3 liters of water, refiltered, washed, and oven dried; cream colored powder; yield 141 g. (72%).

2,4,7-Trichloroquinoline (VII).—This procedure approximates standard practice.[4] A suspension of 100 g. (0.51 mole) of powdered 7-chloro-4-hydroxycarbostyril in 650 ml. of phosphorus oxychloride was refluxed with vigorous stirring until solution was complete (thirty minutes) and for thirty minutes thereafter. The mixture was cooled to room temperature, poured over 8 liters of crushed ice with vigorous stirring, and allowed to stand overnight. The resulting mixture was made alkaline (under cooling) using about 6.5 liters of 20% sodium hydroxide. The suspension of trichloroquinoline (VII) was then filtered and washed thoroughly with warm water until the washings came through alkali-free; yield, 116 g. (98%); m. p. 102–106°. This product was further purified by recrystallizing (with norite treatment) from absolute ethanol; yield 100 g. (84%) white needles; m. p. 104.5–106°. Repeated recrystallizations raised the melting point to 106.5–107.5°.

Anal. Calcd. for $C_9H_4Cl_3N$: C, 46.49; H, 1.73. Found: C, 46.25; H, 1.83.

Summary

2,4,7-Trichloroquinoline has been synthesized by an unequivocal path from 4-chloroanthranilic acid by condensation of the ester with malonic ester, cyclization to 3-carbomethoxy-7-chloro-4-hydroxycarbostyril, hydrolysis, decarboxylation and hydrochlorination. Conditions have been developed to produce the compound in an over-all yield of 60–65%.

CHARLOTTESVILLE, VIRGINIA RECEIVED APRIL 5, 1946

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

Antimalarials. Hydrolysis and Methanolysis of 2,4,7-Trichloroquinoline[1]

BY RUSSELL J. ROWLETT, JR.,[2] AND ROBERT E. LUTZ

4,7-Dichlorocarbostyril (III) and 4,7-dichloro-2-methoxyquinoline (VI) were needed as intermediates in the program[1] of synthesis of a variety of substituted 4 - (dialkylaminoalkylamino) - quinolines[3] for testing as possible antimalarials.

The starting material for the preparation of these two compounds was 2,4,7-trichloroquinoline (II) which has been described in the preceding paper.[4] The 2-chlorine was expected and found to be more reactive than the 4-chlorine,[5] sufficiently so as to be smoothly replaced by hydroxyl upon acid hydrolysis[6]; 4,7-dichlorocarbostyril (III) was thus obtained in good yield. Methanolysis with sodium methoxide, however, was not as specific for the 2-chlorine as was hydrolysis; and a mixture of 4,7-dichloro-2-methoxy- (VI), 2,7-dichloro-4-methoxy- (V) and 7-chloro-2,4-dimethoxyquinolines (IV) was obtained with the relative quantities of these products dependent on the reaction time and temperature. The accompanying diagram illustrates these syntheses and some of the interrelationships which serve as proof of structures of the products.

The required and rigorous proof that hydrolysis of 2,4,7-trichloroquinoline (II) had actually replaced the 2-chlorine and not the 4-chlorine, was obtained by conversion of the product into carbostyril by catalytic hydrogenolysis of the 4,7-chlorines using Raney nickel in the presence of an excess of alkali.

The attempt to make the 2-methoxy compound (VI) from the carbostyril (III) by methylation, although it furnished additional proof of the location of the hydroxyl, led to the unexpected results, namely, N-methylation in the main instead of the hoped for oxygen-methylation. Both methyl iodide and alkali, and diazomethane yielded chiefly 4,7-dichloro-1-methylcarbostyril (VII) which was synthesized in an entirely different and unequivocal fashion from 4-chloro-N-methylanthranilic acid.[7]

The reaction between diazomethane and the amide system of the carbostyril (III), which gave 70% of N-methylation as compared with the 10% yield of the oxygen-methylation product, is to be contrasted with the methylation by diazomethane of carbostyril itself which gives exclusively 2-methoxyquinoline[8] and the diazomethylations of 2- and 4-hydroxypyridines[8,9] where the major products are the methoxy pyridines and where N-methylation occurs only to a very minor extent. However, N-methylation by means of diazomethane occurs in considerable proportion in other cases. It is the dominant reaction in the diazomethylation of cyanuric[10] and 6-hydroxynicotinic acids.[8] It also occurs to a minor extent in the diazomethylation of vitamin B-6,[11a] although the lactone of 2-methyl-3-hydroxy-4-hydroxymethyl-5-carboxypyridine[11b] and 3-hydroxypyri-

(1) The work described in this paper was done under a contract, recommended by the Committee on Medical Research, between the Office of Scientific Research and Development and the University of Virginia.

