (fluoresced under ultraviolet light). Recrystallization from 95% ethanol afforded 2.4 g. (23%) of 2,2′-dimethylstilbene (XVII), m.p. 83.0–83.5°, which was not depressed on admixture with an authentic sample of this compound (lit.[27] m.p. 82–83°, b.p. 176–180 at 10 mm.). A 3.1-g. sample of higher boiling material was obtained, but

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(19) R. E. Lyle, E. J. De Witt, and I. C. Pattison, *J. Org. Chem.*, **21**, 61 (1956).

(20) J. Colonge and M. Reymermier, *Bull. soc. chim. France*, 1531 (1955).

(21) L. Crombie, J. Gold, S. H. Harper, and B. J. Stokes, *J. Chem. Soc.*, 136 (1956).

(22) I. Heilbron and H. M. Bunbury, *Dictionary of Organic Compounds*, Vol. IV, Oxford University Press, New York, 1953, p. 191.

(23) M. L. van Scherpenzeel, *Rec. trav. chim.*, **20**, 149 (1901).

(24) J. von Braun and R. Michaelis, *Ann.*, **507**, 1 (1933).

(25) W. Chalmers, *Can. J. Research*, **7**, 464 (1932).

(26) The dried salts weighed 24.5 g., which was estimated to contain about 7.6 g. (28%) of unchanged bromide XI; see ref. 13.

(27) E. Spath, *Monatsh. Chem.*, **35**, 463 (1914).

it failed to yield any pure substance on distillation or recrystallization.

The two acid extracts of the reaction product were combined and made basic with concd. sodium hydroxide solution. The resulting mixture was extracted with ether. The ether solution was dried and distilled to give 0.32 g. (2%) of 2,3-dimethylbenzyl-2-hydroxyethylmethylamine (XVIa), b.p. 103–105° at 0.40 mm., leaving 0.30 g. of pot residue. The infrared spectrum of this compound showed a strong peak at 772 and a medium peak at 725 cm.$^{-1}$

Methylation of 0.20 g. (0.001 mole) of this product was effected with 1.2 g. (0.012 mole) of methyl bromide in 2 ml. of acetonitrile. After standing overnight, 10 ml. of dry ether was added to precipitate 0.20 g. (70%) of bromide XVIIIa, m.p. 146–147°. After two more recrystallizations, it melted at 146.5–147.0°.

Anal. Calcd. for $C_{13}H_{22}BrNO$: C, 54.17; H, 7.70; N, 4.86. Found: C, 54.29; H, 7.90; N, 4.96.

Independent synthesis of this bromide was accomplished by refluxing a solution of 1.63 g. (0.01 mole) of 2,3-dimethylbenzyldimethylamine[28] (XV) and 1.38 g. (0.01 mole) of ethylene bromohydrin in 10 ml. of acetonitrile for 1 hr. After standing overnight, 30 ml. of dry ether was added to precipitate 1.8 g. (62%) of bromide XVIIIa, m.p. 145–147°. One recrystallization from absolute ethanol–hexane afforded 1.7 g. (59%) of this salt, m.p. 147–148°, which was not depressed on admixture with a sample of bromide XVIIIa obtained by methylating the rearrangement product of quaternary ion Va. The infrared spectra of the two samples were identical.

B. *Reactions of quaternary ion–alcohol* Vb. This reaction was effected essentially as described above for Va, employing 26.2 g. (0.09 mole) of quaternary bromide Vb and 0.30 mole of sodium amide in 500 ml. of liquid ammonia. After 7 hr., the thick, dark blue reaction mixture was neutralized with 16.1 g. of ammonium chloride, and the ammonia replaced by ether. The ether suspension was filtered, and the filtrate was extracted with hydrochloric acid, dried, and distilled to give 1.29 g. (14%) of 2,2′-dimethylstilbene (XVII), b.p. 125–132° at 0.55 mm. (solidified on cooling). One recrystallization from absolute ethanol afforded 0.90 g. (10%) of this hydrocarbon, m.p. 82–83°, and mixed m.p. 82–83°. A 2.1-g. sample of higher boiling material was obtained.

