ANTITUBERCULOSIS AGENTS

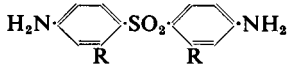
PART I. BISDIALKYLAMINOALKYL SULPHONES AND RELATED SUBSTANCES

BY D. EDWARDS and J. B. STENLAKE

From The School of Pharmacy, The Royal Technical College, Glasgow

Received June 23, 1955

THE use of aromatic amino-sulphones such as dapsone[1] (4:4′-diaminodiphenyl sulphone, I,R=H), solapsone[2,3,4,5] and related compounds in the treatment of tubercular infections and in leprosy is well established. Toxic effects which are often exhibited with dapsone have been circumvented by administration in graded doses.[6] Linnell and Stenlake[7,8] and others[9,10] have also shown that introduction of hydroxy groups into the molecule as in 2:2′-dihydroxy-4:4′-diaminodiphenyl sulphone (I,R=OH) leads to a marked reduction of toxicity, with retention of activity. Poor yields in the synthetic routes to such compounds, and the need to study structural variants have led us to examine a number of related aliphatic compounds.



(I)

Marked *in vitro* activity against *Myco. tuberculosis* is shown by many aliphatic amines[11,12,13,14,15,16], particularly by those with 16 to 20 carbon atoms. They are, however, inactive *in vivo*. A series of long chain aliphatic diamidines[17] also showed activity *in vitro* but proved too toxic for prolonged *in vivo* tests. Many aromatic amines similarly are active *in vitro*[18], but activity *in vivo* appears to be limited to those which are related either to *p*-aminosalicylic acid (PAS) or alternatively to the amino-sulphones (I). Eiseman[19] has shown that polyoxyethylene substituents in the amino groups increase the effective surface concentration of these substances, and some of these compounds possessed *in vitro* activities one thousand times greater than that of the parent sulphone. Peak and Watkins[20] examined the effect of introducing a sulphone group into the carbon chain of aliphatic amines. A series of compounds II (R=C_4H_9, C_8H_{17}, $C_{16}H_{33}$) and (III) were shown to exhibit only low *in vitro* activity, though in many cases the corresponding sulphides were appreciably

$Et_2N{\cdot}CH_2{\cdot}CH_2{\cdot}SO_2{\cdot}R$ (II)

$MeN(CH_2{\cdot}CH_2{\cdot}SO_2{\cdot}C_8H_{17})_2$ (III)

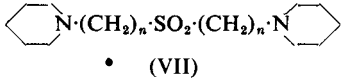
$Et_2N{\cdot}CH_2{\cdot}CH_2{\cdot}SO_2{\cdot}CH_2{\cdot}CH_2{\cdot}NEt_2$ (IV)

$Et_2N{\cdot}(CH_2)_n{\cdot}SO_2{\cdot}(CH_2)_nNEt_2$ (V)

active. No compounds were examined in which the amino groups were separated by a long aliphatic chain, whilst the only example of an $\alpha\omega$-bisdialkylamino sulphone was (IV) which showed low activity.

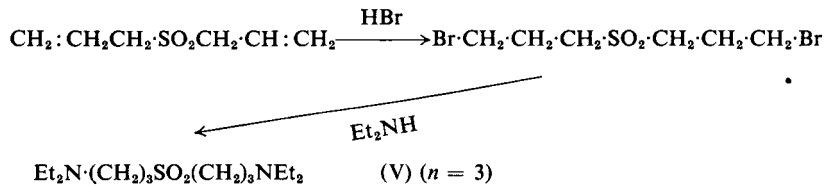
In view of the high activities reported for $\alpha\omega$-bisdialkylaminoalkanes[14] and for the polyoxyethylene derivatives of amino-sulphones[19] it was decided in the first instance to synthesise a series of $\alpha\omega$-bisdialkylamino-alkyl sulphones (V). Three compounds have been prepared in which

n = 3, 6 and 10 respectively (giving chain lengths of 7, 13 and 21 units) to survey the effect of varying chain length. The two latter compounds were obtained via the corresponding sulphides (VI), and in the light of the observation that such compounds can show considerable activity[20], these also have been tested against *Myco. tuberculosis*. Ames and Bowman[14] showed that piperidylalkanes generally were less toxic than the corresponding dialkylaminoalkanes, and we have accordingly extended the range of compounds examined to include the $\alpha\omega$-bis-(1′-piperidyl)-alkyl sulphones (VII, n = 6 and 10) and the corresponding sulphides (VIII).



