595. *Thia- and Dithia-alkanebis(quaternary Ammonium) Salts as Neuromuscular- and Ganglion-blocking Agents.*

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The preparation of a number of thia- and dithia-alkane(bisquaternary ammonium) salts is described.

The discovery that polymethylene(bisquaternary ammonium) salts exert neuromuscular- or ganglion-blocking activities, depending on the length of the polymethylene chain, made it of interest to investigate the replacement of one or more methylene groups in such compounds by a sulphur atom.

Marxer and Miescher recently (*Helv. Chim. Acta*, 1951, **34**, 924) mentioned the preparation of 3-thiapentane-1 : 5-bis(trimethylammonium iodide), and the corresponding chloride had previously been prepared by Lawson and Reid (*J. Amer. Chem. Soc.*, 1925, **47**, 2821). We prepared this iodide (Ro 3-0438) by reaction of the sodium mercaptide, dissolved in ethanol, with 2-chloroethyldimethylamine in a nitrogen atmosphere (cf. Brighton and Emmet Reid, *J. Amer. Chem. Soc.*, 1943, **65**, 438) and quaternisation of the resulting tertiary compound with methyl iodide. This reaction has proved to be general, giving high yields. However, it cannot be used for formation of the dibutyl homologue since the 4-chlorobutyldimethylamine quaternises internally very rapidly to give 1 : 1-dimethylpyrrolidinium chloride. An attempt to overcome this by the use of the method due to Gilman *et al.* (*J. Amer. Chem. Soc.*, 1945, **67**, 1845), *i.e.*, the reaction of 4-chlorobutyldimethylamine hydrochloride with 4-mercaptobutyldimethylamine was not successful. The 4-chlorobutyldimethylamine hydrochloride required for this attempt was prepared by the reduction of *NN*-dimethylsuccinamic acid with lithium aluminium hydride (Avison, *J. Appl. Chem.*, 1951, **1**, 469) and reaction of the resulting 4-hydroxybutyldimethylamine with thionyl chloride. The thiol was prepared by the decomposition of the thiuronium salt from the chloro-compound. However, it was evident that the reaction should be carried out with a quaternary salt and, with this in view, 4-hydroxybutyltrimethylammonium iodide was treated with thionyl chloride; a product was obtained in the form of orange-coloured needles with a high halogen content. The results obtained by Brownell and King (*J. Amer. Chem. Soc.*, 1949, **71**, 2926) on the formation of chloro-

iodates by the action of thionyl chloride on quaternary ammonium iodides suggested that this compound had the structure $Cl\cdot[CH_2]_4\cdot NMe_3\}ICl_2$. Maréchal and Bagot (*Ann. Pharm. France*, 1946, 180) have reported the preparation of 4-bromobutyltrimethylammonium bromide by the quaternisation of 1 : 4-dibromobutane with trimethylamine. We found this method to be impracticable owing to the difficulty of the separation, by crystallisation, of the mono- from the bis-ammonium compound which is formed at the same time.

Finally, 4-chlorobutyltrimethylammonium bromide, prepared from 1-bromo-4-chlorobutane (Star and Hixon, *J. Amer. Chem. Soc.*, 1934, **56**, 1595) and trimethylamine, was condensed with sodium sulphide to give 5-thianonane-1 : 9-bis(trimethylammonium bromide).

In a similar way, 4-thiaheptane-1 : 7-bis(triethylammonium iodide) (Ro 3-0381) was prepared from 3-chloropropyltriethylammonium iodide.

In order to study unsymmetrical thia-compounds, 5-thiaundecane-1 : 11-bis(trimethylammonium iodide) (Ro 3-0462) and 3-thiahexane-1 : 6-bis(trimethylammonium iodide) (Ro 3-0468) were prepared by the reaction of a sodium mercaptide with a chloro-compound, followed by quaternisation of the tertiary compound with methyl iodide. Since RCl and R'SH, or R'Cl and RSH, yield the same sulphide, it is preferable, and sometimes essential, to use the more stable chloro-compound.

