Anal. Calcd. for $C_{18}H_{18}O_3$: C, 70.22; H, 8.16; neut. equiv., 222.3. Found: C, 70.29; H, 7.86; neut. equiv., 224.3.

2-(2,2-Dimethyl-1-pyrrolidyl)-ethyl α-Isoamylmandelate Hydrochloride.—A mixture of 8.0 g. (0.036 mole) of α-isoamylmandelic acid, 7.15 g. (0.036 mole) of 2-(2,2-dimethyl-1-pyrrolidyl)-ethyl chloride hydrochloride, 21 g. (0.15 mole) of anhydrous potassium carbonate, and 100 ml. of methyl isobutyl ketone[6] was heated under reflux for eight hours. Water was added and the solution was extracted with ether. The ether solution was dried over anhydrous potassium carbonate and filtered. Hydrogen chloride gas was passed in until the solution tested strongly acid. The hydrochloride separated as an oil which crystallized on standing. It was recrystallized from a mixture of ethyl acetate and ether giving 11.2 g. (81%) of product, m.p. 109–115°. A second recrystallization from ethyl acetate and Skellysolve C raised the melting point to 113.5–116°.

2-(2,2,4,6-Tetramethyl-1-piperidyl)-ethanol.—A mixture of 141.2 g. (1 mole) of 2,2,4,6-tetramethylpiperidine (obtained from Shell Development Co.) and 80.5 g. (1 mole) of ethylene chlorohydrin was slowly heated until the temperature reached 155°. After cooling an excess of 50% sodium hydroxide solution was added and the mixture was extracted repeatedly with ether. The ether solution was dried over potassium carbonate. After removing the solvent the product was distilled, b.p. 120° (12 mm.), $n^{25}D$ 1.4761. The yield was 62.2 g. (34%).

Anal. Calcd. for $C_{11}H_{23}NO$: N, 8.10. Found: N, 8.04, 8.23.

2-(Hexamethyleneimino)-ethanol.—This was prepared by a procedure similar to that described above using 49.6 g. (0.5 mole) of hexamethyleneimine and 40.3 g. (0.5 mole) of ethylene chlorohydrin. The product was distilled, b.p. 103° (15 mm.), $n^{25}D$ 1.4826.

Anal. Calcd. for $C_8H_{17}NO$: C, 67.10; H, 11.97; N, 9.78. Found: C, 67.52; H, 11.89; N, 9.91.

KALAMAZOO, MICHIGAN

(6) In one run acetone was used as a solvent but no appreciable reaction occurred in 20 hours. In the preparation of the other α-hydroxy acid esters (Table II) acetone or methyl ethyl ketone were satisfactory.

[CONTRIBUTION FROM AVERY LABORATORY, UNIVERSITY OF NEBRASKA]

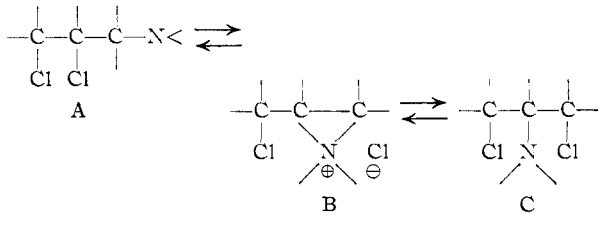
β,γ-Dihalopropylamines. I. 1-Amino-2,3-dichloropropanes and 1,4-Diamino-2,3-dichlorobutanes

BY NORMAN H. CROMWELL AND ALFRED HASSNER

RECEIVED JUNE 24, 1954

The hydrochlorides of 1-piperidino, 1-dimethylamino and 1-dibenzylamino-2,3-dichloropropane have been prepared by chlorine addition to the corresponding allylamine hydrochlorides. Compared with 2-piperidino-1,3-dichloropropane hydrochloride, the 1-piperidino-2,3-dichloropropane hydrochloride is thermally more stable. These compounds react slowly with piperidine to produce triaminopropanes. The dihydrochlorides of 1,4-dipiperidino, 1,4-bis-dimethylamino and 1,4-dimorpholino-2,3-dichlorobutane have been prepared by chlorine addition to the corresponding 1,4-diaminobutene dihydrochlorides. These compounds have been synthesized for pharmacological testing as anti-tumor agents, etc.

As a part of a general program concerned with the syntheses of potential anti-cancer agents it seemed of interest to obtain for pharmacological testing a series of compounds having the functional group arrangement represented by the general formulas A and/or C.[1]



The relationship of the structural arrangements of A and C to that present in the nitrogen mustards is apparent.

Compounds A and C might be expected to be converted to the same potentially pharmacologically important[2,3] intermediate quaternary ethylenimmonium chloride (B) in neutral or basic media.