The combined acid extract of the reaction product was worked up (see above under A) to give 0.7 g. (8%) of 3-dimethylaminopropanol-1, b.p. 73–76° at 33 mm. This amino alcohol was identified by its infrared spectrum and a mixed melting point on its picrate, 63.5–64.5°.

Anal. Calcd. for $C_{11}H_{16}N_4O_8$: N, 16.86; Found: N, 16.98.

There was also obtained 4.7 g. (25%) of 2,3-dimethylbenzyl-3-hydroxypropylmethylamine (XVIb), b.p. 159–163° at 9.4 mm., and at 116–117° at 0.55 mm.

Anal. Calcd. for $C_{13}H_{21}NO$: C, 75.31; H, 10.21; N, 6.76. Found: C, 75.16; H, 10.01; N, 6.76.

The infrared spectrum of this product showed a strong peak at 772 and one of medium intensity at 725 cm.$^{-1}$ A vapor phase chromatogram[14] indicated 1–2% impurity (presumably 2-methylbenzyldimethylamine).

On repeating the experiment employing an addition time of 1 hr., the yield of amino alcohol XVIb was 22%.

Oxidation of 1.0 g. (0.005 mole) of XVIb was effected with 6.85 g. of potassium permanganate in 100 ml. of 0.5 *N* sodium hydroxide solution as described for IVa. After stirring overnight, the reaction mixture was filtered (Norite pad), and the filtrate acidified to give 0.40 g. (44%) of 2-methylisophthalic acid, m.p. 235–240°, and at 240.0–241.5° after recrystallization from ethanol–water, lit.[29] m.p. 238–240°.

Anal. Neut. equiv. Calcd.; 90.1. Found: 89.6.

Methylation of 0.5 g. (0.002 mole) of amino alcohol XVIb was effected with 0.5 g. (0.005 mole) of methyl bromide in 10 ml. of acetonitrile. After standing overnight, 10 ml. of dry ether was added to precipitate 0.60 g. (83%) of bromide XVIIIb, m.p. 165.0–166.5° and at 168.5–169.0° after one recrystallization from ethanol–hexane.

Anal. Calcd. for $C_{14}H_{24}BrNO$: C, 55.63; H, 8.00; N, 4.63. Found: C, 55.44; H, 8.03; N, 4.80.

Independent synthesis of bromide XVIIIb was accomplished by refluxing a solution of 1.63 g. (0.01 mole) of 2,3-dimethylbenzyldimethylamine[28] (XV) and 1.38 g. (0.01 mole) of 3-bromo-propanol-1-in 10 ml. of acetonitrile for 15 min. After standing overnight, 30 ml. of dry ether was added to precipitate 1.0 g. (33%) of bromide XVIIIb, m.p. 168–169° and at 169.5–170.0° after one recrystallization from absolute ethanol–hexane. This m.p. was not depressed on admixture with a sample of bromide XVIIIb obtained from the rearrangement of Vb (see above), and the infrared spectra of the two samples were identical.

Benzylbis(2-hydroxyethyl)methylammonium iodide (XXI). 2,2′-Iminodiethanol was treated with benzyl chloride to form 2,2′-(benzylimino)diethanol, b.p. 188–192° at 9.5 mm., lit.[30] b.p. 176–177° at 6 mm.

To a stirred solution of 29.0 g. (0.15 mole) of this compound in 100 ml. of anhydrous ether was added 42.6 g. (0.30 mole) of methyl iodide. After stirring overnight the salt began to oil out. On cooling in a refrigerator for about 2 weeks crystals slowly formed. The crystals were collected, washed with several portions of dry ether, and dried in a vacuum desiccator. They were recrystallized once from absolute ethanol–hexane to give 30.6 g. (61%) of salt XXI, m.p. 70.0–70.5°.

Anal. Calcd. for $C_{12}H_{20}INO_2$: C, 42.74; H, 5.98; N, 4.15. Found: C, 42.58; H, 6.18; N, 4.13.

