Branched-chain Thia-alkanebis(quaternary Ammonium) Salts as Ganglion-blocking Agents.

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Thia-alkanebisammonium compounds have been synthesised with chain lengths approximating to five and six carbon atoms and having one or two methyl groups attached to the chain.

IN a previous paper (*J.*, 1953, 2998), thia- and dithia-alkanebis(trialkylammonium) salts were described which showed ganglion-blocking activity. These were straight-chain compounds analogous to " Hexamethonium," with sulphur replacing a methylene group. As these sulphides could be considered as derivatives of choline, it was decided to investigate the effect on pharmacological activity of replacement of the choline by a methylcholine group. A few of these branched chain thia- and dithia-compounds have, therefore, been prepared with a methyl group in the α- or β-position to one of the nitrogen atoms. An appreciable increase in activity, as measured on the blood pressure of the cat and blocking of transmission in the cat superior cervical sympathetic ganglion, was caused by the introduction of a methyl group in the β-position. 2-Methyl-3-thiapentane-1 : 5-bis(trimethylammonium iodide) (Ro 3-0484) was found to be about twice as potent as " Hexamethonium " and slightly longer lasting (unpublished work by Drs. B. Pellmont, H. Bächtold, and L. O. Randall).

The thia-compounds were prepared by standard methods, *i.e.*, by reaction of the chloro-compound with a sodium mercaptide or sodium sulphide. The dithia-compound was prepared by oxidation of the thiol with iodine. However, when 1-chloro-2-dimethylaminopropane (Schultz and Sprague, *J. Amer. Chem. Soc.*, 1948, **70**, 48), freshly liberated at 0° from the hydrochloride (the identity of which was shown by the melting point and the melting point of its picrate), was treated with 2-mercaptoethyldimethylamine, the expected product was not obtained; the only material isolated, after quaternisation of the product with methyl iodide, was the known 2-methyl-3-thiapentane-1 : 5-bis(trimethylammonium iodide) :

$$\mathrm{Me_2N{\cdot}CHMe{\cdot}CH_2Cl + NaS{\cdot}CH_2{\cdot}CH_2{\cdot}NMe_2 \longrightarrow Me_2N{\cdot}CH_2{\cdot}CHMe{\cdot}S{\cdot}CH_2{\cdot}CH_2{\cdot}NMe_2}$$

A similar rearrangement occurred when sodium sulphide was used in the place of the mercaptide.

The ease with which 1-chloro-2-dimethylaminopropane isomerises has been demonstrated by Schultz and Sprague (*loc. cit.*) and by Ofner (*J.*, 1951, 1800) in connection with the synthesis of Amidone.

In order to synthesise the required 2 : 5-bisdimethylamino-3-thiahexane, the known 1-dimethylamino-5-hydroxy-3-thiahexane (Laskowski and Clinton, *J. Amer. Chem. Soc.*, 1947, **69**, 519) was converted into the chloride which was condensed with dimethylamine. The non-identity of the product with the compound prepared by the previous synthesis supported the view that the 1-chloro-2-dimethylaminopropane isomerised rapidly in the presence of the sodium mercaptide and reacted largely as 2-chloropropyldimethylamine.

The tertiary bisdimethylamino-compounds obtained by these reactions were quaternised with methyl and ethyl iodide.

EXPERIMENTAL

1 : 5-*Bisdimethylamino*-2-*methyl*-3-*thiapentane*.—To sodium (1·5 g.), dissolved in ethanol (50 ml.), was added 2-mercaptoethyldimethylamine (6·9 g.) in ethanol (8 ml.) in a nitrogen atmosphere. A solution of 2-chloropropyldimethylamine (8 g.) (Washington, Office of Publication Board, Dept. Commerce Report P.B. 981, p. 96) in ethanol (25 ml.) was then added dropwise. The mixture was heated under reflux for 1 hr. and then set aside for 15 hr. The precipitated sodium chloride was filtered off and the filtrate evaporated *in vacuo*. The residual *base* was

distilled, having b. p. 63°/0·2 mm., n_D^{18} 1·4783 (yield 84%) (Found: N, 15·0; S, 16·5. $C_9H_{22}N_2S$ requires N, 14·8; S, 16·9%).

This base (1·9 g.), in benzene (10 ml.), was cooled in ice, and a cold solution of methyl iodide (2·9 g.) in benzene (5 ml.) was added. The semi-solid mixture was set aside for 24 hr., after which it was diluted with ether and filtered, and the solid was washed with ether and dried. Recrystallisation from ethanol gave colourless 2-*methyl*-3-*thiapentane*-1 : 5-*bis*(*trimethylammonium iodide*), m. p. 250° (decomp.) (3·8 g., 81%). After a further recrystallisation the m. p. was 254° (decomp.) (Found: N, 6·0; S, 6·8. $C_{11}H_{28}N_2SI_2$ requires N, 5·9; S, 6·8%).

The corresponding *diethiodide* was prepared from the base (2 g.) and ethyl iodide (3·4 g.) in ethanol (10 ml.) at 75° (5 hr.) and then room temp. (2 days). After two recrystallisations from ethanol–methanol the m. p. was 248—249° (decomp.) (Found: C, 31·7; H, 6·6; N, 5·4. $C_{13}H_{32}N_2SI_2$ requires C, 31·1; H, 6·4; N, 5·6%).