(2) Present location: Jackson Laboratory, E. I. du Pont de Nemours and Co., Wilmington, Del.

(3) The attachment of the dialkylaminoalkylamino side chains to these two chloroquinolines was carried out by Dr. N. L. Drake at the University of Maryland.

(4) Lutz, *et al.*, THIS JOURNAL, **68**, 1285 (1946).

(5) *Cf.* Buchmann and Hamilton, *ibid.*, **64**, 1357 (1942).

(6) This reaction was patterned on the hydrolysis of 2-chloroquinolines by (a) Kaufmann and de Petherd, *Ber.*, **50**, 336 (1917), and (b) Ing, *J. Chem. Soc.*, 2202 (1931).

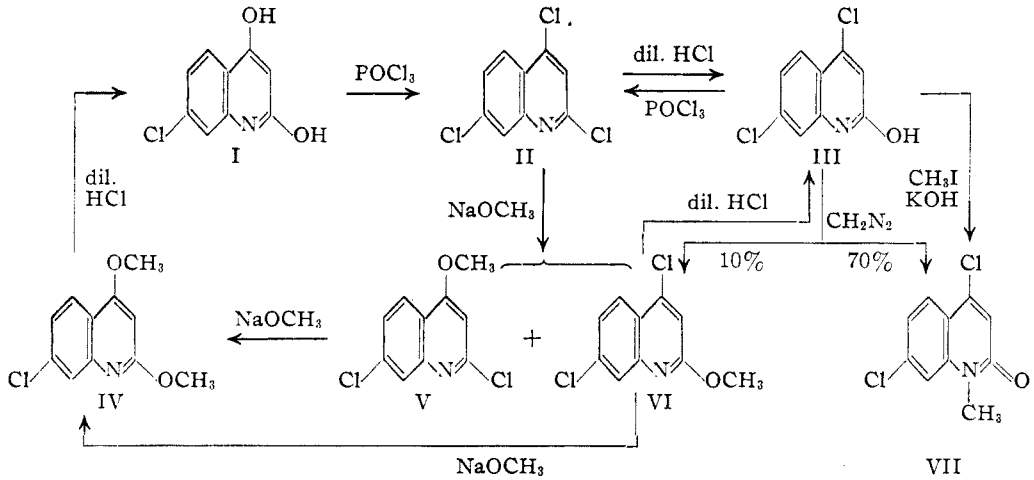
(7) *Cf.* Lutz and co-workers, results to be published.

(8) Meyer, *Monatsh.*, **26**, 1317 (1905).

(9) Pechmann, *Ber.*, **28**, 1625 (1895).

(10) Degering, "Organic Nitrogen Compounds," University Lithoprinters, Ypsilanti, Mich., 1945, p. 354.

(11) (a) Itiba and Miti, *Sci. Papers Inst. Phys. Chem. Research* (Tokyo), **35**, 73 (1938); **36**, 1 (1939); *cf.* also Rosenberg, "Chemistry and Physiology of the Vitamins," Interscience Pub., Inc., New York, N. Y., 1942, p. 201; (b) Harris, Stiller and Folkers, THIS JOURNAL, **61**, 1244 (1939).



dine itself[8] give exclusively the 3-methoxy products.

The alternative approach to the 2-methoxy compound (VI) was methanolysis of 2,4,7-trichloroquinoline (II) by means of sodium methoxide in which it was hoped that this compound would be the main product. The scheme was based on the work of Buchmann and Hamilton,[5] who carried out the analogous ethanolysis of 2,4-dichloroquinoline and obtained a mixture of all three possible products, 4-chloro-2-ethoxy-, 2-chloro-4-ethoxy- and 2,4-diethoxyquinolines, and separated them by steam distillation. The three analogous methanolysis products of 2,4,7-trichloroquinoline (II) differed so little in their steam volatilities that they could not be separated by this method; however, they were fairly easily separated through differences in their solubilities in methanol which increased sharply in the expected order, VI < V < IV.