A possible method of synthesis for compounds of structures A and C involves reaction of the corresponding aminodiols with thionyl chloride. Previous communications from this Laboratory have reported the development of methods of synthesis of aminodiols, $-C(OH)C(OH)CN<$, which might serve as precursors for β,γ-dichloroamines of type A.[4]

Many investigators[1d-f,5] have reported the successful conversion of β-aminoalcohols with thionyl chloride to β-chloroamines. Others[6] have apparently experienced difficulties in attempting to convert aminodiols, $-C(OH)C(N<)C-OH$, to

(1) The ability of various β-haloethylamines to rearrange to quaternary ethylene immonium ions and subsequently to an isomeric β-haloethylamine has been adequately demonstrated in the literature; see for example: (a) N. H. Cromwell and D. J. Cram, THIS JOURNAL, **65**, 301 (1943); (b) N. H. Cromwell and I. H. Witt, *ibid.*, **65**, 308 (1943); (c) N. H. Cromwell, *et al.*, *ibid.*, **75**, 5384 (1953); (d) E. M. Schultz, C. M. Robb and J. M. Sprague, *ibid.*, **69**, 188 (1947); (e) J. F. Kerwin, *et al.*, *ibid.*, **69**, 2961 (1947); (f) P. D. Bartlett, S. D. Ross and C. G. Swain, *ibid.*, **69**, 2971 (1947); (g) S. D. Ross, *ibid.*, **69**, 2982 (1947); (h) C. Golumbic, J. S. Fruton and M. Bergmann, *J. Org. Chem.*, **11**, 518 (1946).

(2) The vesicant properties of tris-(β-chloroethyl)-amine and methylbis-(β-chloroethyl)-amine are well known, see: (a) K. Ward, THIS JOURNAL, **57**, 914 (1935); (b) O. Eisleb, *Ber.*, **74**, 1433 (1941); (c) Jensen and Lundquist, *Dansk. Tidsskr. Farm.*, **15**, 201 (1941). These compounds have been called "nitrogen mustards" because of their relationship structurally and biologically with mustard gas.

(3) Various biological investigations have suggested possible therapeutic applications for such substances, see: (a) A. Gilman and F. S. Philips, *Science*, **103**, 409 (1946); (b) E. Boyland, *Brit. J. Pharmacol.*, **1**, 247 (1946).

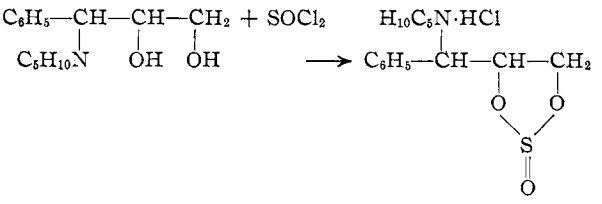
(4) (a) N. H. Cromwell and F. W. Starks, THIS JOURNAL, **72**, 4108 (1950); (b) N. H. Cromwell and N. G. Barker, *ibid.*, **72**, 4110 (1950); (c) N. G. Barker and N. H. Cromwell, *ibid.*, **73**, 1051 (1951); (d) K. C. Tsou and N. H. Cromwell, *J. Org. Chem.*, **15**, 1293 (1950).

(5) (a) N. H. Cromwell and W. E. Fitzgibbons, THIS JOURNAL, **70**, 387 (1948); (b) P. Ofner, *J. Chem. Soc.*, 1800 (1951).

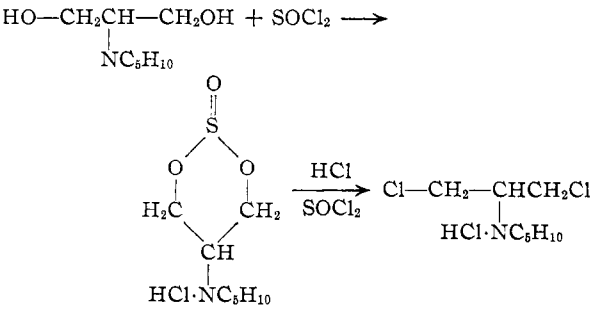
(6) E. R. H. Jones and W. Wilson, *J. Chem. Soc.*, 547 (1949), obtained only the cyclic sulfite from 2-amino-2-methyl-1,3-propanediol, but prepared the desired 2-dimethylamino-2-methyl-1,3-dichloropropane hydrochloride from 2-dimethylamino-2-methyl-1,3-propanediol and thionyl chloride in chloroform solution.

compounds of type C using thionyl chloride. Our present investigations indicate that both 2-amino-1,3-propanediols and 1-amino-2,3-propanediols are difficult to convert to the corresponding dichloroamines on heating with thionyl chloride. Instead the corresponding stable cyclic sulfites are obtained which can be further converted to the desired dichloroamines only after further heating with chloroform solutions of hydrogen chloride in the presence of more thionyl chloride.