A number of disulphides were prepared in which two methylene groups were replaced by sulphur atoms. Taichi Harada (*Bull. Chem. Soc. Japan*, 1929, **4**, 171; *Chem. Zentr.*, 1929, II, 2552) reported the preparation of 3 : 4-dithiahexane-1 : 6-bis(trimethylammonium bromide), and Renshaw, Dreisbach, Ziff, and Green (*J. Amer. Chem. Soc.*, 1938, **60**, 1765) synthesised the corresponding di-iodide and 2 : 5-dimethyl-3 : 4-dithiahexane-1 : 6-bis(trimethylammonium iodide), by air oxidation of the corresponding tertiary amino-thiols followed by quaternisation. Gilman *et al.* (*loc. cit.*) obtained similar tertiary compounds through the oxidation, with iodine, of diethyl-mercaptoethylamines and -mercaptopropylamines.

The preparation of the 3 : 4-dithiahexane-1 : 6-bis(trimethylammonium iodide), described by Renshaw *et al.* (*loc. cit.*), has been repeated, but with oxidation of the sodium mercaptides by iodine in potassium iodide solution. Also, 4 : 5-dithiaoctane-1 : 8-bis(triethylammonium iodide) (Ro 3-0384) and 5 : 6-dithiadecane-1 : 10-bis(trimethylammonium iodide) (Ro 3-0386) were prepared. The thiols were obtained by the method of Renshaw *et al.* (*loc. cit.*) and, for the preparation of Ro 3-0384, the thiol was not isolated but was oxidised directly after liberation from the thiuronium salt.

In tests upon head drop in rabbits and on the neuromuscular preparation in the cat, and also tests in man (unpublished work by Bächtold, Pellmont, and Randall; Hunter, *Brit. J. Pharmacol.*, 1953, **8**, 115) the substances with more than seven atoms between the quaternary nitrogen atoms showed predominantly neuromuscular-blocking action of the decamethonium type. The lower homologues exhibited a depressor action on cat blood pressure and blocked transmission in the cat superior cervical sympathetic ganglion (unpublished work by Bächtold, Pellmont, and Randall).

Experimental

Hydroxy-amines.—4-Hydroxybutyldimethylamine was prepared by Avison's method (*J. Appl. Chem.*, 1951, **1**, 469), or by condensation of dimethylamine with 4-bromobutyl acetate (Smorgonskii and Gol'dfarb, *J. Gen. Chem.* U.S.S.R., 1940, **10**, 1113) in methanol–ether and hydrolysis of the 4-dimethylaminobutyl acetate, to give the desired hydroxy-amine in good yield.

6-*Hydroxyhexyldimethylamine.* The preparation was based on that of 1-6'-hydroxyhexylpiperidine (Avison, *loc. cit.*). Ethyl hydrogen adipate (*Org. Synth.*, **19**, 45) was converted into the acid chloride with thionyl chloride (1½ hr. on the water-bath), and this, with dimethylamine in ether, gave *ethyl* NN-*dimethyladipamate*, b. p. 102—106°/0·25 mm., n_D^{20} 1·4573 (Found : C, 59·2; H, 9·1. $C_{10}H_{19}O_3N$ requires C, 59·7; H, 9·5%). Reduction with lithium aluminium hydride in ether gave 6-*hydroxyhexyldimethylamine*, b. p. 114—116°/12 mm., $n_D^{20\cdot5}$ 1·4482 (Found : N, 9·3. $C_8H_{19}ON$ requires N, 9·6%).

Chloro-compounds.—4-*Chlorobutydimethylamine hydrochloride.* Thionyl chloride was caused

to react with 4-hydroxybutyldimethylamine in benzene; the hygroscopic product had m. p. 118—119° (Found: N, 8·4; Cl^-, 20·7. Calc. for $C_6H_{15}NCl_2$: N, 8·1; Cl^-, 20·6%).

6-*Chlorohexyldimethylamine hydrochloride*, prepared from thionyl chloride and 6-hydroxyhexyldimethylamine in chloroform, had m. p. 110—112° (hygroscopic) (Found: N, 6·6; Cl^-, 18·3. $C_8H_{19}NCl_2$ requires N, 7·0; Cl^-, 17·7%).

3-Chloropropyldimethylamine and 3-chloropropyldiethylamine were prepared by condensing the dialkylamine with 1-bromo-3-chloropropane in ether (Marxer, *Helv. Chim. Acta*, 1941, **24**, 209E).

4-*Chlorobutyltrimethylammonium bromide*. 1-Bromo-4-chlorobutane was added to a solution of trimethylamine in benzene. The quaternisation was carried out at 45—50° for 8 hr. and a further 24 hr. at room temperature. The quaternary *salt* had m. p. 134—136° (Found: N, 6·0. $C_7H_{17}NClBr$ requires N, 6·1%).

