dichloro-4-hydroxyquinoline. The product, recrystallized from 80% ethanol, melted at 261–263° with the evolution of purple fumes. The analysis indicated the presence of two chlorines, one hydroxyl and one iodine. (Calcd. for $C_9H_5Cl_2INO$: C, 31.64; H, 1.48. Found: C, 31.02; H, 1.09.)

7-Chloro-2,4-dimethoxyquinoline (VI). (A) **From 2,7-Dichloro-4-methoxyquinoline (V).**—A solution of 3.2 g. (0.06 mole) of commercial sodium methoxide in 35 ml. of methanol was added to a suspension of 4.5 g. (0.02 mole) of 2,7-dichloro-4-methoxyquinoline (V) in 35 ml. of methanol and the resulting mixture was refluxed for two and one-half hours. The solution was cooled, diluted with an equal volume of water and filtered. The residue was thoroughly washed with water and dried; yield 4.1 g. (92%); m. p. 63–68°. The product was recrystallized from 80% ethanol and 3.7 g. (83%) of colorless needles was obtained; m. p. 74–76°. After two additional recrystallizations it melted at 78.5–80.5°.

Anal. Calcd. for $C_{11}H_{10}ClNO_2$: C, 59.06; H, 4.51. Found: C, 58.73; H, 4.52.

(B) **From 4,7-Dichloro-2-methoxyquinoline (VI).**—A mixture of 1.0 g. (0.0044 mole) of 4,7-dichloro-2-methoxyquinoline (VI) and a solution of 0.3 g. (0.013 mole) of sodium in 20 ml. of methanol was refluxed for six hours and then cooled overnight; 0.37 g. (37%) of starting material crystallized and was identified. The filtrate was evaporated almost to dryness and again filtered, and the residue was thoroughly washed with water; yield of IV, 0.52 g. (52%); m. p. 57–61°. Recrystallization from 80% ethanol yielded colorless needles (m. p. 71–74°) which showed no mixture melting point depression with the sample prepared previously (A).

(C) **From 2,4,7-Trichloroquinoline (II).**—Two grams (0.0086 mole) of 2,4,7-trichloroquinoline (II)[4] was suspended in a solution of 2.8 g. (0.052 mole) of commercial sodium methoxide in 20 ml. of methanol and the mixture was refluxed for twenty-two hours, cooled and filtered. The residue was washed thoroughly with water and 1.9 g. (99%) of colorless needles remained; m. p. 77–80°. A mixture melting point of this and a sample of IV synthesized above (A) showed no depression.

7-Chloro-4-hydroxycarbostyril (I) was obtained upon refluxing a mixture of 0.5 g. of 7-chloro-2,4-dimethoxyquinoline (IV) and 25 ml. of 6 *N* hydrochloric acid for one hour, cooling and filtering the resulting mixture; yield 0.23 g. (56%); m. p. 295–320°. A mixture melting point of this and an authentic sample[4] showed no depression.

Summary

Syntheses and proofs of structure have been given for 4,7-dichlorocarbostyril, 4,7-dichloro-2-methoxyquinoline, 2,7-dichloro-4-methoxyquinoline and 7-chloro-2,4-dimethoxyquinoline.

Evidence has been presented for the greater reactivity of the 2- as compared to the 4-chlorine both in 2,4,7-trichloroquinoline and in the isomeric monomethanolysis products, and for the markedly decreased reactivity of both the 2 and the 4-chlorines in the monomethoxylated compounds as compared with either of the 2 or 4-chlorine reactivities of 2,4,7-trichloroquinoline itself.

Diazomethylation of 4,7-dichlorocarbostyril has been shown to involve chiefly N-methylation.