1-Phenyl-1-piperidino-2,3-propanediol[4d] could not be converted to the desired dichloro compound with boiling concd. hydrochloric acid nor with phosphorus oxychloride. With thionyl chloride in chloroform the hydrochloride of the aminodiol produced 1-phenyl-1-piperidino-2,3-propanediolsulfite hydrochloride.



2-Piperidino-1,3-propanediol[7] was prepared by a lithium aluminum hydride reduction of diethyl-piperidinomalonate,[7] which in turn was synthesized from piperidine and diethyl bromomalonate.[8] This diol reacted with thionyl chloride in chloroform after 30 minutes of refluxing to give 2-piperidino-1,3-propanediolsulfite hydrochloride.[7] When the diol was heated for two hours with excess thionyl chloride while dry hydrogen chloride was passed through the solution a low yield of the desired 2-piperidino-1,3-dichloropropane hydrochloride[7] resulted.



Because of the difficulties in obtaining the 2-amino-1,3-dichloropropanes of type C we turned our attention to the more readily prepared 1-amino-2,3-dichloropropanes of type A. The necessary known allylamines were prepared readily from allyl bromide and the corresponding secondary amine. Chlorine was added to the allylamine hydrochlorides in chloroform solution to produce the 1-amino-2,3-dichloropropane hydrochlorides, the conditions of reaction and isolation techniques being varied somewhat in each case to obtain optimum yields of pure materials. In this way the 1-piperidino-, 1-dimethylamino- and 1-dibenzylamino-2,3-dichloropropane hydrochlorides were obtained in good yields.

1-Dimethylamino-2,3-dichloropropane has been prepared previously by Amundsen and Pitts[9] from 1-dimethylamino-2,3-propanediol and thionyl chloride. The free base obtained from the hydrochloride of our product proved to be identical with theirs.

From a series of melting point experiments it was indicated that 2-piperidino-1,3-dichloropropane hydrochloride rearranges to the isomeric 1-piperidino-2,3-dichloropropane hydrochloride on heating to its melting point at 150°. The mechanism of this change is probably that implied in the representation A ⇄ B ⇄ C. The structures of type A seem to be thermodynamically more stable than those of type C. It is interesting to contrast this result with those reported by Edwards and Hodges[10] who obtained a similar rearrangement during the benzoylation of 1,3-dibromo-2-propanol. From either this material or the isomeric 2,3-dibromo-1-propanol the product was shown to be 2,3-dibromopropylbenzoate.

The relatively low level of reactivity of the halogen atoms in the 1-amino-2,3-dichloropropanes is indicated by the fact that the free bases can be isolated from their hydrochloride salts in the presence of sodium hydroxide and by the severity of the conditions required to obtain their reaction with piperidine. In benzene solution the reaction was extremely slow and much of the starting material remained unchanged after refluxing with piperidine for five hours. When the 1-piperidino-, 1-dimethylamino and 1-dibenzylamino-2,3-dichloropropane hydrochlorides were refluxed for two days with five molar equivalents of piperidine in absolute ethanol good yields of the triaminopropanes resulted. The structure of the 1,2,3-tripiperidinopropane seems certain, while the structures of the products from the latter two indicated reactions may be either 1-dimethylamino- and 1-dibenzylamino-2,3-dipiperidinopropane, respectively, or 2-dimethylamino- and 2-dibenzylamino-1,3-dipiperidinopropane, respectively. A study of the course and mechanism of such changes with these and related compounds is a subject of another current investigation in this Laboratory.

To obtain another series of analogous materials for pharmacological testing certain 1,4-diamino-2,3-dichlorobutane dihydrochlorides have been made by adding chlorine to 1,4-diamino-2-butene dihydrochlorides. Various 1,4-diaminobutenes have been reported in the literature as resulting from the reaction of 1,4-dihalo-2-butenes and four molar equivalents of a secondary amine.[11] The reaction is best carried out by adding the 1,4-dihalo-2-butene, dissolved in ether or benzene, to an ether or benzene solution of four equivalents of the amine;

(7) This compound was made for the first time in this Laboratory by Dr. K. C. Tsou, Ph.D. Thesis, Univ. of Nebr., 1950.

(8) (a) Jones and Wilson, see ref. 6, were unable to reduce diethyl (dimethylamino)-malonate to the corresponding diol using the Bouveault-Blanc method. (b) C. F. Roth, *Ber.*, **15**, 1150 (1882), has prepared the isomeric diol, 1-piperidino-2,3-propanediol, m.p. 79–80°, by heating 1-chloro-2,3-propanediol with piperidine at 100°.

(9) L. H. Amundsen and L. S. Pitts, THIS JOURNAL, **73**, 1494 (1951).

(10) W. G. H. Edwards and R. Hodges, *J. Chem. Soc.*, 3427 (1953).