Thiols.—1-Mercaptoethyldimethylamine was prepared from the chloro-compound, with the thiuronium salt as intermediate, according to the method of Clinton *et al.* (*J. Amer. Chem. Soc.*, 1948, **70**, 950). The higher homologues were prepared in the same way: 3-*mercaptopropyldimethylamine* had b. p. 40—41°/12 mm., n_D^{20} 1·4666 (Found: N, 11·1. $C_5H_{13}NS$ requires N, 11·8%), and 4-*mercaptobutyldimethylamine* had b. p. 84°/35 mm., n_D^{21} 1·4677 (Found: N, 10·7. $C_6H_{15}NS$ requires N, 10·6%). 3-Mercaptopropyldiethylamine was prepared by Gilman *et al.* (*J. Amer. Chem. Soc.*, 1945, **67**, 1845).

1 : 5-*Bisdimethylamino-3-thiapentane*.—Sodium (1 g.) was dissolved in ethanol (25 ml.), in a nitrogen atmosphere, and 2-mercaptoethyldimethylamine (4·2 g.) was added. 2-Chloroethyldimethylamine hydrochloride (6·4 g.) was dissolved in a little water, and the free base was liberated by the addition of 30% sodium hydroxide solution at <0° and extracted with ether. The ethereal solution was dried (Na_2SO_4) and evaporated. The residual oil was dissolved in ethanol (20 ml.), and the solution was added to the ethanolic sodium mercaptide. Immediately a precipitate of sodium chloride was formed. The mixture was heated under reflux for 10 min. and then set aside at room temperature overnight. After removal of the precipitated sodium chloride, the filtrate was evaporated, *in vacuo*, to give a brown oil (6·9 g.). On distillation a forerun of thiol was obtained and then 1 : 5-*bisdimethylamino-3-thiapentane* as a colourless oil, b. p. 58—60°/0·15 mm., n_D^{20} 1·4757 (3·8 g., 54%) (Found: S, 18·1. $C_8H_{20}N_2S$ requires S, 18·2%).

3-*Thiapentane*-1 : 5-*bis*(*trimethylammonium Iodide*) (Ro 3-0438) (Marxer and Miescher, *loc. cit.*).—1 : 5-Bisdimethylamino-3-thiapentane (3 g.) in benzene (15 ml.) at 0° was treated with methyl iodide (5·3 g.) in benzene (15 ml.). Quaternisation started immediately but the mixture was kept for 24 hr. The quaternary salt, after drying, had m. p. 290° (decomp.) (7·9 g.). Recrystallisation from methanol gave colourless crystals, m. p. 298—300° (decomp.) (5·7 g., 73%) (Found: N, 5·7; S, 7·2. Calc. for $C_{10}H_{26}N_2SI_2$: N, 6·1; S, 6·9%).

1 : 6-*Bisdimethylamino-3-thiahexane*.—Sodium (0·9 g.) was dissolved in dry ethanol (30 ml.), in a nitrogen atmosphere, and 2-mercaptoethyldimethylamine (4·2 g.) in ethanol (5 ml.) was added, followed by 3-chloropropyldimethylamine (5 g.) in dry ethanol (15 ml.). Sodium chloride was immediately precipitated and the mixture was heated under reflux for ½ hr. The sodium chloride was filtered off and the filtrate was evaporated, *in vacuo*, to give an oil together with some solid. The oil was extracted with ether and, after evaporation of the ether, distilled to give 1 : 6-*bisdimethylamino-3-thiahexane*, b. p. 57°/0·2 mm., n_D^{21} 1·4742 (5·6 g., 74%) (Found: N, 14·9; S, 16·5. $C_9H_{22}N_2S$ requires N, 14·7; S, 16·8%).

3-*Thiahexane*-1 : 6-*bis*(*trimethylammonium Iodide*) (Ro 3-0468).—1 : 6-Bisdimethylamino-3-thiahexane (2·8 g.) in dry ether (15 ml.) at 0° was treated cautiously with methyl iodide (4·6 g.) in cold dry ether (15 ml.). Quaternisation started immediately but the mixture was kept for 15 hr. The quaternary *salt* was recrystallised from methanol, forming colourless needles (6 g., 86%), m. p. 236·5—237·5° (Found: N, 6·2; I, 53·7. $C_{11}H_{28}N_2SI_2$ requires N, 5·9; I, 53·6%).

