SOME SYMMETRIC α-AMINOACETYL DERIVATIVES OF 4,4'-DIAMINODIPHENYLSULFONE.

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At present 4,4'-diaminodiphenylsulfone and some of its hydrosoluble mono- and bi-substituted derivatives are used to a large extent in the treatment of leprosy. Whereas the lepromatous and tuberculoid forms react more or less satisfactorily when submitted to treatment by these drugs, there remains one form, which, complicated by neurologic symptoms, generally does not respond to this therapy. Although the intermediary metabolism of 4,4'-diaminodiphenylsulfone is not yet completely investigated, a certain specific organotropism may be assumed as the reason wherefore this substance fails to penetrate the perineural tissue. Eventually this may be the cause of the negative results observed when this form is submitted to sulfone therapy.

This paper deals with the preparation of some N-substituted derivatives of 4,4'-diaminodiphenylsulfone made by introduction of some radicals, the presence of which is responsible for characteristic physiological activities of other substances. By this way the hypothetic organotropism, mentioned above, may be modified.

Six new compounds were obtained by symmetric substitution of the alkyl-chlorine atoms of 4,4'-(bis-α-chloracetylamino-)diphenylsulfone by four secondary and two tertiary amines. Similar mono-substituted compounds have been prepared by Knüsli (1), who used them as intermediates for the synthesis of amino-alkyl derivatives of 4,4'-diaminodiphenylsulfone and which possess a cardiotonic activity.

4,4'-(bis-α-chloracetylamino-)diphenylsulfone was prepared by direct condensation of 4,4'-diaminodiphenylsulfone with monochloracetic acid, using phosphorus oxychloride as a dehydrating agent. The procedure was similar to that which has been developed in this Laboratory by Berti and Ziti (2). The resulting compound was condensed with diethylamine, di-n-butylamine, morpholine and piperidine, yielding respectively:

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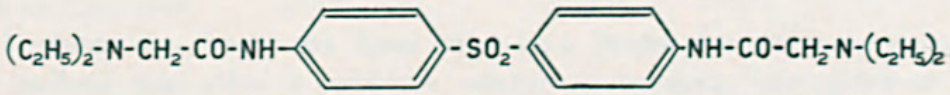
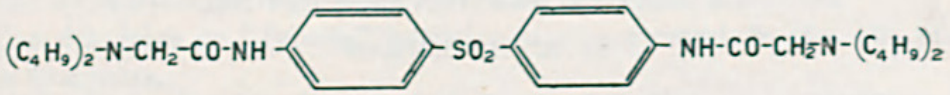
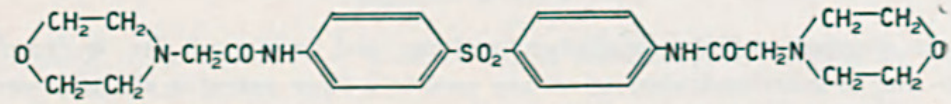


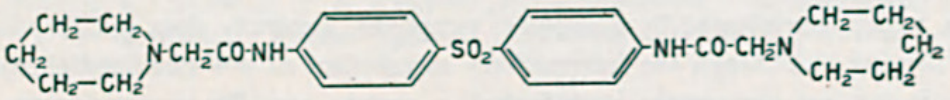
4,4'-(bis-α-diethylaminoacetylamino-)diphenylsulfone (I)



4,4'-(bis-α-di-n-butylaminoacetylamino-)diphenylsulfone (II)



4,4'-(bis-α-N-morpholineacetylamino-)diphenylsulfone (III)

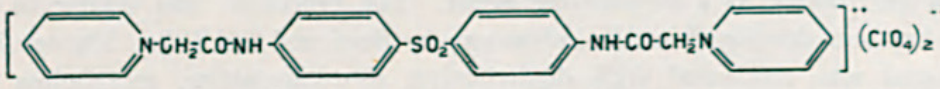


4,4'-(bis-α-N-piperidineacetylamino-)diphenylsulfone (IV)

These substances, obtained in good yields, are liposoluble. Similar derivatives of aniline and substituted anilines, which possess an antipyretic or local-anesthetic activity, have been described by Majert (3), Gaind and Vohra (4), Löfgren and Lindqvist (5) and Büchi, Lauener, Ragaz, Böniger and Lieberherr (6).

The compounds of the second type resulted from the same symmetrical substitution of the alkyl-chlorine atoms of 4,4'-(bis-α-chloracetylamino-)diphenylsulfone by trimethylamine and pyridine respectively. By this way derivatives of 4,4'-diaminodiphenylsulfone, which are quarternary salts of ammonium, were obtained. They are:

4,4'-diaminodiphenylsulfone-N,N'-bis-(carboxymethylene-trimethylammonium chloride or perchlorate) (V)



4,4'-diaminodiphenylsulfone-N,N'-bis-(carboxymethylene-pyridinium perchlorate) (VI)

The chloride of the first substance is hygroscopic and its aqueous solution after some days reveals the odor of trimethylamine. Although it could be

used for pharmacological tests, difficulties in purification, manipulation and melting-point determination suggested the isolation of the base as its perchlorate, according to Hofmann (7), Strack and Hentsch (8). This salt has no pronounced hygroscopicity, is slightly soluble in water and could be purified without decomposition. The pyridinium salt could only be obtained as its perchlorate, because the chloride is so hygroscopic that it could not be isolated.