CHARLOTTESVILLE, VIRGINIA RECEIVED APRIL 5, 1946

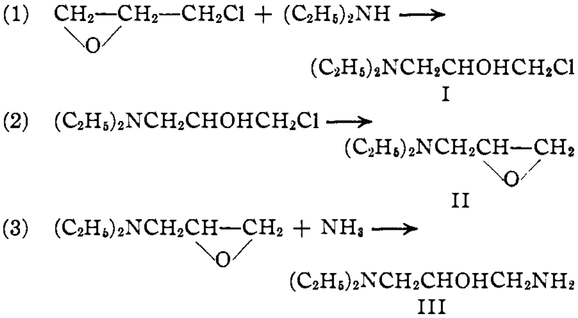
[CONTRIBUTION FROM THE DEPARTMENTS OF CHEMISTRY OF IOWA STATE COLLEGE, THE UNIVERSITY OF ILLINOIS, COLUMBIA UNIVERSITY, AND COOPER UNION]

Synthesis of 1-Diethylamino-2,3-epoxypropane, 3-Diethylamino-2-hydroxypropylamine, and 4-Diethylamino-3-hydroxybutylamine[1]

BY HENRY GILMAN, C. S. SHERMAN, CHARLES C. PRICE, ROBERT C. ELDERFIELD, JOHN T. MAYNARD, ROBERT H. REITSEMA, L. TOLMAN, S. P. MASSIE, JR., F. J. MARSHALL, AND LEON GOLDMAN

In connection with the preparation of certain antimalarial drugs, need arose for rather large amounts of 3-diethylamino-2-hydroxypropylamine (III) and of 4-diethylamino-3-hydroxybutylamine (IV). The synthesis of the former amine has been described in the literature[2,3] with insufficient detail to enable the preparation to be stepped up to a large scale. The latter amine appears to be new. A detailed study of the experimental conditions necessary for optimum yields of both amines has been made.

According to Drozdov and Cherntsov,[2] the course of the reactions by which the hydroxypropylamine derivative (III) is prepared from epichlorohydrin is



$$(1)\quad \underbrace{CH_2-CH_2}_{O}-CH_2Cl + (C_2H_5)_2NH \longrightarrow \underset{I}{(C_2H_5)_2NCH_2CHOHCH_2Cl}$$

$$(2)\quad (C_2H_5)_2NCH_2CHOHCH_2Cl \longrightarrow \underset{II}{(C_2H_5)_2NCH_2\underbrace{CH-CH_2}_{O}}$$

$$(3)\quad (C_2H_5)_2NCH_2\underbrace{CH-CH_2}_{O} + NH_3 \longrightarrow \underset{III}{(C_2H_5)_2NCH_2CHOHCH_2NH_2}$$

This interpretation is borne out by an examination of the experimental conditions involved in reactions (1) and (2). The previous workers, as well as ourselves, normally carried out the reactions without isolation of the intermediate aminochlorohydrin (I). Aqueous diethylamine is used, and the product of the primary reaction (1) is then subjected to the action of a large excess of alkali to reclose the ethylene oxide ring in (II). Reboul[4]

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[1] The work described in this paper was done under contracts, recommended by the Committee on Medical Research, between the Office of Scientific Research and Development and Iowa State College, the University of Illinois, Columbia University, and Cooper Union.

[2] Drozdov and Cherntsov, *J. Gen. Chem. U. S. S. R.*, **4**, 969 (1934).

[3] Eisleb, U. S. Patent 1,790,042, January 27, 1931; *C. A.*, **25**, 1259 (1931).

[4] Reboul, *Bull. soc. chim.*, [2] **42**, 261 (1884).

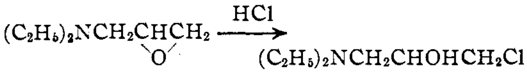
has described a synthesis of *sym*-bis-diethylaminoisopropanol by reaction of epichlorohydrin with diethylamine at temperatures somewhat higher than those described for the formation of the amine epoxide (II) by the Russian workers.

We have investigated the preparation of the epoxide (II) using various proportions of reactants and experimental conditions. Twelve experiments ranging in size from 3 to 12 moles gave yields of 61–63%. Since the major cause for poor yields appears to be due to improper temperature control with resultant overheating of the reaction mixture and formation of bis-diethylaminoisopropanol, it became of importance in connection with larger scale operations to obtain some estimate of the heat required to be dissipated in the reaction. Accordingly, the heat evolved in the reaction of equimolecular quantities of epichlorohydrin and diethylamine was found to be 21 ± 2 kcal.