4-*Thiapentane*-1 : 7-*bis*(*triethylammonium Iodide*) (Ro 3-0381).—(*a*) To sodium sulphide (0·8 g.) in 50% aqueous ethanol (25 ml.), 3-chloropropyltriethylammonium iodide (3·1 g.) in 50% aqueous ethanol (50 ml.) was added. The resulting solution was heated under reflux for 2 hr. After evaporation to dryness, *in vacuo*, the residue was extracted with alcohol. Evaporation and extraction with alcohol was repeated and the alcoholic solution was stored in the refrigerator. Crystals were deposited [m. p. 243—244° (decomp.)]. Recrystallised from ethanol the *di-iodide* had m. p. 257—258° (0·7 g., 25%) (Found: C, 37·1; H, 7·5. $C_{18}H_{42}N_2SI_2$ requires C, 37·8; H, 7·4%).

(*b*) Sodium (0·36 g.) in ethanol (10 ml.) was treated with diethyl-3-mercaptopropylamine (2·2 g.) in ethanol (3 ml.), and then with freshly distilled 3-chloropropyldiethylamine (2·4 g.) in nitrogen, and the whole was heated under reflux for 1 hr., filtered, and evaporated on the water-

bath *in vacuo*. The residual oil was distilled, to give 1 : 7-*bisdiethylamino*-4-*thiaheptane*, b. p. 80—81°/0·03 mm., n_D^{21} 1·4730 (3·1 g., 80%) (Found : C, 64·8; H, 12·3; N, 10·7. $C_{14}H_{32}N_2S$ requires C, 64·6; H, 12·4; N, 10·8%).

This base (1·6 g.) and ethyl iodide (1·25 ml.) in ethanol (5 ml.) were heated under reflux for 6 hr. and then set aside overnight. Crystals separated from the solution and were collected by filtration [m. p. 247—249° (decomp.); 3 g., 85%]. Two recrystallisations from propanol gave colourless crystals (1·7 g.), m. p. 256—257° (decomp.), undepressed in admixture with the product from (*a*) (Found : N, 4·7; S, 5·2. $C_{18}H_{42}N_2SI_2$ requires N, 4·9; S, 5·6%).

5-*Thianonane*-1 : 9-*bis*(*trimethylammonium Bromide*) (Ro 3-0385).—To a boiling solution of sodium sulphide (3 g.) in 50% aqueous ethanol (50 ml.) 4-chlorobutyltrimethylammonium bromide (5·8 g.) in 50% aqueous ethanol (50 ml.) was added, and heating continued for 3 hr. After evaporation of the solution to dryness, *in vacuo*, the residue was extracted with alcohol (the remaining solid was shown to be sodium chloride). Evaporation and extraction with alcohol was twice repeated and the final residue was recrystallised from alcohol with the addition of ethyl acetate, followed by ether until a turbidity appeared (yield : 2·2 g., 43%; m. p. 205—220°). Two further crystallisations gave the *dibromide* (1·3 g., 25%), m. p. 232—233°, very hygroscopic colourless plates (Found : C, 40·0; H, 8·5; S, 8·0. $C_{14}H_{34}N_2SBr_2$ requires C, 39·8; H, 8·1; S, 7·6%).

1 : 11-*Bisdimethylamino*-5-*thiaundecane*.—A solution from sodium (0·5 g.), and dry ethanol (15 ml.) was treated with 4-mercaptobutyldimethylamine (2·7 g.), in ethanol (3 ml.), in a nitrogen atmosphere and then, dropwise with occasional shaking with 6-chlorohexyldimethylamine (2·75 g.; freshly liberated from its hydrochloride) in ethanol (10 ml.). There was an immediate precipitate and the reaction was completed by heating under reflux for ½ hr. Sodium chloride was filtered off and the filtrate was evaporated *in vacuo* to give an oil containing some solid. The oil was extracted with ether and, after drying (Na_2SO_4) of the ethereal solution and evaporation, the residual oily *base* was distilled; it had b. p. 100—105°/0·2 mm. (2·8 g., 64%) (Found : N, 10·7; S, 12·2. $C_{14}H_{32}N_2S$ requires N, 10·8; S, 12·3%)

5-*Thiaundecane*-1 : 11-*bis*(*trimethylammonium Iodide*) (Ro 3-0462).—1 : 11-Bisdimethylamino-5-thiaundecane (2·5 g.) in benzene (10 ml.) at 0° was treated with methyl iodide (3·1 g.) in benzene (5 ml.) and, after 24 hr., the solid was collected and recrystallised from ethanol. A colourless micro-crystalline *salt* was obtained, having m. p. 183—185° (4·1 g., 79%) (Found : C, 34·9; H, 6·6; N, 5·2. $C_{16}H_{38}N_2SI_2$ requires C, 35·3; H, 7·0; N, 5·2%).

