ACTA CHEMICA SCANDINAVICA 10 (1956) 15—19

Bifunctional Amines and Ammonium Compounds

V*. Bis-trialkylammoniumethyl Disulfides, Sulfoxides, and Sulfones

JØRGEN FAKSTORP

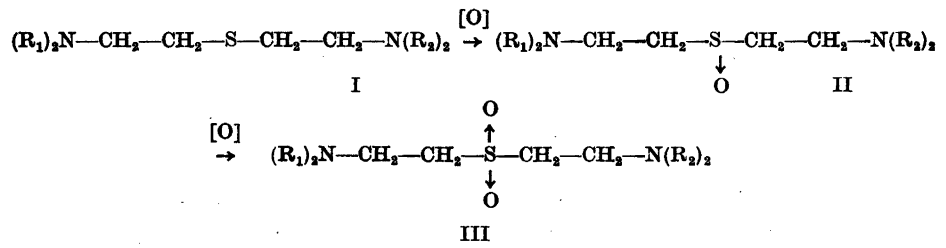
Aktieselskabet Pharmacia, Copenhagen V., Denmark

Oxidized derivatives of bis-alkylammonium sulfides were obtained by oxydation of the *tert.* thiols and sulfides with iodine and bromine water, followed by alkylation. The oxidation with acid or alkaline permanganate gave the expected *tert.* sulfones. However, the quaternization gave products which, most probably, were *1,1-dioxy-4,4-dialkylthiazanium salts.*

In continuation of work concerning the relation between structure and neuropharmacological activity within a series of simple "bolaform" [1] bis-onium salts containing a hetero atom in the alkylene chain, several substances containing an oxidized sulfur function have been prepared for pharmacological evaluation.

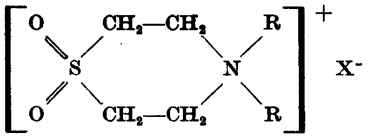
Bis-quaternary ammoniumalkyl sulfoxides and sulfones were available through the corresponding bis-chloro derivatives as described by Lawson and Reid [2] (*cf.*, however, Alexander and McCombie [3]) but in the work described here these types of substances were obtained starting from the corresponding bis-*tert.* aminoalkyl sulfides [4], by oxidation in acid solution with hydrogen peroxide, potassium permanganate or bromine water by conventional procedures[5].

Three sulfoxides were prepared and transformed to the six bis-quaternary salts containing only methyl and ethyl substituents at the nitrogen.



* Part IV. *Acta Chem. Scand.* 8 (1954) 350.

The alkylation of the sulfones to the quaternary ammonium salts met with unexpected difficulties. The products obtained could only in a single instance be purified to correct analysis. The main product of the reaction gave analytical values which were much better in accord with a ring closed product, 1,1-dioxy-4,4-dialkylthiazanium halide (IV).



IV

The appearance of this product is explained in terms of an intramolecular alkylation by a carbonium ion resulting from a cleavage of trialkylamine from normally formed monoquaternary sulfone,

$$(R_1)_2N—CH_2—CH_2—SO_2—CH_2—CH_2—N^+(R_2)_2R_3 \rightarrow$$

$$(R_1)_2N—CH_2—CH_2—SO_2—CH_2—CH_2\oplus + (R_2)_2NR_3 \rightarrow \text{IV}$$

The product obtained might also have been a trialkylammonium vinyl sulfone (V).

$$R_3(R_1)_2N^+—CH_2—CH_2—SO_2—CH=CH_2$$

None of the addition reactions expected are shown by the product obtained. It is also difficult to account for the appearance of the same salt from different starting products in terms of a vinyl sulfone. This appearance necessitates a retention of the N-alkyl substituents present in the original sulfone, while the vinyl sulfone salt should contain N-alkyl substituents of which at least one originated from the alkylating agent.

A dioxy-thiazanium salt (IV) should also result if a dioxy-thiazane was quaternized. The formation of dioxy-thiazane directly from the bis-*tertiary* sulfone is less easy to explain, although some earlier observations support it (see Lawson and Reid [2]). However, this route would also require thiazanium salts (IV) containing both ethyl and methyl at nitrogen. Such products have not been observed.

The four disulfide salts were obtained by the quaternization of bis-2-dimethylaminoethyl disulfide (*cf.* Andrews, Bergel and Morrison [9]) and bis-2-diethylaminoethyl disulfide which in turn resulted either from the corresponding sodium mercaptides by oxidation with iodine (*cf.* Gilman *et al.*[6]) or from iodine oxidation of the sodium aminoalkyl thiosulfates (Bunte salts) according to Bretschneider [7] (*cf.* Westlake and Dougherty [8], and also Peak and Watkins [5]).