Finally, in earlier runs some doubt of the stability of the amine epoxide (II) during distillation arose. To settle this question, a study of its heat stability was made. When pure, the epoxide appears to be relatively stable up to a temperature of about 80°, but the crude or impure material rapidly turns dark and deposits a viscous material, even if stored for only a few hours in the refrigerator.

Likewise, the study of reaction (3) has been carried out under a variety of experimental conditions. Consistent yields of 63–71% can be obtained in runs using up to 4 moles of the amine epoxide (II). It is vital that the reaction mixture be held at a temperature below 3° during the mixing of the reactants, and that the temperature be below 10° during the standing period. In one run in which both operations were carried out at 25°, the yield of the hydroxydiamine (III) dropped to 19%. It has also been possible to substitute aqueous ammonia at atmospheric pressure for alcoholic ammonia in pressure vessels as given in the published procedures. A high ratio of concentrated aqueous ammonia to epoxide leads to the best yields. That the epoxide (II) opened substantially exclusively to yield the hydroxydiamine (III) was indicated by homogeneity determinations on the condensation product of (III) with 4,7-dichloroquinoline.[5] Since some doubt also existed as to the stability of the hydroxydiamine during distillation, a study was made of its behavior when subjected to heat. The compound is relatively stable in either the pure or crude state provided temperatures above about 125° are not used in the distillation of it.

Synthesis of the hydroxybutylamine (IV) was accomplished from the amino epoxide (II) by the reactions

(4) 

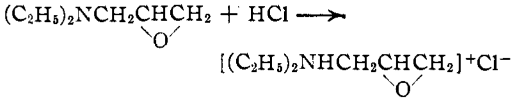
$$(C_2H_5)_2NCH_2\underset{\diagdown O \diagup}{CHCH_2} \xrightarrow{HCl} (C_2H_5)_2NCH_2CHOHCH_2Cl$$

(5) $(C_2H_5)_2NCH_2CHOHCH_2Cl + KCN \longrightarrow (C_2H_5)_2NCH_2CHOHCH_2CN$

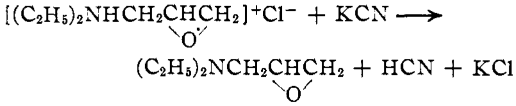
(6) $(C_2H_5)NCH_2CHOHCH_2CN \xrightarrow[Ni]{H_2} (C_2H_5)_2NCH_2CHOHCH_2CH_2NH_2$

The product of reaction (4), 3-diethylamino-2-hydroxypropyl chloride was not isolated because of the possibility of loss through polymerization. Reaction (5) was carried out as described for the preparation of ethyl cyanohydrin.[6] The reduction of 3-diethylamino-2-hydroxypropylcyanide was carried out with hydrogen and Raney nickel.

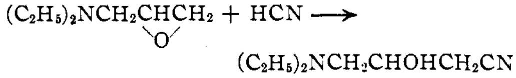
In reaction (5), it was found that if the reaction flask was warmed too rapidly, hydrogen cyanide was evolved from the mixture. This seemed to suggest that the 3-diethylamino-2-hydroxypropyl chloride may be present, at least in part, as the hydrochloride of 1,2-epoxy-3-diethylaminopropane (reaction (4a)). The subsequent reactions would then be as shown in (5a) and (5b).

(4a) 

$$(C_2H_5)_2NCH_2\underset{\diagdown O \diagup}{CHCH_2} + HCl \longrightarrow [(C_2H_5)_2NHCH_2\underset{\diagdown O \diagup}{CHCH_2}]^+Cl^-$$

(5a) 

$$[(C_2H_5)_2NHCH_2\underset{\diagdown O \diagup}{CHCH_2}]^+Cl^- + KCN \longrightarrow (C_2H_5)_2NCH_2\underset{\diagdown O \diagup}{CHCH_2} + HCN + KCl$$

(5b) 

$$(C_2H_5)_2NCH_2\underset{\diagdown O \diagup}{CHCH_2} + HCN \longrightarrow (C_2H_5)_2NCH_2CHOHCH_2CN$$