EXPERIMENTAL

*4,4'-(bis-α-chloracetylamino-) diphenylsulfone**).- In a porcelain dish 24.8 g. of 4,4'-diaminodiphenylsulfone (0.1 M) were mixed with 30 g. of monochloracetic acid (0.31 M) and warmed on the water-bath to 80°, until the sulfone dissolved completely in the excess of acid. After cooling, 16 g. of phosphorus oxychloride (0.1 M) were slowly added under constant manual stirring, which was continued until a semisolid mass was formed. This was warmed on the water-bath until the evolution of hydrogen chloride ceased. In order to dissolve the metaphosphoric acid formed and to remove the excess of monochloracetic acid, the product was ground in a mortar in presence of cold water, filtered and thoroughly washed. The crude, white substance was dried and yielded 31 g. (77%). It is insoluble in water, ethanol and ether, being slightly soluble in acetic acid and aqueous acetone. After six recrystallizations from aqueous acetone, the white, prismatic crystals had a constant melting point of 200.7 — 200.8°.**)

ANAL. Calculated for $C_{16}H_{14}O_4N_2Cl_2S$: N, 6.99%. Found N, 7.17%.

I. — *4,4'-(bis-α-diethylaminoacetylamino-)diphenylsulfone.* — A mixture of 9 g. of 4,4'-(bis-α-chloracetylamino-)diphenylsulfone (0.022 M) and a solution of 8 g. of diethylamine (0.11 M) in 150 ml. of 60% aqueous ethanol was refluxed for six hours. The resulting, homogen solution was treated with active charcoal and filtered. On cooling, colourless, prismatic needles crystallized, yielding 9 g. (84%). After five recrystallizations from ethanol a constant melting point of 151.2 — 152.6° was obtained***)

ANAL. Calculated for $C_{24}H_{34}O_4N_4S$: N, 11.8%. Found N, 11.84%.

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* This substance has already been described, however the melting points are different. So Powell, Shonle and Van Arendonk (9) report 185-186°, Ganapathi, Delivala and Rajagopalan (10) 191-192°.

** All melting point determinations reported in this paper were carried out with Anschütz thermometers.

*** The substance is soluble in hot peanut-oil.

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II. — *4,4'-(bis-α-di-n-butylaminoacetylamino-)diphenylsulfone.* — To a solution of 14 g. of di-n-butylamine (0.11 M) in 100 ml. of ethanol were added 10 g. of 4,4'-(bis-α-chloracetylamino-)diphenylsulfone (0.025 M). The mixture was refluxed for 30 minutes, when complete solution occured. After boiling for more 30 minutes, the solution was treated with active charcoal and filtered. White, rectangular leaflets crystallized on cooling, which after filtration were thoroughly washed with cold water. The yield was 8 g. (54%). After four recrystallizations from ethanol they melted at 150.8 — 151.6°.*)

ANAL. Calculated for $C_{32}H_{50}O_4N_4S$: N, 9.54%. Found N, 9.70%.

III. — *4,4'-(bis-α-N-morpholineacetylamino-)diphenylsulfone.* — A mixture of 10 g. of 4,4'-(bis-α-chloracetylamino-)diphenylsulfone (0.025 M) and a solution of 10 g. of morpholine (0.11 M) in 100 ml. of 50% aqueous ethanol was refluxed for one hour, when the starting material dissolved completely. On further heating for half an hour, white crystals formed, which, after filtration from the cold solution, yielded 9.4 g. (75%). After six recrystallizations from ethanol, the colourless, tetragonal leaflets had a constant melting point of 242.4 — 243.6°.*)

ANAL. Calculated for $C_{24}H_{30}O_6N_4S$: N, 11.14%. Found N, 11.23%.

IV. — *4,4'-(bis-α-N-piperidineacetylamino-)diphenylsulfone.* — In a solution of 8 g. of piperidine (0.9 M) in 100 ml. of ethanol were suspended 10 g. of 4,4'-(bis-α-chloracetylamino-)diphenylsulfone (0.025 M). After heating the mixture for five minutes, the starting material has dissolved completely and ten minutes later white crystals began to form. After cooling, the crude product was filtered and dried, yielding 9.5 g. (75%). Five recrystallizations from ethanol gave white prismatic crystals, which melted at 244.6 — 246.6°.*)

ANAL Calculated for $C_{26}H_{34}O_4N_4S$: N, 11.23%. Found N, 11.1%.