The location of the 2-methoxy group of VI was established by hydrochloric acid hydrolysis to 4,7-dichlorocarbostyril (III). Hydrolysis of the dimethoxy compound (IV) required more prolonged acid treatment and gave the known 7-chloro-4-hydroxycarbostyril (I)[4]; this confirmed the obvious location of the 2,4-methoxyls. Since this dimethoxy compound was obtained from both of the monomethoxy compounds (V and VI) and since the structure of the 2-methoxy compound (VI) has been demonstrated (above) the structure of the 4-methoxy isomer (V) follows by difference.

Upon study of conditions of methanolysis of the trichloroquinoline (II) it was found that a three to one molar ratio of sodium methoxide to the compound, in refluxing methanol for two hours, produced the maximum yield of the desired 2-methoxy isomer (IV) (see Table I). The best yield of the 4-methoxy compound was obtained by the same procedure but with the refluxing time shortened to a half hour; the yield fell sharply upon longer refluxing. And after prolonged refluxing the dimethoxy compound became the sole product.

TABLE I

$NaOCH_3$ reflux, hr.	% Yield of methoxy compounds 2-OCH_3	4-OCH_3	2,4-di-OCH_3
0.25	30.5	..[12]	..[12]
0.5	31.5	40	..
1.0	31.5	31	10
2.0	46.5	8	20
2.25	40.5	..	..
2.5	32	..	..
22.0	0	0	99

The rapidly decreasing yield of the 2-chloro-4-methoxy isomer (V) under longer refluxing coupled with the fact that sodium methoxide fairly rapidly converted this product (V) into 7-chloro-2,4-dimethoxyquinoline (IV) (yield 92% in 2.5 hr.), and the fact that the 4-chloro-2-methoxy isomer (VI) suffered only 52% conversion to the dimethoxy compound (IV) even after six hours of refluxing, further illustrated the generally greater reactivity of the 2-chlorine as compared with the 4-chlorine. This is consistent with a similar observation reported by Buchmann and Hamilton[5] in the case of the analogous 2-chloro-4-ethoxy- and 4-chloro-2-ethoxyquinolines.

It is significant also that the methanolysis of 2,4,7-trichloroquinoline (II) to either of the 2 or 4-monomethoxy isomers (VI and V) proceeded more rapidly (half an hour) than the succeeding methanolysis of these products to the 2,4-dimethoxy compound (the monomethoxy isomer VI required more than six hours and the isomer V, two and a half hours); this demonstrated that the introduction of one methoxyl in place of either the 2 or 4-chlorine greatly decreases the reactivity of the remaining chlorine to a point below that of either chlorine of 2,4,7-trichloroquinoline.

In conclusion from the foregoing results it is evident that the methanolysis of 2,4,7-trichloroquinoline (II) proceeds simultaneously by two paths, (a) through the 2-methoxy compound (VI)

(12) Because the original object of this investigation was the preparation of the 2-methoxy compound, the filtrates in some of the earlier experiments were not concentrated individually for the recovery of the 4-methoxy and 2,4-dimethoxy products.

which slowly undergoes a second methanolysis to the dimethoxy compound (IV), and (b) through the 4-methoxy compound which is relatively much more rapidly converted to the dimethoxy compound.

Acknowledgment.—The authors wish to express their appreciation to Dr. P. S. Bailey for assistance in the proof of structure of 4,7-dichlorocarbostyril and to Misses Geraldine Alley and Joyce Blume for the microanalyses reported here.