Experimental

1-Diethylamino-2,3-epoxypropane, II.—In all experiments, the following preferred general procedure was used. In a 5-liter round-bottom three-necked flask equipped with a mechanical stirrer, dropping funnel, and thermometer were placed 1112 g. of epichlorohydrin (Shell Development Co.), 864 g. of diethylamine and 36 g. of water. This solution was stirred vigorously for six hours, during which the temperature of the mixture was maintained at 28–30° by means of a water-bath. At first the reaction required considerable cooling, but if the temperature dropped much below 28° the reaction did not go very rapidly. If the temperature exceeded 34–35°, the result was not appreciably changed, although in such a case dissipation of the evolved heat was much more difficult and stronger cooling was necessary to keep the reaction under control. At the end of six hours, or when no further heat was evolved, the solution was cooled to 20°. With vigorous stirring, a solution of 560 g. of sodium hydroxide in 912 ml. of water was added at such a rate as to keep the temperature at 20–25°, after which the mixture was stirred for forty minutes and poured into 2 liters of water. The upper layer was separated, and the aqueous layer was extracted with three 200-ml. portions of ether. Carbon tetrachloride also may be used for the extraction. The ether extracts were added to the oil and the combined solution was dried over potassium hydroxide. The preparation should be carried up to this point without interruption. The material may be stored in the ice-box at this stage. After separating the ethereal layer from the potassium hydroxide solution formed on the bottom of the flask and removal of the ether, the residue was distilled at reduced pressure, yielding 951–965 g. (62–63%) of material boiling at 62–65° (20 mm.). The final product was perfectly clear after distilla-

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(5) Drake *et al.*, THIS JOURNAL, **68**, 1214 (1946).

(6) Kendall and McKenzie, "Org. Syn.," Coll. Vol. I, 2nd ed., John Wiley & Sons, Inc., New York, N. Y., p. 256.

tion, but on standing, even in the ice-box, a slight cloudiness appeared.

When reasonably pure, the epoxide is not unduly sensitive toward heat, at least for a short time, such as during distillation. A sample collected at 58–66° (24 mm.) was heated for four hours at 80°, and, on redistillation, was recovered.

Heat of Reaction of Epichlorohydrin and Diethylamine (Reaction 1).—The apparatus consisted of a 200-ml. three-necked flask equipped with a mechanical stirrer, reflux condenser, and a thermometer. The flask was placed in a mechanically agitated water calorimeter containing 500 ml. of water and consisting of a can insulated with one layer of 1-cm. asbestos rope and six layers of asbestos paper.

The heat capacity of the system during the time of the reaction was estimated by neutralizing a solution of 70 g. of potassium hydroxide in 70 ml. of water with an equivalent amount of concentrated hydrochloric acid over a period of eighty-five minutes. By measuring the volumes and temperature rises of the reaction mixture and the water in the thermostat, the heat capacity of the system was about 520 cal. per degree.

Under the same conditions used in the calibration experiment, a mixture of 66.7 g. (0.7 mole) of epichlorohydrin, 51.8 g. (0.7 mole) of diethylamine and 2.16 g. (0.12 mole) of water was placed in the flask, stirring was started, and the temperature rise of the reaction mixture and water was followed. The temperature of the bath rose from 27.3° to 45.5° over a period of ninety-five minutes, at the end of which time the reaction mixture was 49.5°. The highest temperature of the reaction mixture was 52.7° after eighty minutes, and no refluxing of the amine was observed. The cooling of the system was followed over a period of two and a half hours in order to calculate radiation heat losses. The temperature of the system fell off evenly after the ninety-minute reaction period, indicating that the reaction was substantially complete at the end of this time.

The heat gain of the thermostat water corresponded to 9.46 kcal., radiation losses were calculated to be about 4.84 kcal., and the heat gain of the reaction mixture (heat capacity estimated to be about 60 cal. per degree) at 49.5° was about 0.25 kcal. The total heat of the reaction, therefore, was about 14.55 kcal. per 0.71 mole, or 20.8 kcal. per mole.

On working up the reaction mixture, the yield of epoxide was about 50%, the formation of some bis-diethylaminopropanol being indicated by the relatively non-volatile residue. This is not considered significant as far as the estimated heat of reaction is concerned in view of the admitted limits of error of the heat measurements. The heat of reaction noted, however, probably approximates fairly closely that likely to be encountered in larger scale runs.