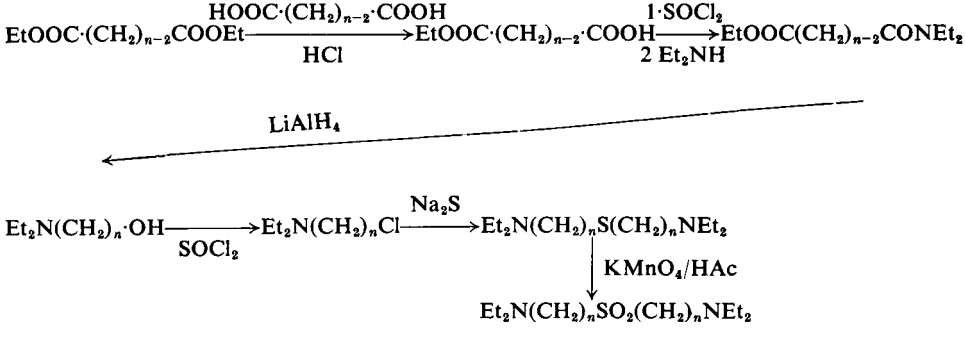
(VII)

Bis-3-diethylaminopropyl sulphone (V, n = 3) was obtained from diallyl sulphone according to the following scheme:



Considerable difficulty was experienced initially with the hydrobromination of diallyl sulphone to give bis-3-bromopropyl sulphone the yields varying eratically and without explanation. Consistent yields (43 per cent.) were finally obtained by passing dry hydrogen bromide slowly through a solution of diallyl sulphone in carbon tetrachloride continuously for 20 hours, the reaction mixture being raised to boiling initially and periodically every three hours. Continuous reaction at the boiling point of the solvent gave much resinous material, and small yields of product which was difficult to isolate. On one occasion small amounts of two monobromosulphones were isolated. Bis-3-bromopropyl sulphone was readily converted to the required bis-3-diethylaminopropyl sulphone V (*n* = 3) in 53 per cent. yield (isolated as the dihydrochloride) by reaction with diethylamine in hot benzene.

The medium and long chain compounds, V (*n* = 6 and 10), VI (*n* = 6 and 10), VII (*n* = 6 and 10), VIII (*n* = 6 and 10) were obtained by an adaptation of the methods described by Andrews, Bergel and Morrison[21]



for the preparation of the analagous $\alpha\omega$-trimethylalkylammonium sulphides, as outlined above. The sulphides were readily oxidised to the corresponding sulphones in good yield using potassium permanganate in glacial acetic acid.

Introduction of a hydroxy group into the molecule of aromatic amino-sulphones markedly reduces toxicity[7,8]. Examination of similarly hydroxylated aliphatic amino-sulphones was desirable, and we therefore considered the possibility of preparing a series of sulphones (IX), which in respect of the hydroxyl group are analagous to 2:2′-dihydroxy-4:4′-diaminodiphenyl sulphone. One route to such a series of compounds

$$Et_2N(CH_2)_nCHOH\cdot CH_2\cdot SO_2\cdot CH_2\cdot CHOH\cdot(CH_2)_nNEt_2 \qquad (IX)$$

via the corresponding $\alpha\beta$-unsaturated sulphones is particularly attractive in that there exists an analogy between these intermediates and certain of the long chain fatty acids which have been isolated from the tubercle bacillus[22,23,24,25,26]. Many of these acids are $\alpha\beta$-unsaturated, and it is known that they are largely responsible for tubercle formation, one of the characteristic signs of the disease. Little is known of their function in the metabolism of the organism, and it was felt that a study of some unsaturated compounds might provide a useful means of probing the importance of such unsaturation.