Rearrangement of quaternary iodide XXI. To a stirred solution of 0.50 mole of potassium amide in 900 ml. of liquid ammonia and 350 ml. of purified tetrahydrofuran was added rapidly (1 min.)[31] 30.0 g. (0.089 mole) of salt XXI. A bright yellow color was produced initially, but it rapidly changed to brown. After stirring under a Dry Ice–acetone condenser for 5 hr., 26.75 g. (0.50 mole) of solid ammonium chloride was added, and the ammonia displaced by 300 ml. of dry ether. The salts were removed by filtration, and the filtrate dried over anhydrous magnesium sulfate. After removing the solvent, the residue was distilled to give 1.24 g. (8%) of 2-hydroxyethylmethylbenzylamine (XXIII), b.p. 85–91 at 0.55–0.57 mm., 1.65 g. of a mid-fraction, b.p. 91.0–156.5 at 0.57 mm., and 9.85 g. (53%) of 2,2′-(*o*-xylylimino)diethanol (XXII), b.p. 156.5–158.5 at 0.60–0.70 mm., leaving 1.86 g. of pot residue.

A vapor phase chromatogram[14] of the product XXIII showed it to contain about 10% of an impurity, but the major peak was only enhanced when the product was mixed with an authentic sample of XXIII (b.p. 133–135 at 13 mm., lit.[32] b.p. 133–135 at 14 mm.), prepared from benzyl chloride and 2-methylaminoethanol. The product XXIII was treated with methyl bromide in acetonitrile to give, after two recrystallizations from absolute ethanol–hexane, quaternary salt IIIa, m.p. 127–128, which was not depressed on admixture with an authentic sample of IIIa (m.p. 129–130).

A vapor phase chromatogram[14] of the product XXII showed it to contain traces of two other compounds. Redistillation of the product led to considerable decomposition and failed to remove the impurities.

Oxidation of 2.09 g. of product XXII was effected with 15.8 g. of potassium permanganate in 100 ml. of 0.5 *N*

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[28] W. R. Brasen and C. R. Hauser, *Org. Syntheses*, **34**, 63 (1954).

[29] R. C. Elderfield and O. L. McCurdy, *J. Org. Chem.*, **21**, 295 (1956).

[30] W. S. Gump and E. J. Nikawitz, U. S. Patent **2,504,-977** (1950) [*Chem. Abstr.*, **44**, 6880 (1950)].

[31] When a longer addition time was employed the salt oiled out before the addition was complete.

[32] C. Mannich and R. Kuphal, *Arch. Pharm.*, **250**, 539 (1912).

sodium hydroxide solution essentially as described above for IVa. After stirring for 36 hr., the mixture was worked up to give 0.52 g. (33%) of phthalic acid, m.p. 187–188° and at 192–193° (sealed tube) after one recrystallization from water. Lit.[33] m.p. 191° (sealed tube) (identified as described above).

Independent synthesis of XXII was accomplished by refluxing a solution of 41.6 g. (0.225 mole) of *o*-xylyl bromide and 23.7 g. (0.225 mole) of 2,2′-iminodiethanol in 400 ml. of acetonitrile for 1.5 days. The acetonitrile was distilled, and a cold solution of 13.0 g. of sodium hydroxide in 100 ml. of water was added. The resulting basic mixture was extracted three times with ether and the ether extracts dried over anhydrous magnesium sulfate. The solvent was removed, and the residue was distilled to give 34.0 g. (72%) of amino dialcohol XXII, b.p. 153–155° at 0.55 mm. and at 172–174° at 0.95–1.00 mm. on redistillation.

Anal. Calcd. for $C_{12}H_{19}NO_2$: C, 68.86; H, 9.15; N, 6.69. Found: C, 68.63; H, 9.20; N, 6.57.

The infrared spectrum of this product was identical with that of XXII obtained from the rearrangement of quaternary salt XXI, except for a very small absorption at 700 cm.$^{-1}$ in the spectrum of the latter, which was probably due to the presence of a trace of amino alcohol XXIII.

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[33] See ref. 22, p. 192.