Unfortunately no method is available for the preparation of "asymmetric" disulfides, a type of compound which would be of considerable pharmacological interest.

A report on the pharmacology of the compounds reported in this paper will appear elsewhere.

EXPERIMENTAL *

Bis-2-dimethylaminoethyl sulfoxide (II, $R_1 = R_2 = CH_3$)

The bis-hydrobromide was obtained according to Peak and Watkins [5] by oxidation of 17.6 g (0.1 mole) of bis-2-dimethylaminoethyl sulfide dissolved in 75 ml of water with 20 (approx. 0.2 mole) of bromine dissolved in 1 000 ml of water and 1 500 ml of 99 % ethanol. The evaporation residue was dissolved in 1 500 ml of 99 % ethanol containing 75 ml of water. Upon cooling the *bis-hydrobromide* separated. Yield 29 g (85 %), m. p. 215° C. (Found: Br 44.75. Calc. for $C_8H_{22}N_2SOBr_2$ (354.1): Br 45.13). It was not possible to isolate the free sulfoxide in a pure form neither from the bis-hydrobromide nor by oxidation of sulfide with hydrogen peroxide (v. s.) owing to decomposition of the free base during distillation.

The *bis-methoiodide* (As-7366) was obtained from 14.5 g (0.042 mole) of the bis-hydrobromide dissolved in 50 ml of anhydrous ethanol in which 1.94 g of sodium (0.084 mole) were previously dissolved. After removal of sodium bromide, 8 g of methyl iodide was added to the solution and this mixture kept overnight. There was obtained 12.5 g (64 %) of bis-methoiodide, m. p. 230–233° C (decomp.) (from methanol-water 5:1). (Found: I 53.19. Calc for $C_{10}H_{26}N_2SOI_2$ (476.2): I 53.30).

Bis-ethobromide (As-7367) obtained in like fashion from 14.5 g of the bis-hydrobromide and 11 g of ethyl bromide. Yield 11 %, m. p. 205–208° C (diss. methanol, reprecipitd. ether). (Found: Br 38.81. Calc. for $C_{12}H_{30}N_2SO\ Br_2$ (410.3): Br 38.96).

Bis-2-diethylaminoethyl sulfoxide (II, $R_1 = R_2 = C_2H_5$)

Bis-2-diethylaminoethyl sulfide, 11.6 g (0.05 mole) was mixed with 50 ml of water and then added to a cooled mixture of 8.4 g of 30 % hydrogen peroxide and 12 ml of concentrated hydrochloric acid in 70 ml of methanol. The volume was made up to 200 ml with water and the mixture allowed to stand at room temperature for two days. The contents were made strongly alkaline with sodium hydroxide solution, extracted with ether after supersaturation with sodium chloride, the ether extract dried over potassium carbonate, the ether removed through a 30 cm Vigreux column. The residue distils under evolution of a gas. There was obtained 9.5 g (78 %) of a deeply yellow oil, b. p. 148–149° C at 1 mm Hg. (Found: C 57.14; H 11.30; N 11.20. Calc. for $C_{12}H_{28}N_2SO$ (248.4): C 58.01; H 11.36; N 11.30).

Bis-methoiodide (As-7432) obtained at room temperature as previously described from base and an excess of methyl iodide in acetone containing ethanol. Yield 38 %, m. p. 235–238° C (decomp.) (from ethanol-water 5:1). (Found: N 5.31; I 46.48. Calc. for $C_{14}H_{34}N_2SOI_2$ (532.3): N 5.46; I 47.71).

Bis-ethobromide (As-7490). From 2.48 g (0.01 mole) of sulfoxide and 2.78 g of ethyl bromide in 25 ml of acetone containing 5 ml of ethanol. Yield 3.5 g (75 %), m. p. 211° C (acetone-methanol 2:1). (Found: Br 35.17. Calc. for $C_{16}H_{38}N_2SOBr_2$ (466.3): Br 34.29).

Bis-(2-dimethyl-2′-diethyl)-aminoethyl sulfoxide (II, $R_1 = CH_3$; $R_2 = C_2H_5$)

A bis-hydrobromide was prepared from 20.4 g of the corresponding sulfide. Yield 31 g (81 %), m. p. 210–212° C. (Found: Br 41.92. Calc. for $C_{10}H_{26}N_2SO\ Br_2$ (382.2): Br 41.81). The free base decomposed upon treatment of the hydrobromide with alkali and was not obtained pure.