(11) (a) R. Willstätter and T. Wirth, *Ber.*, **46**, 537 (1913); (b) G. H. Morey, U. S. Patent 2,415,020, *C. A.*, **41**, 3252 (1947); U. S. Patent 2,440,724, *C. A.*, **42**, 5466 (1948); (c) J. J. Roberts and W. C. S. Ross, *J. Chem. Soc.*, 4288 (1952); (d) L. H. Amundsen, *et al.*, THIS JOURNAL, **73**, 2118 (1951).

in the case of the less reactive dibenzylamine heating is required. The dihydrochlorides of these 1,4-diamino-2-butene compounds are not soluble in chloroform.

Various conditions for adding chlorine[12] to the double bond in the 1,4-diamino-2-butene compounds and their dihydrochlorides were investigated. The best yields of pure products resulted from the reaction of the dihydrochlorides carried out in methanol with dry chlorine. In this way 1,4-bisdimethylamino-, 1,4-dipiperidino- and 1,4-dimorpholino-2,3-dichlorobutane dihydrochloride were obtained in fair yields. We were unable to obtain the chlorine addition product from 1,4-bisdibenzylamino-2-butene. It was established that none of these chlorine addition products contained the functional grouping $>N^+Cl^-Cl$ by testing with acidified potassium iodide solution.

Several of the β,γ-dichloroamines reported here either have been or are being tested in mice for activity against Sarcoma-180 by the Sloan–Kettering Institute for Cancer Research, New York, N. Y. Also they are being tested for antihistaminic, anticonvulsant, adrenolytic and preganglionic blockade activity by Smith, Kline and French Laboratories, Philadelphia, Pa. The results of these biological studies will be reported elsewhere.

Acknowledgment.—The work described here was initiated in 1949 under Research Grant C-760 from the National Cancer Institute, U. S. Public Health Service and completed under Research Grant G-57 from the National Science Foundation.

Experimental[13]

1-Phenyl-1-piperidino-2,3-propanediolsulfite Hydrochloride.[7]—A 1.45-g. sample of 1-phenyl-1-piperidino-2,3-propanediol[4d] was dissolved in 15 ml. of chloroform and the solution saturated with dry hydrogen chloride gas. To this solution was added 1.6 ml. of thionyl chloride. After standing for 30 minutes at room temperature 100 ml. of dry ether was added to the reaction mixture and an oily precipitated product was separated by decantation of the supernatant liquid. This product was extremely hygroscopic and could be recrystallized only with considerable care from methanol and dry ether; m.p. 84–86° (dec. sealed tube), wt. 1.3 g. A sodium fusion showed this compound to contain sulfur.

Anal. Calcd. for $C_{14}H_{20}ClNO_3S$: Cl, 11.16. Found: Cl, 11.03.

Attempts to chlorinate this diol by boiling with concd. hydrochloric acid for several hours returned only the starting material. Treatment of the compound with phosphorus oxychloride and pyridine gave no identifiable materials.

Diethyl Piperidinomalonate.[7]—Using the conditions described by Jones and Wilson[6] for the preparation of diethyl (dimethylamino)-malonate, diethyl piperidinomalonate was obtained in 70% yield from piperidine and diethyl bromomalonate; b.p. 153–155° (15 mm.), $n^{29}D$ 1.460.

Anal. Calcd. for $C_{12}H_{21}NO_4$: C, 59.24; H, 8.70; N, 5.77. Found: C, 59.35; H, 8.92; N, 5.68.

2-Piperidino-1,3-propanediol.[7]—A 21.8-g. sample of diethyl piperidinomalonate in 150 ml. of dry ether was added to a 300 ml. of ether solution of 1.4 molar equiv. of lithium aluminum hydride. The reaction mixture was refluxed for six hours and the usual hydrolysis and isolation procedure followed. Distillation of the oil product gave 4.45 g. (39% yield) of a pale yellow oil, b.p. 150–151° (3 mm.). The hydrochloride of this material was too hygroscopic to handle.

Anal. Calcd. for $C_8H_{17}NO_2$: C, 60.34; H, 10.77; N, 8.80. Found: C, 60.70; H, 10.63; N, 9.00.

2-Piperidino-1,3-propanediolsulfite Hydrochloride.[7]—Using conditions similar to those described previously except that the reaction mixture was refluxed for 30 minutes, 2.70 g. of 2-piperidino-1,3-propanediol produced 4.40 g. of 2-piperidino-1,3-propanediolsulfite hydrochloride, m.p. 153–154°.

Anal. Calcd. for $C_8H_{16}ClNO_3S$: C, 39.75; H, 6.62; N, 5.80; Cl, 14.68. Found: C, 40.17; H, 6.75; N, 5.77; Cl, 14.73.