In an attempt to find a general method which would be applicable to all compounds, we examined the reaction between bromine, red phosphorus and dibutyl sulphone. No bromination occurred after refluxing for six hours. We therefore turned our attention to the preparation of the short chain compound (X) by the following route, based on a preparation of benzyl 3-bromoprop-1-enyl sulphone by Rothstein[27].

$$CH_2:CH\cdot CH_2\cdot SO_2\cdot CH_2\cdot CH:CH_2 \xrightarrow{Br_2} BrCH_2\cdot CHBr\cdot CH_2\cdot SO_2\cdot CH_2\cdot CHBr\cdot CH_2Br$$

$$BrCH_2\cdot CH:CH\cdot SO_2\cdot CH:CH\cdot CH_2Br \xrightarrow{Et_2NH} Et_2N\cdot CH_2CH:CH\cdot SO_2\cdot CH:CH\cdot CH_2NEt_2$$

(Pyridine)

(X)

Direct bromination of dialkyl sulphone gave bis-2:3-dibromopropyl sulphone which was readily dehydrobrominated with pyridine in hot benzene to bis-3-bromoprop-1-enyl sulphone. The latter on treatment with diethylamine gave bis-3-diethylamino-prop-1-enyl sulphone (X) which was isolated as its hydrochloride. The product decolourised potassium permanganate in alkaline solution, but otherwise showed complete lack of reactivity at the double bonds, giving no reaction with hydrobromic acid, bromine, iodine monochloride and tetranitromethane. With monoperphthalic and perbenzoic acids reaction was negligible at room temperature and no useful products could be isolated. Attempts to obtain the corresponding bis-3-diethylamino-2-hydroxypropyl sulphone

by this route were therefore abandoned. Alternative routes to these compounds are being examined.

Bacteriological Results

The preliminary bacteriological examination of the above compounds was kindly carried out by Dr. S. R. M. Bushby of the Wellcome Research Laboratories. The tuberculostatic activity was measured against *Myco. tuberculosis, var hominis* (CN3679) both in Dubos medium and in the egg-agar solid medium of Peizer and Schecter, and also against *Myco. tuberculosis var hominis*, H37 Rv in Peizer and Schecter medium only. The results for the more active compounds are shown in Table I. None

TABLE I

Tuberculostatic activity of bisdialkylaminoalkyl sulphones

Compound	Incubation (days)	Minimum inhibiting concentration μg./ml.					
		Dubos medium				Peizer and Schecter medium	
		Strain CN 3679				H 37Rv	CN 3679
		Expt. 1	Expt. 2	Expt. 3	Expt. 4		
Bis-3-diethylaminoprop-1-enyl sulphone dihydrochloride	7	8	8	16	8	—	—
	14	8	16	62	16	500	250
	21	—	—	—	—	500	500
Bis-10-diethylaminodecyl sulphide dihydrochloride	7	2	4	4	2	—	—
	14	4	8	4	4	62	125
	21	—	—	—	—	62	125
Bis-10-diethylaminodecyl sulphone dihydrochloride	7	62	62	31	62	—	—
	14	62	62	31	62	250	125
	21	—	—	—	—	250	250
Bis-10-(1′-piperidyl)-decyl sulphide dihydrochloride	7	4	8	<1	4	—	—
	14	4	8	4	8	125	125
	21	—	—	—	—	125	125
Bis-10-(1′-piperidyl)-decyl sulphone dihydrochloride	7	16	31	16	31	—	—
	14	16	31	16	62	125	125
	21	—	—	—	—	125	125
Isoniazid(*iso*nicotinic acid hydrazide)	7	0·06	0·06	0·06	0·06	—	—
	14	0·06	0·06	0·06	0·06	0·06	0·06
	21	—	—	—	—	0·06	0·06
Streptomycin sulphate	7	—	0·30	—	—	—	—
	14	—	0·30	—	—	—	2·50
	21	—	—	—	—	—	2·50

of the compounds examined showed activity of the same order as that of isoniazid or streptomycin. As expected the compounds with the longer chains were, in general, more active than those with short chains, whilst sulphides were more active than the corresponding sulphones. A surprisingly high level of activity was shown by the short chain unsaturated sulphone, bis-3-diethylamino-prop-1-enyl sulphone, this being the most active of the sulphones examined. It is intended that future work should be directed towards producing a series of unsaturated compounds, and related β-hydroxy compounds.

EXPERIMENTAL

Melting points are uncorrected.

Bis-2:3-*dibromopropyl sulphone* was prepared by the method of Lewin[22].

Bis-3-*bromoprop*-1-*enyl sulphone.* Bis-2:3-dibromopropyl sulphone (46·6 g.) was dissolved in hot benzene (160 ml.). Pyridine (17 ml.) was slowly added to the hot solution (15 min.) with continuous stirring, and the mixture refluxed for a further 30 minutes. When cold the benzene solution was washed with water, dried (Na_2SO_4) and evaporated to yield a yellowish mass of crystals (crude yield 61 per cent.). Recrystallisation from carbon tetrachloride gave colourless needles of *bis*-3-*bromoprop*-1-*enyl* sulphone, m.pt. 73 to 74° C. Found: C, 23·8; H, 2·9; Br, 52·7 per cent. $C_6H_8O_2SBr_2$ requires C, 23·7; H, 2·7; Br, 52·6 per cent.