2-*Methyl*-3-*thiahexane*-1 : 6-*bis*(*trimethylammonium Iodide*).—Sodium (1 g.) was dissolved in dry ethanol (30 ml.) in a nitrogen atmosphere, and 3-mercaptopropyldimethylamine (4·5 g.) in ethanol (5 ml.) was added. 2-Chloropropyldimethylamine in ethanol (15 ml.) was added dropwise, with occasional shaking, and the mixture was heated under reflux on a water-bath for 1 hr. After a further 30 min., the salt which had been precipitated was filtered off. The filtrate was evaporated and the residue was distilled *in vacuo*. The fraction, b. p. 67—69°/0·4 mm., n_D^{21} 1·4755, was collected (4·3 g., 56%). Quaternisation with methyl iodide in ether gave the *methiodide* (97%), which after two recrystallisations from ethanol–methanol had m. p. 199—200° (4·25 g., 89%) (Found: C, 29·5; H, 6·5; N, 5·1; S, 6·9. $C_{12}H_{30}N_2SI_2$ requires C, 29·5; H, 6·2; N, 5·7; S, 6·6%).

The corresponding diethiodide (prep.: 5 hr. at the b. p., overnight at room temp.), when crystallised from ethanol had m. p. 200—201° (7·3 g., 51%) (Found: C, 32·5; H, 7·0; N, 5·0. $C_{14}H_{34}N_2SI_2$ requires C, 32·6; H, 6·6; N, 5·4%).

1 : 5-*Bisdimethylamino*-2 : 4-*dimethyl*-3-*thiapentane* (Method according to Gilman *et al.*, *J. Amer. Chem. Soc.*, 1945, **67**, 1846).—Hydrated sodium sulphide ($Na_2S,9H_2O$) (30 g.) was heated at 120°, dissolving in its water of crystallisation. Hydrogen sulphide was then bubbled through the solution for several hours, until it was saturated. Nitrogen was substituted for the hydrogen sulphide, and 2-chloropropyldimethylamine (13·1 g.), freshly liberated from its hydrochloride, was added dropwise with stirring. The stirred solution was heated under reflux for 1 hr., cooled in ice, and extracted 3 times with ether. The ethereal extract was dried (Na_2SO_4), the ether evaporated, and the residual oil distilled. 2-Mercaptopropyldimethylamine distilled first, b. p. 50°/22 mm. (3·65 g.), and then 1 : 5-*bisdimethylamino*-2 : 4-*dimethyl*-3-*thiapentane*, b. p. 72—74°/0·6 mm., n_D^{22} 1·4786 (3·5 g.) (Found: N, 13·3; S, 15·6. $C_{10}H_{24}N_2S$ requires N, 13·7; S, 15·7%).

The *dimethiodide*, prepared in benzene at 0°, formed plates, m. p. 230° (decomp.), from methanol–ethanol (Found: C, 29·2; H, 6·0; N, 5·7; S, 7·1. $C_{12}H_{30}N_2SI_2$ requires C, 29·5; H, 6·2; N, 5·7; S, 6·6%).

2 : 5-*Dimethyl*-3 : 4-*dithiahexane*-1 : 6-*bis*(*trimethylammonium Iodide*) (cf. Renshaw *et al.*, *ibid.*, 1938, **60**, 1765).—Iodine (4·2 g.) dissolved in aqueous potassium iodide (12 g. in 60 ml.) was added, with water cooling, to 2-mercaptopropyldimethylamine (3·6 g.) dissolved in 5N-sodium hydroxide (6 ml.). The colourless mixture was made alkaline with sodium hydroxide solution and extracted 4 times with ether. The ethereal solution was dried (Na_2SO_4) and, after filtration, the ether was evaporated to give an oil (3·1 g.). This was dissolved in dry ether (10 ml.) and cooled in ice. Methyl iodide (4·1 g.), in dry ether (10 ml.), was added and the mixture was allowed to warm to room temperature. The solid quaternary salt which had separated was collected by filtration and dried. After two (or more) recrystallisations from ethanol–methanol, it had m. p. 223° (decomp.) (2·45 g.) (Found: C, 27·3; H, 5·8; N, 5·5. Calc. for $C_{12}H_{30}N_2S_2I_2$ (C, 27·7; H, 5·8; N, 5·4%). Renshaw *et al.* (*loc. cit.*) give m. p. 207—208° (decomp.).

Attempted Preparation of 3-*Thiahexane*-1 : 5-*bis*(*trimethylammonium Iodide*).—1-Chloro-2-dimethylaminopropane was liberated from the hydrochloride (13 g.), m. p. 102—104° (Schultz and Sprague, *J. Amer. Chem. Soc.*, 1948, **70**, 48), at 0° with 30% sodium hydroxide solution. The oil was separated and the aqueous layer was extracted twice with ether. The oil and the ethereal solution were combined and set aside in the refrigerator while drying (KOH). After filtration, the ether was evaporated *in vacuo* at room temperature. 1-Chloro-2-dimethylaminopropane (8 g.) remained as an oil.