2-Piperidino-1,3-dichloropropane Hydrochloride.[7]—A 4.25-g. sample of 2-piperidino-1,3-propanediol in 30 ml. of chloroform was added to 10 ml. of thionyl chloride. This mixture was refluxed for two hours while dry hydrogen chloride was bubbled through the solution. Removal of the chloroform and excess thionyl chloride by distillation left a solid residue which was recrystallized after decolorization with Nuchar from acetone–ether solutions; wt. 2.0 g., m.p. 170–172° dec. when placed in the melting point bath at 90° and heated at the rate of 3° per minute; m.p. 150° when placed in the bath at 147°, resolidifying at 154° and then remelting at 168–170° while raising the temperature at the rate of 3° per minute.

Anal. Calcd. for $C_8H_{16}NCl_3$: C, 41.31; H, 6.94; N, 6.02. Found: C, 41.68; H, 6.95; N, 5.90.

N-Allylpiperidine.—This material was prepared from allyl bromide and two molar equivalents of piperidine in ether solution at room temperature to give a 95% yield of a colorless oil, b.p. 154–155° (literature[14] b.p. 155–156° (749 mm.)).

1-Piperidino-2,3-dichloropropane Hydrochloride.—A 50-g. sample of N-allylpiperidine was dissolved in 200 ml. of ether and dry hydrogen chloride passed in to give a hygroscopic solid product. This crude material was filtered and dissolved in 200 ml. of chloroform and the solution saturated with tank chlorine gas over a period of one hour at 10°. After standing overnight at 0–10° the solvent was removed by distillation. The crude solid hydrochloride was not recrystallized readily so it was converted to the free base by shaking with aqueous potassium carbonate in the presence of ether. Dry hydrogen chloride was passed into the dry ether solution of the free base to produce a hygroscopic solid which after two recrystallizations from a mixture of methanol, acetone and wet ether produced 24.5 g. of a colorless hydrochloride, m.p. 176–177°.

Anal. Calcd. for $C_8H_{16}NCl_3$: C, 41.31; H, 6.94. Found: C, 41.36; H, 6.97.

When a 50–50 mixture of this compound with 2-piperidino-1,3-dichloropropane hydrochloride was placed in a melting point bath at 90° and heated at the rate of 3° per minute it showed slight softening at 150° but melted completely at 174–176°. When such a mixture was placed in the bath at 150° it melted instantaneously, resolidified as the temperature was raised at the rate of 3° per minute, and then remelted at 169–171°. No bubbling was observed during these experiments.

N,N-Dimethylallylamine.—This amine was prepared from dimethylamine and allyl bromide in dry ether using the directions of Broich and Partheil[15]; yield 95%, b.p. 61° (726 mm.), literature[15] b.p. 64° (753 mm.); picrate, m.p. 94–96°, literature[15] m.p. 95°. This amine forms a hygroscopic hydrochloride with dry hydrogen chloride in ether.

1-Dimethylamino-2,3-dichloropropane Hydrochloride.—A 26.2-g. sample of the dry crude hydrochloride of N,N-dimethylallylamine was dissolved in 100 ml. of dry chloroform and tank chlorine gas passed into the solution cooled to 10° over a period of one hour. After standing at room temperature overnight the reaction mixture was cooled and the colorless product removed by filtration, wt. 29 g., m.p. 160–165°; recrystallized from a mixture of acetone and methanol, m.p. 165–167°.

(12) After this investigation had been started Ross and his co-workers reported the preparation of some 1,4-diamino-2,3-dibromobutane dihydrobromides for biological testing in their extensive cancer research program at Chester Beatty Research Institute, London, see ref. 11c.

(13) Microanalyses were determined by the Clark Microanalytical Laboratory, Urbana, Ill. All m.p.'s reported are those obtained by placing the sample in the bath 10° below the m.p. and heating at the rate of 3° per minute unless otherwise indicated.

(14) N. Menschutkin, *Chem. Zentr.*, **70**, I, 1066 (1899); H. Hoerlein and R. Kneisel, *Ber.*, **39**, 1429 (1906).

(15) A. Partheil and H. V. Broich, *ibid.*, **30**, 618 (1897).

Anal. Calcd. for $C_5H_{12}NCl_3$: C, 31.13; H, 6.28; Cl^-, 18.41. Found: C, 31.38; H, 6.49; Cl^-, 18.17.

A sample of this hydrochloride was allowed to stand for one-half hour in a water solution containing one molar equivalent of sodium hydroxide and the free base extracted with chloroform. Evaporation of the solvent gave an oil, $n^{25}D$ 1.458 (literature[9] $n^{20}D$ 1.4582); picrate, m.p. 104–106° (literature[9] m.p. 104–104.7°).

N,N-Dibenzylallylamine Hydrochloride.—This amine had been made previously.[16] For our purposes the crude hydrochloride was prepared as follows. Dibenzylamine (88.5 g.) and 27.3 g. of allyl bromide were dissolved in 150 ml. of dry benzene and refluxed for six hours. The dibenzylamine hydrobromide was removed by filtration. The benzene solution was washed with water, dried and saturated with dry hydrogen chloride gas. The hygroscopic hydrochloride was removed and used in the following chlorination without further purification.