Bis-3-*diethylaminoprop*-1-*enyl sulphone dihydrochloride.* Bis-3-bromoprop-1-enyl sulphone (3·65 g.) was dissolved in hot benzene (55 ml.). Diethylamine (7 ml.) was added and the mixture refluxed for 15 minutes. When cold the benzene solution was washed with water, dried (Na_2SO_4) and evaporated. The residual oily base was dissolved in dilute hydrochloric acid (10 per cent.; 9 ml.) and the solution cautiously evaporated. The semi-crystalline residue, recrystallised from absolute ethanol, gave colourless needles of *bis*-3-*diethylaminoprop*-1-*enyl sulphone dihydrochloride* (2·3 g.; 53 per cent.), m.pt. 192 to 193° C. Found: C, 46·5; H, 7·7; Cl, 19·8 per cent. $C_{14}H_{30}O_2N_2SCl_2$ requires C, 46·5; H, 8·4; Cl, 19·6 per cent. The corresponding *dipicrate* had m.pt. 188 to 189° C. (decomp.). Found: 42·2; H, 4·3 per cent. $C_{26}H_{34}O_{16}N_8S$ requires C, 41·8; H, 4·6 per cent.

Bis-3-*bromopropyl sulphone.* Diallyl sulphone (4·2 g.) was dissolved in carbon tetrachloride (100 ml.) and a crystal of benzoyl peroxide added. The solution was heated to boiling and dry hydrogen bromide passed in whilst the solution cooled, and thereafter for 19·5 hours. The solution was brought to the boil at 3 hourly intervals, being allowed to cool to room temperature during the intervening periods. The product separated as a yellow oil which formed a solid crystalline mass on standing overnight. Evaporation of the benzene and crystallisation of the residue from ether gave *bis*-3-*bromopropyl sulphone* as colourless plates, m.pt. 85 to 86° C. (3·7 g.; 43 per cent.). Found: C, 23·8; H, 4·1; Br, 51·8 per cent. $C_6H_{12}O_2SBr_2$ requires C, 23·4; H, 3·9; Br, 51·9 per cent. A subsequent experiment in which hydrogen bromide was only passed in for 8 hours gave the same product in 39·2 per cent. yield.

2-*Bromopropyl prop*-2′-*enyl sulphone* and 3-*bromopropyl prop*-2′-*enyl sulphone.* Diallyl sulphone (6·5 g.) was dissolved in carbon tetrachloride (100 ml.) and a crystal of benzoyl peroxide added. The solution was heated to boiling and dry hydrogen bromide passed in for 5 hours, whilst the solution was refluxed. Removal of the solvent gave a tarry residue, which was extracted with hot ether, benzene and ethanol to yield a liquid (1·48 g.). The liquid on further reaction in carbon tetrachloride with dry hydrogen bromide for 7 hours, followed by chromatography from benzene on a mixture of activated charcoal and powdered cellulose (1:1)

gave a crystalline solid (1·67 g.). Chromatography of this solid from benzene on alumina gave two fractions. The first small fraction recrystallised from ether gave 2-*bromopropyl prop*-2′-*enyl sulphone*, m.pt. 102·5 to 103·5° C. Found: C, 32·1; H, 5·4 per cent. $C_6H_{10}O_2SBr$ requires C, 32·1; H, 5·3 per cent. The second much larger fraction after repeated recrystallisation from ether gave 3-bromopropyl prop-2′-enyl sulphone, m.pt. 72 to 74° C. Found: C, 31·8; H, 4·9 per cent. $C_6H_{10}O_2SBr$ requires C, 32·1; H, 5·3 per cent.

Bis-3-*diethylaminopropyl sulphone*. Bis-3-bromopropyl sulphone (4·64 g.) in benzene (100 ml.) was refluxed for 1 hour with diethylamine (8 ml.). When cold the benzene solution was washed with water, dried (Na_2SO_4) and evaporated. The residual oily base was dissolved in dilute hydrochloric acid (10 per cent.; 12·5 ml.) and the solution cautiously evaporated. The solid residue recrystallised from absolute ethanol (dried) gave colourless hygroscopic needles of *bis*-3-*diethylaminopropyl sulphone dihydrochloride* m.pt. 186·5 to 187° C. (2·93 g., 53 per cent.). Found: N, 7·4; Cl, 19·3 per cent. $C_{14}H_{34}O_2N_2SCl_2$ requires N, 7·7; Cl, 19·4 per cent.