Experimental[13]

4,7-Dichlorocarbostyril (III). (A) From 2,4,7-Trichloroquinoline (II).—A mixture of 118 g. (0.51 mole) of 2,4,7-trichloroquinoline[4] (m. p. 103–106°), 1200 ml. of 6 *N* hydrochloric acid and 850 ml. of dioxane (necessary to prevent volatilization of the trichloroquinoline and condensation in the reflux condenser) was gently refluxed, with vigorous stirring; the solid slowly melted and dissolved forming a dark brown solution, and white crystals gradually precipitated. Refluxing was continued for one and one-half hours after the first crystals appeared. The mixture was cooled, diluted with water to a total volume of 7 liters and allowed to stand until no further precipitation occurred (overnight). The mixture was filtered and the light brown residue was repeatedly washed with water; yield 96.2 g. (89%); m. p. 259–261°. The solution of the product in 2.6 l. of *n*-butanol with added Darco was refluxed for one hour, filtered and cooled (overnight). Filtration yielded 78.7 g. (72%); m. p. 260–261.5°. Repeated recrystallization from 95% ethanol gave colorless needles; m. p. 260–261.5°.

Anal. Calcd. for $C_9H_5Cl_2NO$: C, 50.50; H, 2.35; N, 6.54. Found: C, 50.43; H, 2.68; N, 6.68.

(B) Preparation from 4,7-Dichloro-2-methoxyquinoline (VI).—A solution of 0.5 g. of 4,7-dichloro-2-methoxyquinoline (VI) in 25 ml. of 6 *N* hydrochloric acid was refluxed for thirty minutes; white crystals precipitated during the heating. The mixture was cooled, filtered and the residue washed with water; yield 0.3 g.; m. p. 261–264°. (A mixture melting point with the sample prepared in (A) showed no depression.)

Conversion to 2,4,7-trichloroquinoline (II)[4] was accomplished by the action of refluxing phosphorus oxychloride. A mixture melting point of the sample produced and one of pure 2,4,7-trichloroquinoline[4] showed no depression.

Hydrogenolysis to carbostyril was carried out at atmospheric pressure by means of Raney nickel as catalyst in the presence of a four-mole excess of potassium hydroxide. A mixture melting point of the product (m. p. 195–197°) and an authentic sample showed no depression.

4-Chlorocarbostyril.[5,14,15]—The procedure used above for the conversion of 2,4,7-trichloroquinoline (II) to 4,7-dichlorocarbostyril (III) was applied also to the preparation of 4-chlorocarbostyril from 2,4-dichloroquinoline[16] and an almost quantitative yield was obtained, m. p. 252–254°. (Buchmann and Hamilton[5] obtained it by hydrolysis of 4-chloro-2-ethoxyquinoline, m. p. 254°.)

4,7-Dichloro-1-methylcarbostyril (VII). (A) By Diazomethylation of III.—A mixture of 5 g. (0.024 mole) of 4,7-dichlorocarbostyril (III), 200 ml. of absolute ether, 25 ml. of methanol and 116 ml. of an ether solution containing 0.05 mole of diazomethane, was allowed to stand at room temperature with occasional shaking for forty-eight hours; a light yellow solution resulted. The ether was evaporated under reduced pressure and the remaining white solid was recrystallized from 95% ethanol; yield 4.3 g., m. p. 125–132°. A 0.2-g. sample of the crude product was sublimed under reduced pressure (68–72° (2 mm.)) and two volatile fractions were removed; 0.01 g., m. p. 93–95°, and 0.01 g., m. p. 91–93° (total yield 10%). Mixture melting points of both fractions with 4,7-dichloro-2-methoxyquinoline (VI) showed no depression. The residue (0.14 g. (70%); m. p. 158–160°) was 4,7-dichloro-1-methylcarbostyril (VII) and showed no mixture melting point depression with a sample of this compound of m. p. 161–161.5° the preparation of which will be described in a succeeding publication.[7]

(B) By Methylation with Methyl Iodide.—4,7-Dichloro-1-methylcarbostyril (VII) was obtained as the sole product from 4,7-dichlorocarbostyril (III) by refluxing a 60-ml. methanol solution of 0.025 mole each of the latter, methyl iodide and potassium hydroxide for four hours. The solution was cooled and the white solid which precipitated was filtered and the residue washed with water; yield 5.1 g. (95%); m. p. 152–155°. After recrystallization from absolute ethanol it melted at 153–154° and showed no mixture melting point depression with the sample previously prepared in (A).