Bis-methoiodide (As-7588). From the bis-hydrobromide in ethanol-sodium ethylate. Yield 59 %, m. p. 223–224° C (ethanol-water 5:1). (Found: I 50.55. Calc. for $C_{12}H_{30}N_2SOI_2$ (504.4): I 50.32).

* All melting points and boiling points are uncorrected. The nitrogen and halogen values are semi-micro determinations by Mrs. G. Speggers of this laboratory. Carbon and hydrogen values are micro determinations by Messrs. W. Egger and A. Grossmann, University of Copenhagen.

Bis-ethobromide (As-7589). The reaction was carried out in a sealed glass tube at 100° C for 3 hours. Yield 36 %, m. p. 163–170° C (methanol). (Found: Br 38.34. Calc. for $C_{14}H_{32}N_2SOBr_2$ (438.3): Br 36.46).

Bis-2-dimethylaminoethyl sulfone (III, $R_1 = R_2 = CH_3$)

The bis-hydrochloride prepared according to Peak and Watkins [5] by permanganate oxidation in acetic acid solution *. Yield 41 % m. p. 245–247° C (from ethanol-methanol-water 10:5:3). (Found: Cl 25.27. Calc. for $C_8H_{22}N_2SO_2Cl_2$ (281.3): Cl 25.21).

Bis-methoiodide (As-7696) directly from the bis-hydrochloride. Yield 30 %, m. p. 268–272° C (decomp.) (from dilute ethanol). (Found: I 49.37. Calc. for $C_{10}H_{26}N_2SO_2I_2$ (492.2): I 51.56). Another product is isolated by the fractional crystallization, m. p. 294° C, apparently a ring-closed product, *1,1-dioxy-4,4-dimethylthiazanium iodide* (IV, R = CH_3). (Found: I 44.13. Calc. for $C_6H_{14}NSO_2I$ (291.2): I 43.58).

1,1-dioxy-4,4-dimethylthiazanium bromide (IV, R = CH_3). Directly from the bis-hydrochloride. Yield approx. 10 %; m. p. 320° C (decomp.). (Found: C 29.35; H 5.77; Br 32.50. Calc. for $C_6H_{14}NSO_2Br$ (244.1): C 29.53; H 5.78; Br 32.73). It was not possible to secure any of the desired bis-ethobromide.

Bis-2-diethylaminoethyl sulfone (III, $R_1 = R_2 = C_2H_5$)

2-Diethylaminoethyl sulfide (23.8 g) dissolved in a stirred solution of 11.8 g of concentrated sulfuric acid in 150 ml of water was cooled to room temperature and a solution of 21.1 g of potassium permanganate was added at a rate sufficient to keep the mixture at a temperature of approximately 60° C. After one night the mixture is made strongly alkaline, the precipitate removed by suction on a layer of Theorit, the mixture extracted continuously with 400 ml of ether for 12 hours in a *Kutscher-Steudel* extractor, the ether extract dried over potassium carbonate and the bis-hydrochloride precipitated by addition of dry HCl gas. Yield 16.7 g (50 %), m. p. 204° C (Ref.[5] reports 202° C). (Found: Cl 21.10. Calc. for $C_{12}H_{30}N_2SO_2Cl_2$ (337.4): Cl 21.11). The free base decomposes when distilled or even by being kept in alkaline solution.

1,1-dioxy-4,4-diethylthiazanium iodide (IV, R = C_2H_5). Directly from an aliquot part of the ether extract by dilution with acetone and addition of a 50 % excess of methyl iodide. Yield 35 %, m. p. 225–227° C (dilute ethanol). (Found: I 39.83. Eq. w. (perchloric acid titration) 312. Calc. for $C_8H_{18}NSO_2J$ (319.2): I 39.76). None of the desired open chain methoiodide was ever isolated in numerous experiments.

1,1-dioxy-4,4-diethylthiazanium bromide (IV, R = C_2H_5). Prepared in similar fashion. Yield 11 %, m. p. 234° C (from dilute ethanol). (Found: Br 28.85. Calc. for $C_8H_{18}NSO_2Br$ (272.2): Br. 29.32).

Bis-(2-dimethyl-2'-diethyl)-aminoethyl sulfone (III, $R_1 = CH_3$, $R_2 = C_2H_5$).

A *bis-hydrochloride* prepared from 20.4 g of bis-(2-dimethyl-2'-diethyl)-aminoethyl sulfide was obtained by alkaline permanganate oxidation in a yield of 12 g (40 %), m. p. 250° C (from dilute ethanol). (Found: Cl 22.96. Calc. for $C_{10}H_{26}N_2SO_2Cl_2$ (309.4): Cl 22.96.)