V. — *4,4'-diaminodiphenylsulfone-N,N'-bis-(carboxymethylene-trimethylammonium salts).*

Chloride. — In a pressure flask, 100 g. of finely ground 4,4'-(bis-α-chloracetylamino-)diphenylsulfone (0.25 M) were mixed with 300 ml. of an ethanolic solution of trimethylamine at 27% by weight (1.2 M). This suspension was diluted with 150 ml. of water and shaked on a machine. After 6 hours the starting material dissolved completely. Shaking was continued for additional 18

* The substance is soluble in hot peanut-oil

hours. The solution was concentrated on the water-bath, the excess of trimethylamine being evaporated simultaneously. The resulting viscous solution was poured into 1,000 ml. of acetone, in which by some manual stirring with a glass rod, a white semisolid mass separated. By filtration, 140 g. of a white, amorphous and extremely hygroscopic product was obtained, which immediately was dissolved in 140 ml. of water, treated with active charcoal, filtered and added to 1,000 ml. of acetone. On standing overnight in an ice-box, a good precipitation resulted. The product, filtered and dried over sulfuric acid, yielded 84 g. (65%). The salt lost trimethylamine at 260° and did not melt until 280°.

ANAL. Calculated for $[C_{22}H_{32}O_4N_4S]^{++}Cl_2^{--}$: N, 10.79%. Found N, 10.4%. *)

Perchlorate. — To a solution of 80 g. 4,4'-diaminodiphenylsulfone-N,N'-bis(carboxymethylene-trimethylammonium chloride) in 150 ml. of cold water, a 70% solution of perchloric acid was added until complete precipitation. The white crystals were filtered and washed with cold water and afterwards purified by recrystallization from boiling water. The yield was 60 g. (35%). After five recrystallizations from water the prismatic crystals melted at 262.8 — 263.8° with decomposition.

ANAL. Calculated for $[C_{22}H_{32}O_4N_4S]^{++}(ClO_4)_2^{--}$: N, 8.65%. Found N, 8.51%.

VI. — *4,4'-diaminodiphenylsulfone-N,N'-bis-(carboxymethylene-pyridinium perchlorate)*. To a suspension of 20 g. of 4,4'-(bis-α-chloracetylamino-)diphenylsulfone (0.05 M) in 160 ml. of dry methanol were added 46.7 g. of pyridine (0.6 M). The mixture was refluxed on the water-bath and after 2 hours the starting material has dissolved, the solution being heated for more 3 hours and filtered while hot. When cold, 500 ml. of ether were added, causing a good precipitation. After filtration, the yellowish, semisolid and very hygroscopic mass was dissolved in 100 ml. of water. The solution was filtered and concentrated in vacuo, in order to remove all remaining pyridine. The resulting, viscous liquid was redissolved in 200 ml. of water, the solution being purified by active charcoal and filtered. A 70% solution of perchloric acid was added until complete precipitation. After filtering and washing with cold water, a yield of 16 g. (47%) was obtained. The white leaflets after five recrystallizations from boiling water melted at 280.0 — 282.6° with decomposition.

ANAL. Calculated for $[C_{26}H_{24}O_4N_4S]^{++}(ClO_4)_2^{--}$: N, 8.15%. Found N, 8.27%.

* Better analytical results could not be obtained, in view of the instability of the substance.

SUMMARY

The synthesis of 4,4'-(bis-α-chloracetylamino-)diphenylsulfone is described. This was condensed with

a) four secondary amines, being obtained 4,4'-(bis-α-diethylaminoacetylamino-)diphenylsulfone, 4,4'-(bis-α-di-n-butylaminoacetylamino-)diphenylsulfone, 4,4'-(bis-α-N-morpholineacetylamino-)diphenylsulfone and 4,4'-(bis-α-N-piperidineacetylamino-)diphenylsulfone.

b) trimethylamine and pyridine, resulting respectively 4,4'-diaminodiphenylsulfone-N,N'-bis-(carboxymethylene-trimethylammonium chloride or perchlorate) and 4,4'-diaminodiphenylsulfone-N,N'-bis-(carboxymethylene-pyridinium perchlorate). These new derivatives of 4,4'-diaminodiphenylsulfone may have some influence upon the neurologic forms of leprosy.

RESUMO

Descreve-se a sintese da 4,4'-(bis-α-cloroacetilamino-)difenilsulfona. Esta foi condensada com

a) quatro aminas secundarias, obtendo-se: 4,4'-(bis-α-dietilaminoacetilamino-)difenilsulfona, 4,4'-(bis-α-di-n-butilaminoacetilamino-)difenilsulfona, 4,4'-(bis-α-N-morfolinoacetilamino-)difenilsulfona e 4,4'-(bis-α-N-piperidinoacetilamino-)difenilsulfona.

b) trimetilamina e piridina, resultando respetivamente 4,4'-diaminodifenilsulfona-N,N'-bis-(carboximetileno-trimetilamonio) cloreto ou perclorato e 4,4'-diaminodifenilsulfona-N,N'-bis-(carboximetileno-piridinio) perclorato.

Espera-se que estes novos derivados da 4,4'-diaminodifenilsulfona tenham uma influença sobre as formas nervosas da lepra.

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