1-Dibenzylamino-2,3-dichloropropane Hydrochloride.—The oily hydrochloride prepared in the previous experiment was dissolved in 150 ml. of chloroform and chlorine gas passed into the cooled solution for 45 minutes. After standing open at 0° overnight the solution was evaporated under vacuum with steam-bath heating to a thick amber colored gum. This material was crystallized from acetone to give a total of 38.6 g. of colorless crystals, m.p. 146–150° (starting with 27.3 g. of allyl bromide in the previous experiment). Recrystallization from a mixture of acetone and wet ether raised the m.p. to 150–153°.

Anal. Calcd. for $C_{17}H_{20}NCl_3$: C, 59.23; H, 5.85; N, 4.09; Cl^-, 10.28. Found: C, 59.28; H, 5.98; N, 4.32; Cl^-, 10.33.

1,2,3-Tripiperidinopropane.—A 4.65-g. sample of 2,3-dichloro-1-piperidinopropane hydrochloride and five molar equivalents of piperidine in 50 ml. of abs. ethanol were refluxed for two days. The ethanol was removed under vacuum and the residual material mixed with dry ether and petroleum ether and the piperidine hydrochloride removed by filtration. The filtrate was shaken with aqueous sodium carbonate and dried. The solvent was removed and the oil distilled from a small Hickman still at a pot temperature of 255° (0.12 mm.) to give 3.0 g. (51% yield) of a colorless liquid, $n^{26}D$ 1.5032.

Anal. Calcd. for $C_{18}H_{35}N_3$: C, 73.65; H, 12.02. Found: C, 73.36; H, 11.86.

Reaction of 1-Dimethylamino-2,3-dichloropropane Hydrochloride with Piperidine.—The reactivity of this β,γ-dichloroamine hydrochloride was studied under various conditions:

(a) **In benzene solution** after refluxing the β,γ-dichloroamine hydrochloride with five molar equivalents of piperidine for five hours only 41% of the expected piperidine hydrochloride was obtained. From the benzene solution about 25% of the unchanged β,γ-dichloroamine was isolated and identified as its picrate, m.p. 105–106°.[9]

(b) **In absolute ethanol** (30 ml.) 6 g. (0.0313 mole) of the hydrochloride and 14.8 g. (0.174 mole) of pure piperidine were refluxed for 40 hours. This triaminopropane was isolated by the procedure outlined above for 1,2,3-tripiperidinopropane and distilled from a Hickman still, pot temperature 133° (0.1 mm.); wt. 6 g. (76% yield), $n^{28.5}D$ 1.4837.

Anal. Calcd. for $C_{15}H_{31}N_3$: C, 71.04; H, 12.36. Found: C, 71.02; H, 12.44.

This material is either 1-dimethylamino-2,3-dipiperidinopropane or 2-dimethylamino-1,3-dipiperidinopropane.

Reaction of 1-Dibenzylamino-2,3-dichloropropane Hydrochloride with Piperidine.—When five molar equivalents of piperidine were allowed to stand at room temperature with the β,γ-dichloroamine hydrochloride in ethanol solution for three weeks, only 36% of the expected amount of piperidine hydrochloride could be obtained as a by-product. Therefore, 4 g. (0.0116 mole) of the β,γ-dichloroamine hydrochloride was refluxed for 40 hours with 5.1 g. (0.061 mole) of pure piperidine in absolute ethanol. The yield of the by-product, piperidine hydrochloride was 98%. Distillation of the oily triaminopropane from a Hickman still, pot temperature 262° (0.15 mm.), gave a pale yellow viscous liquid, $n^{27}D$ 1.5473 yield 64%.

Anal. Calcd. for $C_{27}H_{39}N_3$: C, 79.95; H, 9.69; N, 10.36. Found: C, 80.34; H, 9.66; N, 9.98.

(16) J. v. Braun and R. Schwarz, *Ber.*, **35**, 1279 (1902).

This product is either 1-dibenzylamino-2,3-dipiperidinopropane or 2-dibenzylamino-1,3-dipiperidinopropane.

***trans*-1,4-Bisdimethylamino-2-butene Dihydrochloride.**—A solution of 85 g. (1.88 moles) of dimethylamine in 300 ml. of dry ether was stirred and cooled to 0–5° while 50 g. (0.4 mole) of 1,4-dichloro-2-butene (76.5% *trans*, 23.5% *cis*)[17] was added slowly with cooling over a period of an hour. The reaction mixture was allowed to come to room temperature and stand for 24 hours. Excess dimethylamine was removed under vacuum and a 94% yield of the by-product dimethylamine hydrochloride filtered from the reaction mixture. Dry hydrogen chloride was passed into the filtrate and the precipitated dihydrochloride removed and recrystallized from methanol and ether; yield 63 g. (73% yield), m.p. 279°.

