175. *Syntheses of some β-Chlorinated Amines.*

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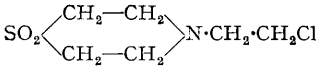
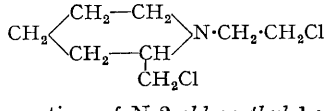
Some analogues of 2 : 2′ : 2″-trichlorotriethylamine have been synthesised. The compounds have a physiological action similar to but less marked than that of the parent substance.

Many β-chlorinated tertiary amines, such as 2 : 2′ : 2″-trichlorotriethylamine (McCombie and Purdie, *J.*, 1935, 1217) are known to be vesicant, whilst many quaternary salts containing the group $N{\cdot}CH_2{\cdot}CH_2X$ (X = $CO{\cdot}NH_2$ etc.) are highly toxic. In view of their relationship to, and derivability from, "mustard gas" and its

(I.) 



(II.)

toxic sulphone, the syntheses now described included the preparation of N-2-*chloroethyl*-1 : 4-*thiazan dioxide* (I), but it was found that the thiazan dioxide ring is not in itself a physiologically active group.

Whilst the simpler homologues of 2 : 2′ : 2″-trichlorotriethylamine had vesicant properties of a similar order, this physiological action is less marked in more complex compounds. A cyclic compound (II), analogous to an alkaloid, showed no outstanding toxic characteristics.

Experimental.

Di-(2-chloroethyl)allylamine.—Diethanolamine (15 g.), allyl bromide (15 g.), and anhydrous sodium carbonate (10 g.) were mixed, with cooling, and reaction was completed by warming on a water-bath for 2 hours. The product, diluted with alcohol, was filtered and fractionally distilled; *di-(2-hydroxyethyl)allylamine* was thus obtained as a colourless oil, b. p. 124°/2 mm. (Found: C, 58·2; H, 10·1. $C_7H_{15}O_2N$ requires C, 57·9; H, 10·0%). This was treated in chloroform

solution with a slight excess of thionyl chloride, and *di*-(2-*chloroethyl*)*allylamine* was isolated by basifying the reaction product and fractionating in a vacuum as a colourless liquid, b. p. 80°/3 mm. (Found : C, 46·5; H, 7·29; Cl, 39·1. $C_7H_{13}NCl_2$ requires C, 46·2; H, 7·14; Cl, 39·0%). On being kept it slowly turned brown, and deposited crystals of a dimer.

2-*Chloroethyldi*-(2-*chloro*-n-*propyl*)*amine*.—Ethanolamine (40 g.) and propylene oxide (70 g.) were mixed, with cooling, under reflux. After 12 hours, the mixture was heated to 100° for 2 hours and then cooled. A sticky mass of 2 : 2′ : 2″-trihydroxyethyldi-*n*-propylamine remained. Part of this was converted into the *hydrochloride* by treatment, under chloroform, with gaseous hydrogen chloride. The hydrochloride solidified after treatment with dry acetone, and was recrystallised from anhydrous alcohol, giving colourless crystals, m. p. 132° (Found : C, 45·3; H, 9·7; Cl, 16·3. $C_8H_{20}O_3NCl$ requires C, 45·0; H, 9·4; Cl, 16·7%). The remainder of the base was treated with twice its weight of thionyl chloride and diluted with chloroform (2 : 1), and reaction was completed by heating on the water-bath. After removing the solvent, the product was basified, extracted with chloroform, dried (Na_2SO_4), and distilled. 2-*Chloroethyldi*-(2-*chloro*-n-*propyl*)*amine* was obtained as a colourless oil, b. p. 117°/3 mm. (Found : C, 41·8; H, 7·1; Cl, 46·1. $C_8H_{16}NCl_3$ requires C, 41·3; H, 6·9; Cl, 45·9%). It formed a *picrate*, m. p. 117·5° (Found : C, 36·6; H, 3·8. $C_{14}H_{19}O_7N_4Cl_3$ requires C, 36·8; H, 3·1%), and a moderately soluble mercurichloride. On being kept the base darkened and gave a crystalline deposit of a dimer.

Di-(2-*chloroethyl*)-2-*chloro*-n-*propylamine*.—Diethanolamine (40 g.), propylene oxide (30 g.), and chloroform (50 c.c.) were mixed, with cooling, under reflux, and after a day the product was heated to 100° for 6 hours. Removal of the chloroform and excess of propylene oxide left a gummy mass of 2 : 2′ : 2″-trihydroxydiethyl-*n*-propylamine. Part of this was converted (as above) into the *hydrochloride* which crystallised from alcohol–ether in needles, m. p. 147° (Found : C, 42·2; H, 8·9; Cl, 17·8. $C_7H_{18}O_3NCl$ requires C, 42·1; H, 9·0; Cl, 17·8%). The remainder of the base was converted (as above) into *di*-(2-*chloroethyl*)-2-*chloro*-n-*propylamine*, which was a colourless oil, b. p. 114°/4 mm. (Found : C, 38·9; H, 6·4. $C_7H_{14}NCl_3$ requires C, 38·5; H, 6·4%). It gave a sparingly soluble mercurichloride, m. p. 143°.