4,7-Dichloro-2-methoxyquinoline (VI).—A solution of 11.7 g. (0.51 mole) of sodium in 350 ml. of methanol was added to a suspension of 39.4 g. (0.17 mole) of 2,4,7-trichloroquinoline (II)[4] in 350 ml. of methanol. The resulting mixture was gently refluxed for thirty minutes, cooled in ice for thirty minutes and filtered. (See following procedure for investigation of the filtrate.) The solid residue was washed repeatedly with water (washings added to the filtrate) and after superficial drying was recrystallized from 95% ethanol; yield 10.5 g.; m. p. 92–94°. Concentration of the ethanol filtrate yielded an additional 1.6 g. of 4,7-dichloro-2-methoxyquinoline; m. p. 91–93°. The total yield was 12.1 g. (31.2%). Repeated recrystallization from 95% ethanol yielded long, hairy, colorless needles; m. p. 95.5–96°.

Anal. Calcd. for $C_{10}H_7Cl_2NO$: C, 52.65; H, 3.09. Found: C, 52.46; H, 3.45.

An attempt to prepare 4,7-dichloro-2-methoxyquinoline (VI) from 4,7-dichlorocarbostyril (III) by the action of dimethyl sulfate on the sodium salt in the usual manner[17] was unsuccessful.

2,7-Dichloro-4-methoxyquinoline (V).—The original methanol filtrate from the preparation (above) of 4,7-dichloro-2-methoxyquinoline (VI) was diluted with 200 ml. of water, cooled and filtered. The residue was washed with water and dried; yield 21.3 g.; m. p. 99–110°. The product was recrystallized from 95% ethanol and 15.5 g. (40%) of the 4-methoxy isomer was obtained; m. p. 122–124°. Repeated recrystallization from 95% ethanol yielded colorless needles; m. p. 125–126°.

Anal. Calcd. for $C_{10}H_7Cl_2NO$: C, 52.65; H, 3.09; N, 6.14. Found: C, 52.61; H, 3.25; N, 6.35.

The mixture melting point of 4,7-dichloro-2-methoxyquinoline (VI) and 2,7-dichloro-4-methoxyquinoline (V) was 81–93°. Neither 4,7-dichloro-2-methoxy (VI) nor 2,7-dichloro-4-methoxyquinoline (V) was converted to 2,4,7-trichloroquinoline (II) by the action of refluxing phosphorus oxychloride (six hours).

Numerous attempts were made to increase the yield of the 2-methoxy isomer (VI). Varying the mole ratio of sodium methoxide and 2,4,7-trichloroquinoline (3:1) had no appreciable effect on the yields of the two isomers. Table I (see Theoretical Section) illustrates the results of varying the length of time at which the methanolysis was carried out at the constant temperature of refluxing methanol. Two other temperatures, 0° and 20°, were investigated. At 0° no methanolysis at all occurred. At 20° the yield of the 2-methoxy product (VI) was inversely proportional to the length of time; 32.5% in 6.5 hr., 24.5% in 18 hr., and 18% in 60 hr.

Hydriodic acid hydrolysis of 2,7-dichloro-4-methoxyquinoline (V) was attempted in an effort to prepare 2,7-

(13) All melting points are corrected.

(14) Friedlaender and Weinberg, *Ber.*, **15**, 2679 (1882).

(15) Baeyer and Bloom, *ibid.*, **15**, 2147 (1882).

(16) Prepared by method of Brooker and Smith, THIS JOURNAL, **59**, 67 (1937).

(17) Hiers and Hager, "Organic Syntheses," Coll. Vol. I, 2nd ed., John Wiley and Sons, Inc., New York, N. Y., 1941, p. 58.

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) $CH_2(O)CH-CH_2Cl + (C_2H_5)_2NH \longrightarrow (C_2H_5)_2NCH_2CHOHCH_2Cl$ (I)

(2) $(C_2H_5)_2NCH_2CHOHCH_2Cl \longrightarrow (C_2H_5)_2NCH_2CH(O)CH_2$ (II)

(3) $(C_2H_5)_2NCH_2CH(O)CH_2 + NH_3 \longrightarrow (C_2H_5)_2NCH_2CHOHCH_2NH_2$ (III)

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]

(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).