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UNITED STATES PATENT OFFICE

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BIS-QUATERNARY SALTS OF 1:10-BIS-(DI-ALKYLAMINO)-5:6-DITHIA-DECANE

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2 Claims. (Cl. 260—567.6)

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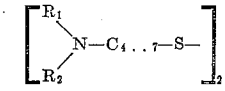
The present invention is concerned with improvements in or relating to bis-(aminoalkyl)-disulphides, more particularly bis-(dimethyl- or diethyl-aminoalkyl)-disulphides wherein the alkyl group is a butyl, amyl, hexyl or heptyl group, and quaternary salts thereof.

Bis-dimethylaminoethyl- and bis-dimethylaminopropyl-disulphides in the form of their dimethiodides are already known [see J. A. C. S., 1938, 60, 1765]. The preparation of bis-diethylaminoethyl-disulphide and bis-diethylaminopropyl-disulphide has also been disclosed [see J. A. C. S. 1945, 67, 1345 et seq.]. The free bases were produced by treating the diethylaminoethyl-thiol or diethylaminopropyl-thiol, in the form of its sodium salt, with iodine.

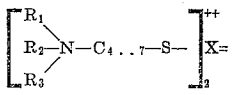
It has now been found, according to the present invention, that quaternary salts of bis-(dimethyl- and diethylaminoalkyl) disulphides having from 4 to 7 carbon atoms in the alkyl groups thereof have a particularly high curare-like activity when compared with similar compounds having a lesser number of carbon atoms in the alkyl groups thereof.

Accordingly the present invention comprises bis-(dimethyl- and diethyl-aminoalkyl)-disulphides wherein the alkyl group is a butyl, amyl, hexyl or a heptyl group and quaternary salts thereof.

The compounds of the present invention can be represented by the following general formula:

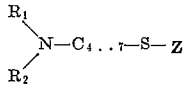


and



wherein R_1 and R_2 are methyl or ethyl, R_3 is an alkyl group, preferably methyl or ethyl, $C_{4..7}$ represents a butyl, amyl, hexyl or heptyl group and X= represents two halogen ions, preferably iodine ions, or a divalent anion such as a sulphate ion, and are new substances.

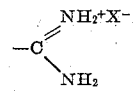
The present invention further provides a process for the manufacture of the aforesaid novel compounds, which comprises oxidizing by means of iodine a compound of the general formula



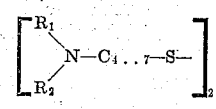
wherein R_1 and R_2 stand for methyl or ethyl, $C_{4..7}$ represents a butyl, amyl, hexyl or heptyl

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group, and Z represents an alkali metal, hydrogen or the radical

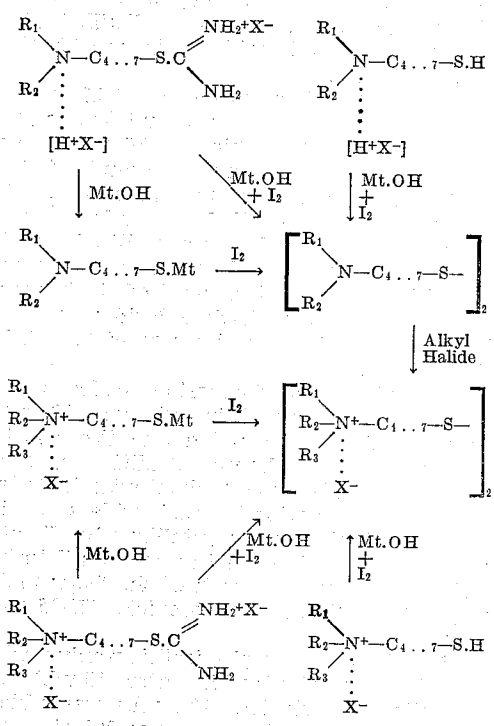


X being a halogen atom, or a hydrohalide or alkyl halide thereof, and, as the case may be, reacting the disulphide of the general formula



formed with an alkyl halide or a dialkyl sulphate to produce the corresponding quaternary nitrogen base.

The various modes of formation of the compounds of the present invention can be better understood by reference to the following formula-scheme which is given by way of illustration:



wherein R_1, R_2, R_3 and $—C_{4..7}—$ have the values given hereinbefore, X^- is a halogen atom and Mt. is an alkali metal.

The various reactions may best be conducted in aqueous solution, preferably in the absence of air.

The curare-like activity of bis-(dimethylaminobutyl)-disulphide dimethiodide, one embodiment of the present invention, for example, is about equal to that of tubocurarine in the dog as test animal; that is, about ten times as great an activity as that of bis-(diethylaminopropyl)-disulphide diethiodide which is a previously prepared member of this class of substance. This striking enhancement of activity was surprising in view of the homologous nature of the series.

The following examples illustrate the manner in which the novel substances of the present invention may be prepared:

EXAMPLE 1

Preparation of 1-dimethylamino-butane-thiol-(4)

Succinic anhydride (60 g.) was added slowly to 27% ethanolic dimethylamine (102 g.), cooled in ice. The mixture was left at 15° C. for 12 hours and then cooled to 0° C. for 1 hour. The N,N-dimethyl-succinamic acid which separated was filtered off and recrystallized from benzene. It melted at 84–85° C. Yield: 54% (46.6 g.).