Sodium (1·55 g.) was dissolved in ethanol (48 ml.), and 2-mercaptoethyldimethylamine (7·1 g.) in dry ethanol (8 ml.) was added in a nitrogen atmosphere. Then the chloro-amine (8 g.) in ethanol (20 ml.) was added dropwise with shaking. Sodium chloride was precipitated immediately. The mixture was heated under reflux for ½ hr. and, after cooling, filtered, and the filtrate was evaporated *in vacuo*. The residual oil was distilled, having b. p. 69°/0·05 mm., n_D^{20} 1·4768 (8·2 g., 66%) (Found : N, 15·0; S, 16·5. Calc. for $C_9H_{22}N_2S$: N, 14·7; S, 16·8%). Its picrate had m. p. 137—140°, not depressed in admixture with the picrate of 1 : 5-bisdimethylamino-2-methyl-3-thiapentane. The methiodide, prepared in benzene, after two recrystallisations from methanol had m. p. 253—254° (decomp.), undepressed in admixture with 2-methyl-3-thiapentane-1 : 5-bis(trimethylammonium iodide), m. p. 254° (decomp.) (Found : C, 28·0; H, 6·0; N, 5·2. Calc. for $C_{11}H_{28}N_2SI_2$: C, 27·9; H, 6·0; N, 5·9%). The picrates derived from these two samples of methiodide had the same m. p. (231°) and there was no depression of the m. p. when they were mixed.

5-*Chloro*-1-*dimethylamino*-3-*thiahexane Hydrochloride*.—Thionyl chloride (9·5 ml.) in dry chloroform (25 ml.) was added during 1½ hr. to a stirred solution of 1-dimethylamino-5-hydroxy-3-thiahexane (20 g.) (Laskowski and Clinton, *loc. cit.*) in dry chloroform (60 ml.) at −30°. The solution was then stirred for 1 hr. at room temperature, heated under reflux for a further hour, and allowed to cool before addition of dry ether (300 ml.). The flocculent precipitate of needles was collected and recrystallised from ethanol–ethyl acetate by addition of ether; this *salt* had m. p. 95·5° (19 g., 71%) (Found : N, 5·9; S, 14·5. $C_7H_{17}NSCl_2$ requires N, 6·4; S, 14·7%). The free base, liberated from the hydrochloride, had b. p. 50—51°/0·18 mm., n_D^{22} 1·4875.

1 : 5-*Bisdimethylamino*-3-*thiahexane*.—5-Chloro-1-dimethylamino-3-thiahexane (8 g.), freshly liberated from the hydrochloride, 5N-sodium hydroxide (9 ml.), and 28% w/v aqueous dimethylamine (9 ml.) were mixed and shaken for 16 hr. The oily layer was separated and the aqueous layer was extracted with ether. When the ethereal extract and the oil were combined, part of the oil remained undissolved and was washed out with water. The ethereal solution was dried (Na_2SO_4) and evaporated and the residual *base* distilled (b. p. 40—2°/0·1 mm., $n_D^{21·5}$ 1·4735; 3·6 g., 43%) (Found: N, 15·1; S, 17·1. $C_9H_{22}N_2S$ requires N, 14·7; S, 16·8%). The picrate, prepared in alcohol, had m. p. 125°.

Reaction with methyl iodide in ether at 0° was rapid. After 3 days at room temp. the *dimethiodide* was filtered off. Recrystallised twice from methanol, it had m. p. 238—240° (decomp.) (47%) (Found : C, 27·6; H, 5·9; N, 5·8. $C_{11}H_{28}N_2SI_2$ requires C, 27·9; H, 6·0; N, 5·9%). The picrate had m. p. 211—211·5°.

The *diethiodide*, prepared in boiling ethanol (5 hr.) and recrystallised twice from ethanol, had m. p. 203—204° (47%) (Found : C, 30·7; H, 6·4; N, 5·3. $C_{13}H_{32}N_2SI_2$ requires C, 31·1; H, 6·4; N, 5·6%).

Attempted Preparation of 1 : 5-*Dimethyl*-3-*thiapentane*-1 : 5-*bis*(*trimethylammonium Iodide*).—By the method given for the preparation of 1 : 5-bisdimethylamino-2 : 4-dimethyl-3-thiapentane, but by treating the sodium sulphide with 1-chloro-2-dimethylaminopropane (16·6 g.), an oil was obtained which, on distillation, gave a thiol (1·5 g.), b. p. 46°/12 mm., and also an oil (6·2 g.), b. p. 59—63°/0·2 mm., $n_D^{20·5}$ 1·4786. The methiodide, prepared from the latter in benzene in good yield and recrystallised from methanol–ethanol, had m. p. 230—231° (decomp.), and there was no depression in admixture with the 2 : 4-dimethyl compound of m. p. 229—230° (decomp.). Also, the picrate from the methiodide had m. p. 213—215° (decomp.) and there was no depression of this m. p. in admixture with the picrate of the 2 : 4-dimethyl compound of m. p. 212—214° (decomp.).

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