Attempts to prepare the bis-methoiodide and the bis-ethobromide resulted in the above mentioned 1,1-dioxy-4,4-diethylthiazanium halides.

* There is an error in Peak's and Watkins' [5] experimental description. The amount of permanganate used should be three times higher.

Bis-2-dimethylaminoethyl disulfide

a) From 18.0 g (0.171 mole) of 2-dimethylaminoethane thiol according to the procedure of Gilman *et al.*[6]. Yield 11.3 g (32 %) of faintly yellow, pungent smelling liquid, b. p. 136—138° C at 18—20 mm Hg. (Found: C 45.88; H 9.47; N 13.00. Calc. for $C_8H_{20}N_2S_2$ (208.4): C 46.10; H 9.65; N 13.44).

b) From 36 g of the hydrochloride of 2-dimethylaminoethyl chloride was obtained 9.0 g (17 %) of sodium 2-dimethylaminoethyl thiosulfate, m. p. 152° C (from ethanol), following the procedure of Peak and Watkins[5]. (Found: N 6.73. Calc. for $C_4H_{10}O_3S_2NNa$ (207.3): N 6.77). The thiosulfate decomposes when exposed to moist air, presumably under formation of disulfide.

This product, 5.2 g (0.025 mole), dissolved in 90 ml of 1 % hydrochloric acid and treated with excess iodine according to Bretschneider [7] gave 2.7 g (42 %) of the disulfide, b. p. 134° C at 12 mm Hg. (Found: N 13.36. Calc. N 13.44). It was not possible to obtain the disulfide from the thiosulfate *in situ*.

Bis-methoiodide (As-11032). Yield 85.2 %, m. p. 238—240° C (washed with acetone). (Found: I 51.32. Calc. for $C_{10}H_{26}N_2S_2I_2$ (492.3): I 51.55).

Bis-ethobromide (As-11031). Yield 86.6 %, m. p. 237° C (from ethanol). (Found: Br 36.16. Calc. for $C_{10}H_{26}N_2S_2Br_2$ (426.4): Br 37.48).

Bis-2-diethylaminoethyl disulfide

Obtained in 37 % yield by the mercaptide-iodine procedure, b. p. 172° C at 12 mm Hg (Gilman *et al.* [6] report 155—160° C at 20 mm Hg). From the original alcoholic oxidation mixture a precipitate is secured which upon crystallization from dilute ethanol melts at 197° C and has been shown to be a *bis-hydroiodide*. (Found: N 5.34; I 47.36. Calc. for $C_{12}H_{30}S_2N_2I_2$ (530.3): N 5.38; I 48.78). This is obtained in amounts corresponding to 18 % free sulfide.

The total yield obtained *via* the thiosulfate route (*cf.* Bretschneider [7]) was 68 %. The disulfide could not be obtained directly from the thiosulfate reaction mixture.

Bis-methoiodide (As-8872). Yield 83 %, m. p. 208—210° C (from acetone-methanol 2:1). (Found: I 47.26. Calc. for $C_{14}H_{34}S_2N_2I_2$ (548.4): I 46.31).

Bis-ethobromide (As-8802). Yield 37 %, m. p. 215° C (from acetone-methanol 2:1). (Found: Br 33.76.) Calc. for $C_{12}H_{30}S_2N_2I_2$ (520.5): Br 33.16).

Acknowledgement: The technical assistance of Miss Jytte Christiansen is gratefully acknowledged.

REFERENCES

1. Fuoss, R. M. and Edelson, D. *J. Am. Chem. Soc.* **73** (1951) 269.
2. Lawson, W. E. and Reid, E. E. *Ibid.* **47** (1925) 2821.
3. Alexander, J. R. and McCombie, H. *J. Chem. Soc.* **1931** 1913.
4. Fakstorp, J. and Christiansen, J. *Acta Chem. Scand.* **8** (1954) 346.
5. Peak, D. A. and Watkins, T. I. *J. Chem. Soc.* **1951** 3292.
6. Gilman, H., Plunkett, M. A., Tolman, L., Fulhart, L. and Broadbent, H. S. *J. Am. Chem. Soc.* **67** (1945) 1846.
7. Bretschneider, H. *Österr. Akad. Wiss. Math. naturw. Klasse Sitzber. Abt. II b* **159** (1950) 385.
8. Westlake, H. E. Jr. and Dougherty, G. *J. Am. Chem. Soc.* **64** (1942) 149.
9. Andrews, K. J. M., Bergel, F. and Morrison, A. L. *J. Chem. Soc.* **1953** 2998.

Received September 13, 1955.