N,N-dimethyl-succinamic acid (34.9 g.) was extracted from a Soxhlet into a stirred solution of lithium aluminium hydride (21 g.) in dry, boiling ether (1200 ml.) in a nitrogen atmosphere over the period of 24 hours. The complex formed was decomposed while in ether solution with ice-cold water and acidified 50% sulphuric acid. After washing with ether the acid solution was made strongly alkaline with 30% sodium hydroxyde and continuously extracted with ether for 24 hours. The ethereal solution was dried over anhydrous sodium carbonate, the ether distilled off and the residue consisting of 4-dimethylamino-butane-ol-(1), distilled at 14 mm. pressure when its boiling point was 80–81° C. Yield: 49% (13.8.).

4-dimethylamino-butane-ol-(1) (13.1 g.) was dissolved in benzene (40 ml.) and the solution added slowly to thionyl chloride (16 ml.) in benzene (40 ml.). The mixture was then heated for 3 hours under reflux on the water-bath. The benzene was then distilled off under reduced pressure and the residue recrystallized by dissolving in ethanol and adding ether. A further recrystallization gave the required 4-dimethylaminobutyl-chloride hydrochloride; melting point 112–115° C. (very hygroscopic). Yield: 65% (12.5 g.).

4-dimethylaminobutyl-chloride hydrochloride (12.5 g.) was dissolved in ethanol (20 ml.). Thiourea (5.5 g.) was added and the solution was refluxed for 15 hours. Addition of ethyl acetate precipitated the 4-dimethylaminobutyl-isothiouronium chloride hydrochloride as a viscous syrup which was recrystallized by dissolving in ethanol, adding ethyl acetate until turbid and then scratching the walls of the flask; melting point 180–183° C. (hygroscopic). Yield 63% (11.4 g.).

4-dimethylaminobutyl-isothiouroniumchloride (11.4 g.) was dissolved in water (15 ml.) and 5 N caustic soda solution (18.4 ml.) was added. The mixture was heated at about 90° C. for 1 hour on a water-bath, then cooled in ice and extracted with ether. After drying the ethereal solution over anhydrous sodium sulphate the ether was evaporated and the 1-dimethylamino-butane-thiol-(4) formed distilled; boiling point 84° C. at 35 mm. Yield: 64% (3.9 g.).

EXAMPLE 2

Bis-(δ-trimethylammonium-butyl)-disulphide diiodide

1-dimethylamino-butane-thiol-(4) (0.5 g.) was dissolved in 5 N caustic soda solution (0.7 cc.) and iodine, dissolved in potassium iodide solution, was added until a faint yellow color appeared. The excess of iodine was removed with a few drops of sodium sulphite solution and the resulting colorless solution was made definitely alkaline with dilute sodium hydroxide solution. An oil separated which was extracted with ether. The ethereal extract was dried over caustic soda and the ether was evaporated, finally in vacuo. A colorless oil (0.4 g.) remained. The methiodide was prepared by taking up the oil in dry benzene (5 cc.) and adding methyl iodide (0.4 cc.). A yellow oil separated which crystallized on standing. Recrystallization from alcohol gave colorless crystals (0.5 g.), melting point 184–186° C. A further recrystallization slightly raised the melting point to 188–189° C. (uncorrected).

EXAMPLE 3

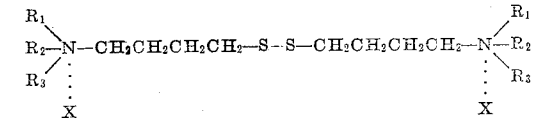
1-dimethylamino-butane-thiol-(4) (6.6 g.) was dissolved in 5 N caustic soda solution (9.3 cc.) and a solution of iodine (8.2 g.) in potassium iodide solution was added slowly. After filtration the reaction mixture was made strongly alkaline with caustic soda solution. An oil separated which was extracted three times with ether. The ethereal extract was dried over anhydrous sodium sulphate and after filtration the ether was evaporated. The residual oil was distilled and 1:10-bis-(dimethylamino)-5:6-dithiadecane was collected, boiling point 130° C./0.2 mm. Yield: 70% (4.65 g.).

The required methiodide was prepared by dropping methyl iodide (3.2 cc.) dissolved in dry benzene (20 cc.) into a solution of the 1:10-bis-(dimethylamino)-5:6-dithiadecane (4.65 g.) in dry benzene (40 cc.) contained in a flask fitted with a reflux condenser. During the addition the flask was shaken and cooled. The quaternary salt separated and the reaction mixture was allowed to stand for 15 hours. The slightly yellow product was collected by filtration, washed with ether, dried and recrystallized from ethanol, with two small crystals of sodium sulphite to decolorize the solution. Colorless crystals (9.1 g.) of the product were obtained, M. P. 194–195° C. A further recrystallization raised the melting point to 195–196° C.

This application is a continuation-in-part of our copending application Serial No. 243,582, filed August 24, 1951, now abandoned.

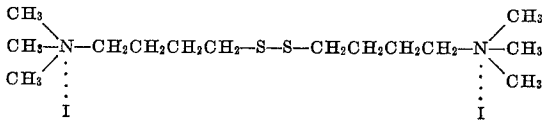
We claim:

1. A compound having the formula



wherein R_1, R_2 and R_3 each represents an alkyl radical having not more than two carbon atoms, and X represents an anion.

2. A compound having the formula



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