[CONTRIBUTION NO. 1102 FROM THE DEPARTMENT OF CHEMISTRY, UNIVERSITY OF PITTSBURGH]

The Direction of Opening of Styrene Oxide by Acetic Acid[1]

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Oxidation of the acetolysis products of styrene oxide after equilibration for various lengths of time gives mixtures of phenacyl acetate (XIII), acetylmandelic acid (XIV), 2-acetoxy-2-phenylethyl acetylmandelate (XVIII), 2-acetoxy-1-phenylethyl acetylmandelate (XIX), and benzoic acid. The variation with time of the ratio of acetylmandelic acid to phenacylacetate indicates that the predominant product of the ring opening reaction is 2-acetoxy-2-phenylethanol (XII) and that this rearranges slowly in the reaction medium to a mixture rich in 2-acetoxy-1-phenylethanol (X). A mechanism for the formation of the complex esters XVIII and XIX is proposed.

Eliel[2] has called attention to the confusion that sometimes arises in the study and interpretation of the openings of unsymmetrical epoxides due to contradictory experimental results. The reasons which he lists for this state of affairs include difficulties in separating and analyzing for the two isomeric products, rearrangements occurring during the synthesis of authentic specimens of possible isomeric products and sensitivity of the product ratio to minor changes in reaction conditions. To this list of difficulties, we should now like to add one more, namely the possibility of a rearrangement of the first formed isomer to the product that would have been formed first had it opened in the other possible direction.

The opening of epoxides[3] under acidic conditions is thought to occur by coordination of a proton or other Lewis acid with the epoxide oxygen followed by a nucleophilic attack on one of the carbon atoms of the epoxide ring. This latter step is thought to have both SN 1 and SN 2 character. Because of the formal positive charge on the ring oxygen atom, the transition state (Fig. 1) for the nucleophilic step in the acid catalyzed reactions is thought to involve more bond breaking than that for the nonacid catalyzed reactions.

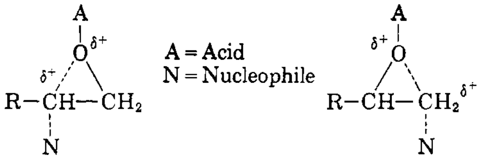

Fig. 1. Possible transition states for acid-catalyzed ring openings of unsymmetrical epoxides

Propylene oxide (I. R = methyl), with a variety of acidic reagents, gives mixtures of products (II and III. R = methyl, in the case of alcohols and phenols) arising from ring openings at the secondary and primary positions.[4–6] The acid ring openings of styrene oxide (I. R = phenyl), which has a phenyl group capable of stabilizing a positive charge, is supposed to involve a much higher degree of SN1 character, thereby favoring attack at the secondary carbon atom. This expectation is born out in the reaction of styrene oxide with methanol[7] and allyl alcohol.[8,9] In both cases, the very predominant

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[1] (a) Taken, in part, from the Master's thesis of Marylou Dughi, at the University of Pittsburgh, 1960; (b) Present address of M.D.: Ciba Pharmaceutical Products Inc., Summit, N. J.

[2] E. L. Eliel, in *Steric Effects in Organic Chemistry*, M. S. Newman, ed., John Wiley and Sons, New York, 1956, p. 106.

[3] For recent reviews of epoxide reactions, see reference 2 and R. E. Parker and N. S. Isaacs, *Chem. Revs.*, **59**, 737 (1959).

[4] A. R. Sexton and E. C. Britton, *J. Am. Chem. Soc.*, **70**, 3606 (1948).

[5] H. C. Chitwood and B. T. Freure, *J. Am. Chem. Soc.*, **68**, 680 (1946).

[6] C. A. Stewart and C. A. VanderWerf, *J. Am. Chem. Soc.*, **76**, 1259 (1954).

[7] W. Reeve and I. Christoffel, *J. Am. Chem. Soc.*, **72**, 1480 (1950).

[8] F. N. Hayes and C. Gutberlet, *J. Am. Chem. Soc.*, **72**, 3321 (1950). In this paper, the erroneous conclusions of Swern *et al.*[9] are corrected.

[9] D. Swern, G. N. Billen, and H. B. Knight, *J. Am. Chem. Soc.*, **71**, 1152 (1949).