3-Diethylamino-2-hydroxypropylamine (III).—In a 5-liter three-necked flask equipped with a mechanical stirrer, dropping funnel, and thermometer, was placed 4 liters of ammonium hydroxide (sp. gr. 0.90). The solution was cooled in an ice–salt-bath until the temperature was 0–3°. While maintaining this temperature, 516 g. of 1-diethylamino-2,3-epoxypropane (once distilled and collected over a 4° range) was added with stirring over a period of two hours. After the addition, the stirring was continued for an hour longer at 0–10° and the mixture was allowed to stand at room temperature overnight. The clear solution was then transferred to a single neck flask attached to a condenser set downward for distillation. Most of the water was then removed at water pump vacuum while heat was applied gradually as the distillation proceeded. The residue was transferred to a Claisen flask and distilled at reduced pressure, yielding 320–330 g. (55–57%) of material boiling at 80–84° (0.4 mm.) or 116–117° (24 mm.), n^{20}_{D} 1.4660, d^{20}_{4} 0.9305; neut. equiv., 74; calcd., 73.

3-Diethylamino-2-hydroxypropyl Cyanide.—To a cold solution of 139 g. of II in 100 ml. of alcohol contained in a 2-liter three-necked flask equipped with a stirrer, immersed thermometer, and a dropping funnel, was added a cold solution of 92.7 ml. of hydrochloric acid (sp. gr. 1.19) in 100 ml. of alcohol while stirring and cooling by means of an ice-bath so that the temperature did not rise above 25°. To this vigorously stirred solution was added 74 g. of powdered potassium cyanide (95%), the ice-bath was removed, and the flask was fitted with a reflux condenser and heated by means of a water-bath to 65–70°. The reaction was slow but somewhat exothermic, and intermittent cooling was necessary to prevent refluxing from becoming too violent. After one hour the reaction was heated to 85° and refluxing was regular but not violent. After six hours of heating at 85°, the mixture was allowed to cool to room temperature and the potassium chloride precipitate was removed by filtration and washed with several portions of acetone until nearly colorless. Addition of the acetone washings to the original filtrate caused the precipitation of more potassium chloride which was filtered off. The filtrate was distilled at atmospheric pressure to remove acetone and ethanol, and the distillation was stopped when the temperature reached 92°. The red-brown residual liquid was distilled *in vacuo*. The fraction boiling at 108–115° (5 mm.) was collected as fairly pure material. The yield was 105–120 g. (62–71%). The cyanide was redistilled, yielding a colorless liquid boiling at 108° (3 mm.), n^{32}_{D} 1.4473.

4-Diethylamino-3-hydroxybutylamine.—A solution of 160 g. of the above cyanide in 100 ml. of anhydrous liquid ammonia containing 10 g. of Raney nickel catalyst was hydrogenated for two hours (2300 pounds pressure). At the end of the hydrogenation, the temperature was 175°. The contents of the bomb were taken up in ether, the catalyst was removed, and the ether was distilled at atmospheric pressure. The residue was fractionally distilled *in vacuo*, yielding 102 g. (62%) of colorless liquid boiling at 99–106° (4–4.5 mm.) (more than 95% distilled at 101–102°). When redistilled, the amine boiled at 93.5–95° (2 mm.).

Anal. Calcd. for $C_8H_{20}ON_2$: C, 60.0; H, 12.6. Found: C, 60.3; H, 12.5.

A solid derivative obtained with phenyl isothiocyanate melted at 95–96°.

Anal. Calcd. for $C_{15}H_{25}ON_3S$: C, 61.0; H, 8.5. Found: C, 61.2; H, 8.7.

Summary

1. A detailed study of the optimum conditions for the preparation of 1-diethylamino-2,3-epoxypropane and of 3-diethylamino-2-hydroxypropylamine has been made.

2. The heat of reaction of epichlorohydrin and diethylamine has been shown to be about 21 kcal. per mole.

3. A synthesis of 4-diethylamino-3-hydroxybutylamine is described.

AMES, IOWA
NEW YORK, N. Y.
URBANA, ILLINOIS

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