N-*Methyl*-N-(2-*hydroxyethyl*)*morpholinium Iodide*.—*N*-(2-Hydroxyethyl)morpholine, b. p. 901°/3 mm., was obtained by heating together ethanolamine, 2 : 2′-dichlorodiethyl ether, and anhydrous potassium carbonate. It reacted with methyl iodide, with much heat evolution, to give a white solid *product* which crystallised from absolute alcohol in plates, m. p. 127° (Found : C, 30·8; H, 5·9. $C_7H_{16}O_2NI$ requires C, 30·8; H, 5·9%). Attempts to replace the hydroxyl group by chlorine were not successful.

N-2-*Hydroxyethyl*-1 : 4-*thiazan Dioxide Hydrochloride*.—Divinyl sulphone (24 g.) was added to a solution of ethanolamine (12 g.) in water (100 c.c.), and reaction was completed by refluxing for ½ hour. Hydrochloric acid (25 c.c.; *d* 1·16) was added, and the mixture was evaporated on a water-bath. On treatment with alcohol the residue crystallised, giving 39 g. (91% of theory) of the required product, which after recrystallisation from alcohol had m. p. 172° (Found : Cl′, 16·4. $C_6H_{14}O_3NClS$ requires Cl′, 16·4%). The *phenylurethane* of the base (from alcohol) had m. p. 110—111° (Found : C, 52·2; H, 5·91. $C_{13}H_{17}O_4NS$ requires C, 52·3; H, 6·08%).

N-2-*Chloroethyl*-1 : 4-*thiazan Dioxide Hydrochloride*.—The crude hydrochloride, prepared as above, was treated with pyridine (16 c.c.), and then warmed with a solution of thionyl chloride (20 c.c.) in chloroform (100 c.c.). After an hour the mixture was cooled and shaken with water, the chloroform layer was separated and dried, and the solvent was removed. The required product solidified on cooling. It crystallised from benzene–petroleum and had m. p. 63°. The *hydrochloride* crystallised from dilute alcohol, m. p. 188—189° (Found : Cl′, 14·9; hydrolysable Cl, 30·1. $C_6H_{13}O_2NCl_2S$ requires Cl′, 15·1; hydrolysable Cl, 30·3%).

Some of the free base was heated in a tube exposed in the vapours of boiling decalin; it melted and then resolidified, giving a *dimeric piperazinium salt* (Found : Cl′, 17·6. $C_{12}H_{24}O_4N_2Cl_2S_2$ requires 17·9%).

NN-*Di*-(2-*chloroethyl*)*piperidinium Chloride*.—*N*-(2-Hydroxyethyl)piperidine (cf. Leffler and Brill, *J. Amer. Chem. Soc.*, 1933, **55**, 365; Tullock and McElvain, *ibid.*, 1939, **61**, 961) and ethylene chlorohydrin were heated on a water-bath for 12 hours. The product, *di*-(2-*hydroxyethyl*)*piperidinium chloride*, was ground with acetone, filtered off, washed with acetone, and so obtained as very deliquescent crystals, m. p. 192—193° (Found : Cl′, 16·8. $C_9H_{20}O_2NCl$ requires Cl′, 16·9%). This salt (17·5 g.), thionyl chloride (15 c.c.), and chloroform (50 c.c.) were heated for 2 hours on the water-bath. Solvent was removed, and the residue was ground with cold acetone and filtered off. It crystallised from the minimum quantity of boiling 98% alcohol in colourless, very deliquescent plates of *di*-(2-*chloroethyl*)*piperidinium chloride monohydrate*, m. p. 218° (decomp.) [Found : Cl′, 13·5; loss of wt. at 110°, 5·8. $(C_9H_{18}NCl_2)^+Cl^-,H_2O$ requires Cl′, 13·4; H_2O, 6·8%].

dl-2-*Chloromethyl*-N-(2-*chloroethyl*)*piperidine* (II).—Ethyl *dl*-pipecolinate was prepared by catalytic reduction of picolinic acid hydrochloride and esterification of the product. It was reduced with sodium and alcohol to *dl*-2-hydroxymethylpiperidine (m. p. 75°; b. p. 100—102°/6 mm.), which was then refluxed with ethylene chlorohydrin and potassium carbonate in alcohol. This gave *dl*-2-hydroxymethyl-*N*-(2-hydroxyethyl)piperidine as a thick oil, b. p. 142—145°/3 mm., which could not be induced to solidify. Its *picrate*, prepared in benzene solution, crystallised from acetone–petrol (Found : C, 43·3; H, 5·01; N, 14·2. $C_{14}H_{20}O_9N_4$ requires C, 43·3; H, 5·15; N, 14·4%).

The free base was treated with thionyl chloride in chloroform solution. Removal of the solvent left a dark coloured residue which was extracted 3 times with ether; the remaining solid was then recrystallised from acetone giving dl-2-*chloromethyl*-N-(2-*chloroethyl*)*piperidine hydrochloride*, m. p. 145° (Found : Cl′, 15·4. $(C_8H_{16}NCl_2)^+Cl^-$ requires Cl′, 15·4%). The corresponding base was prepared only in benzene solution.

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