Ethyl NN-*pentamethyleneadipamate* was prepared from ethyl hydrogen adipate[31] as described by Avison[32], b.pt. 169 to 172°C./3 mm. (literature b.pt. 148 to 152°C./0·5 mm.). Found: C, 64·8; H, 9·3; N, 6·2 per cent. Calc. for $C_{13}H_{23}O_3N$, C, 64·7; H, 9·6; N, 5·8 per cent.

Ethyl NN-*diethyladipamate*. Ethyl hydrogen adipate[31] (26·25 g.) was refluxed with excess thionyl chloride for 1·5 hours. After removal of excess thionyl chloride, the residue, in ether (200 ml.), was treated with a solution of diethylamine (35 ml.) in ether (50 ml.). The ethereal solution was extracted first with water (to remove diethylamine hydrochloride), then with aqueous sodium carbonate (to remove ethyl hydrogen adipate) and then washed with water. The resulting ethereal solution was dried (Na_2SO_4), evaporated, and the residual liquid distilled to yield *ethyl* NN-*diethyladipamate*, b.pt. 144° C./3 mm., $n_D^{17.5}$ 1·4572 (27·9 g., 81 per cent.). Found: N, 5·9 per cent. $C_{12}H_{23}O_3N$ requires N, 6·1 per cent.

Ethyl NN-*diethylsebacamate* was prepared from ethyl hydrogen sebacate[31] (31·7 g.) by the above method. *Ethyl* NN-*diethylsebacamate* was obtained as a colourless oil, b.pt. 183 to 190° C./3 mm., n_D^{19} 1·4571 (22·3 g., 57 per cent.). Found: C, 67·3; H, 10·9; N, 4·95 per cent. $C_{16}H_{31}O_3N$ requires C, 67·3; H, 10·9; N, 4·9 per cent.

Ethyl NN-*pentamethylenesebacamate* was prepared from ethyl hydrogen sebacate[31] (23·6 g.) by the above method. *Ethyl* NN-*pentamethylenesebacamate* was obtained as a colourless oil, b.pt. 208 to 211° C./3·5 mm., $n_D^{18.5}$ 1·4757 (20·1 g., 66 per cent.). Found: C, 68·2; H, 9·9; N, 4·5 per cent. $C_{17}H_{31}O_3N$ requires C, 68·6; H, 10·5; N, 4·7 per cent.

6-*Hydroxyhexyldiethylamine*. Ethyl *NN*-diethyladipamate (27·9 g.) in dry ether (60 ml.) was slowly run into a stirred hot suspension of lithium aluminium hydride (9 g.) in dry ether (400 ml.). The addition was continued at a rate which was just sufficient to keep the solution boiling, addition being complete within approximately 15 minutes. The reaction mixture was cooled in ice, and water added dropwise sufficient to decompose the excess lithium aluminium hydride. After treatment with sodium

hydroxide solution (20 per cent.; 200 ml.) the ethereal solution was evaporated and the residual oil distilled to give 6-hydroxyhexyldiethylamine, b.pt. 110° C./5·5 mm., n_D^{15} 1·4575 (18·9 g., 90 per cent.). Work[33] gives b.pt. 96 to 99° C./2 mm.

6-*Hydroxyhexlpiperidine* was prepared from ethyl *NN*-pentamethyleneadipamate (21·1 g.) by the above method, and was obtained as a colourless oil, b.pt. 123° C./3·5 mm., n_D^{19} 1·4781 (14·4 g., 89 per cent.). Sauer and Adkins[34] give b.pt. 96° C./1 mm., n_D^{25} 1·4730.

10-*Hydroxydecyldiethylamine* was prepared from ethyl *NN*-diethylsebacamate (22 g.) by the above method and was obtained as a colourless oil, b.pt. 146° C./3 mm., $n_D^{19·5}$ 1·4602 (15·5 g., 88 per cent.). Schinzel and Benoit[35] give b.pt. 178 to 183° C./16 mm.