Anal. Calcd. for $C_8H_{20}N_2Cl_2$: Cl^-, 32.95. Found: Cl^-, 32.75.

This dihydrochloride was soluble in water or hot alcohol. A sample was converted to the free diamine by treatment with aqueous sodium hydroxide in a 90% yield, b.p. 70° (22 mm.), b.p. 65° (17 mm.), b.p. 171–172° (735 mm.), $n^{28}D$ 1.437; picrate, m.p. 220–222°. Willstätter[11a] prepared this compound in 62% yield from 1,4-dibromo-2-butene in benzene solution; b.p. 65° (17 mm.), b.p. 171–172° (723 mm.); picrate, m.p. 222–223°.

***trans*-1,4-Dipiperidino-2-butene and Dihydrochloride.**—In an analogous manner to that used in the previous experiment, except that the free base was isolated directly from the ether reaction mixture, a 71% yield of the colorless crystalline diamino compound was obtained from 1,4-dibromo-2-butene (mainly *trans*)[18]; m.p. 51–51.5° recrystallized from petroleum ether (b.p. 36–40°).

Anal. Calcd. for $C_{14}H_{26}N_2$: C, 75.61; H, 11.78; N, 12.60. Found: C, 75.68; H, 11.80; N, 12.53.

The dipicrate was prepared from the free base in ethanol, m.p. 205–206°.

Anal. Calcd. for $C_{26}H_{32}N_8O_{14}$: C, 45.88; H, 4.73. Found: C, 45.65; H, 4.78.

Ross and co-workers[11c] have obtained this compound as an oil in 58% yield using benzene as the reaction media. Their picrate showed m.p. 191–193°.

With dry hydrogen chloride in ether solution the diamine gave a dihydrochloride, recrystallized from methanol; m.p. 302° dec.

Anal. Calcd. for $C_{14}H_{28}N_2Cl_2$: Cl^-, 23.96. Found: Cl^-, 24.01.

***trans*-1,4-Dimorpholino-2-butene and Dihydrochloride.**—This compound was prepared in an analogous manner in 70% yield, m.p. 90–92°, recrystallized from methanol; Ross[11c] reported m.p. 90–91.5°.

Anal. Calcd. for $C_{12}H_{22}O_2N_2$: C, 63.68; H, 9.78; N, 12.38. Found: C, 63.40; H, 9.57; N, 12.19.

The dihydrochloride was prepared in an ether–benzene mixture from the diamine and dry hydrogen chloride and recrystallized from methanol; yield 79%, m.p. 282–285°.

Anal. Calcd. for $C_{12}H_{24}O_2N_2Cl_2$: Cl^-, 23.69. Found: Cl^-, 23.59.

***trans*-1,4-Bisdibenzylamino-2-butene and Dihydrochloride.**—A 26-g. sample of 1,4-dibromo-2-butene was refluxed for eight hours with 95 g. (4 molar equiv.) of dibenzylamine in benzene solution. The by-product dibenzylamine hydrobromide was removed in 97% yield. Evaporation of the benzene and recrystallization of the residue from benzene and petroleum ether gave 32.5 g. (60% yield) of long, colorless crystals, m.p. 112–114°.

Anal. Calcd. for $C_{32}H_{34}N_2$: C, 86.05; H, 7.67; N, 6.27. Found: C, 85.87; H, 7.64; N, 6.13.

The dihydrochloride was prepared in benzene solution and recrystallized from methanol, m.p. 256–258° dec. This compound was insoluble in water.

Anal. Calcd. for $C_{32}H_{36}N_2Cl_2$: Cl^-, 13.65. Found: Cl^-, 13.59.

1,4-Diamino-2,3-dichlorobutane Dihydrochlorides.—After trying several sets of conditions for adding chlorine to the

(17) Generously supplied by The Polychemicals Department, E. I. du Pont de Nemours and Co., Wilmington, Del., and specified to have this composition.

(18) From Columbia Organic Chemical Co., Inc., Columbia, So. Carolina, and claimed to be mainly of this form.

double bond in the 1,4-diamino-2-butene compounds including treatment of either the free bases or the dihydrochlorides in such media as air, water, ether, chloroform and benzene, the following were settled on as producing the desired addition products in the highest yields.

In general the 1,4-diaminobutene dihydrochloride (5 g.) was dissolved in methanol (150–200 ml.) and dry tank chlorine gas passed into the solution at room temperature for 30 minutes. The solutions were allowed to stand for one to four hours until precipitation of the product seemed to be completed. The colorless, powdery products were removed by filtration and washed with cold methanol. In some instances the yields were increased by adding dry ether to the reaction mixture filtrates. The products were recrystallized either from methanol, from methanol and water, or from methanol–ether mixtures. These compounds were more soluble in water than in methanol. Contamination of these compounds with the starting material often raised rather than lowered the m.p. of the product.