3 : 4-*Dithiahexane*-1 : 6-*bis*(*trimethylammonium Iodide*) (Ro 3-0426) (Renshaw *et al.*, *loc. cit.*).—2-Mercaptoethyldimethylamine (3 g.) in 5N-sodium hydroxide (5·6 ml.) was treated with iodine (4·25 g.) in aqueous potassium iodide (12 g. in 60 ml.). Making the mixture strongly alkaline with 5N-sodium hydroxide precipitated an oil which, after being taken up in ether, dried (Na_2SO_4) and recovered, distilled at 72°/0·1 mm. (2·1 g., 70%). This was treated in dry benzene (8 ml.) with methyl iodide (2 ml.), with cooling. The quaternary salt started to crystallise immediately and, next morning, was filtered off and recrystallised from methanol (yield : 4·3 g., 88%). A further recrystallisation raised the m. p. from 236° to 240° (decomp.) (Found : C, 24·5; H, 5·3; I, 51·8. Calc. for $C_{10}H_{26}N_2S_2I_2$: C, 24·4; H, 5·3; I, 51·6%).

1 : 8-*Bisdiethylamino*-4 : 5-*dithiaoctane* (Gilman *et al.*, *loc. cit.*).—*S*-3-Diethylaminopropylthiuronium chloride hydrochloride (7·6 g.) was warmed in 5N-sodium hydroxide (17·4 ml.) for 20 min. at *ca.* 90°. Iodine (3·7 g.) in potassium iodide solution was then added to the solution of the liberated thiol until free iodine remained (practically all the iodine was used). After filtration, the slight excess of iodine was removed with sodium sulphite, the disulphide extracted with ether, and the ethereal solution dried (NaOH). After removal of the ether, the residual oil (3·1 g.) was distilled; it had b. p. 130—136°/0·5 mm. (2 g., 51%) (Found : C, 57·6; H, 10·5; N, 10·4. Calc. for $C_{14}H_{32}N_2S_2$: C, 57·5; H, 11·0; N, 9·6%).

4 : 5-*Dithiaoctane*-1 : 8-*bis*(*triethylammonium Iodide*) (Ro 3-0384).—1 : 8-Bisdiethylamino-4 : 5-dithiaoctane (1 g.) in benzene (5 ml.) and ethyl iodide (1 ml.) at 45° for 3 hr. and then overnight at room temperature gave a quaternary *salt* (1 g.) which, recrystallised from ethanol, had m. p. 232° (0·85 g., 41%). Further recrystallisation raised the m. p. to 236° (Found : C, 36·0; H, 7·5; S, 10·2. $C_{18}H_{42}N_2S_2I_2$ requires C, 35·8; H, 7·0; S, 10·6%).

1 : 10-*Bisdimethylamino*-5 : 6-*dithiahexane*.—4-Mercaptobutyldimethylamine (3·9 g.) was dissolved in dilute sodium hydroxide solution, and iodine (4·9 g.) in 20% aqueous potassium iodide (100 ml.) was added. The solution was then made strongly alkaline and extracted with ether. The ethereal solution was dried (Na_2SO_4) and evaporated; the residual oily *base* had b. p. 110—112°/0·3 mm. (2·6 g., 67%) (Found : C, 54·7; H, 10·9; N, 10·4. $C_{12}H_{28}N_2S_2$ requires C, 54·5; H, 10·7; N, 10·6%).

5 : 6-*Dithiahexane*-1 : 10-*bis*(*trimethylammonium Iodide*) (Ro 3-0386).—1 : 10-Bisdimethylamino-5 : 6-dithiadecane (2·6 g.) in dry benzene (15 ml.) was treated with methyl iodide (1·8 ml.) with cooling and kept for 3 days. The product was then collected (m. p. 182—184°). Recrystallisation from alcohol gave colourless 5 : 6-*dithiadecane*-1 : 10-*bis*(*trimethylammonium iodide*), constant m. p. 198—199° (5·1 g., 95%) (Found : C, 30·5; H, 6·4; I, 45·8. $C_{14}H_{34}N_2S_2I_2$ requires C, 30·7; H, 6·3; I, 46·3%).

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