1,4-Bisdimethylamino-2,3-dichlorobutane dihydrochloride: yield 60%, m.p. 238° dec.

Anal. Calcd. for $C_8H_{20}N_2Cl_4$: C, 33.60; H, 7.04; N, 9.79; Cl, 49.54; Cl^-, 24.77. Found: C, 33.72; H, 7.22; N, 9.59; Cl, 49.26; Cl^-, 24.55.

1,4-Dipiperidino-2,3-dichlorobutane dihydrochloride: yield 70%, m.p. 248° dec. *Anal.* Calcd. for $C_{14}H_{28}N_2Cl_4$: C, 45.91; H, 7.70. Found: C, 45.80; H, 7.74.

1,4-Dimorpholino-2,3-dichlorobutane dihydrochloride: yield 60%, m.p. 245° dec.

Anal. Calcd. for $C_{12}H_{24}N_2O_2Cl_4$: C, 38.94; H, 6.53; Cl^-, 19.15. Found: C, 39.34; H, 6.59; Cl^-, 18.8.

None of the above compounds released iodine from acidified potassium iodide solutions, showing that no positive (on nitrogen) chlorine was present. It has not yet been possible to obtain the 2,3-dichloro addition product of 1,4-bisdibenzylamino-2-butene dihydrochloride.

LINCOLN, NEBRASKA

[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY OF THE UNIVERSITY OF ROCHESTER]

An Infrared Study of Hydrogen Bonding Involving the Thiol Group[1]

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A study of the infrared spectra of a series of aminothiols of the type $R_2N(CH_2)_nSH$ (n = 3 or 4) has given no indication of hydrogen bonding involving the –S–H group. Further studies on mixtures of sulfoxides and thiol compounds, and on thiobenzoic acid alone, indicate that hydrogen bonding through the –S–H group is negligible. The –S–D stretching frequency in thiophenol-*d* and *n*-hexanethiol-*d* has been found to occur at 1839 and 1870 cm.$^{-1}$, respectively. The synthesis of several new aminothiols and aminoalcohols is reported. Thiol compounds are found to react with carbon tetrachloride in the presence of tertiary bases at room temperature to yield mainly the disulfide and the amine hydrochloride; the reaction presumably involves a displacement with the formation of $-SCCl_3$ compounds, which then react further.

Cryoscopic,[2] spectroscopic[3] and calorimetric[4] studies indicate that the thiol group shows only a slight tendency to form hydrogen bonds, and it has been suggested[5] that an important reason for the differing chemical properties of oxygen and sulfur analogs is the relative absence of hydrogen bonding in the latter. It seemed desirable to investigate the hydrogen bonding ability of the thiol group in more detail,[6] and the most favorable cases appeared to be[3a,7] aminothiols of type I

$$R_2N(CH_2)_nSH \quad I$$

A series of these compounds, where R_2 is $(C_2H_5)_2$, $(C_6H_5)_2$ and piperidyl, was accordingly prepared and studied. Most of these compounds are described adequately in Table II. An unexpected complication, discussed later, prevented the use of carbon tetrachloride as solvent for the infrared measurements, but the results of measurements in benzene solution and in the pure liquid are given in Table I. There is no evidence for the expected shift in the –S–H frequency, and with the piperidyl derivatives, the frequency in solution was actually lower than in the pure liquid. *n*-Hexanethiol absorbed at 2555 cm.$^{-1}$ compared to 2584 cm.$^{-1}$ for most of the aminothiols.

TABLE I

ABSORPTION IN THE S-H REGION OF COMPOUNDS OF TYPE $R_2N(CH_2)_nSH$

Compound R_2	n	Absorption, cm.$^{-1}$ Pure liquid	Absorption, cm.$^{-1}$ 0.2 M soln. in benzene
$(C_2H_5)_2$	3	2584	2584
$(C_2H_5)_2$	4	2584	2584
C_5H_{10}[a]	3	2617	2584
C_5H_{10}[a]	4	2617	2584
$(C_6H_5)_2$	3	2577	2584

[a] 1-Piperidyl.

It has been found that the sulfoxide grouping is a strong donor grouping for the formation of hydrogen bonds with hydroxyl groups[8] and we therefore investigated the effect of added diphenyl sulfoxide and the crystalline aliphatic diisobutyl sulfoxide on the –S–H frequency of benzene solutions of thiophenol and of thiobenzoic acid. In 0.2 M solution in benzene, thiophenol and thiobenzoic acid showed bands at 2584 and 2577 cm.$^{-1}$, respec-

(1) This research was supported by the United States Air Force, through the Office of Scientific Research of the Air Research and Development Command. This article is not subject to copyright.

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