10-*Hydroxydecylpiperidine* was prepared from ethyl *NN*-pentamethylenesebacamate (19·6 g.) by the above method and was obtained as colourless platelets (from ether), m.pt. 59·5° C. (14·3 g., 90 per cent.). Price, Guthrie, Herbrandson and Peel[36] gave m.pt. 60 to 61° C.

6-*Chlorohexyldiethylamine*. Thionyl chloride (8 ml.) in benzene (30 ml.) was slowly added to a solution of 6-hydroxyhexyldiethylamine (18·9 g.) in benzene (100 ml.). The greyish crystalline mass obtained after removing the solvent was dissolved in water (20 ml.), cooled to 0° C. and basified by the addition of sodium hydroxide solution (30 ml., 20 per cent.). Extraction with ether, evaporation of the solvent, and distillation of the residual oil gave 6-chlorohexyldiethylamine, b.pt. 102·5° C./11 mm., n_D^{16} 1·4513 (19·8 g., 95 per cent.). Found: C, 63·1; H, 11·8 per cent. Calc. for $C_{10}H_{22}NCl$: C, 62·6; H, 11·6 per cent. Work[25] gives b.pt. 118 to 120° C./19 mm.

6-*Chlorohexylpiperidine* was prepared from 6-hydroxyhexylpiperidine (13·8 g.) by the above method, and was obtained as a colourless oil, b.pt. 131° C./12·5 mm., $n_D^{17·5}$ 1·4752 (10 g., 66 per cent.). *6-Chlorohexylpiperidine hydrochloride* was obtained in the usual way as colourless plates, m.pt. 154·5 to 155° C. Found: C, 55·0; H, 9·6; N, 5·8 per cent. $C_{11}H_{22}NCl$ requires C, 55·0; H, 9·6; N, 5·8 per cent.

10-*Chlorodecyldiethylamine* was prepared from 10-hydroxydecyldiethylamine (15·1 g.) by the above method, and was obtained as a colourless oil, b.pt. 161° C./12 mm., n_D^{20} 1·4562 (14 g., 86 per cent.). Schinzel and Benoit[35] gave b.pt. 173 to 176° C./17 mm.

10-*Chlorodecylpiperidine* was prepared from 10-hydroxydecylpiperidine (14·2 g.) by the above method, and was obtained as a colourless oil, b.pt. 151 to 152° C./5 mm., n_D^{18} 1·4753 (14·5 g., 95 per cent.). Price, Guthrie, Herbrandson and Peel[36] give analytical figures for this compound, but no constants, except the hydrochloride m.pt. 135 to 136° C. Found: equiv. IV (by titration) 263, $C_{15}H_{30}NCl$ requires equiv. IV 260.

Bis-6-diethylaminohexyl sulphide. 6-Chlorohexyldiethylamine (19·8 g.) in ethanol (10 ml.) was slowly added to a hot solution of anhydrous sodium sulphide (5·5 g.) in water (6 ml.) and ethanol (10 ml.), and the mixture refluxed for 3·25 hours with continuous stirring. The residual liquor remaining after removing the bulk of the ethanol by distillation was poured into water (400 ml.) and extracted with ether. The ethereal

solution was dried (Na_2SO_4) and evaporated and the residual oil fractionally distilled. After a forerun of unchanged chlorohexyldiethylamine, *bis-6-diethylaminohexyl sulphide* was obtained as a pale straw coloured oil, b.pt. 208 to 209° C./5·5 mm., n_D^{19} 1·4757 (13 g., 72·5 per cent.). Found: C, 69·6; H, 12·3; N, 8·1 per cent. Equiv. (titration 172·5) $C_{20}H_{44}N_2S$ requires C, 69·7; H, 12·9; N, 8·1 per cent. Equiv. 172·3. *Dihydrochloride* (from ethanol), m.pt. 130·5 to 131·5° C. Found: C, 57·4, H, 11·2; N, 6·7 per cent. $C_{20}H_{46}N_2SCl_2$ requires C, 57·5; H, 11·1; N, 6·7 per cent.

Bis-6-(1′-*piperidyl*)-*hexyl sulphide* was prepared from 6-chlorohexylpiperidine (9·8 g.) by the above method, and was obtained as a yellow oil, b.pt. 230 to 231° C./3 mm., $n_D^{16·5}$ 1·5022 (5·7 g., 64 per cent.). *Dihydrochloride* (from ethanol-ether), m.pt. 226·5 to 227·5° C. Found: C, 59·5; H, 10·5; N, 6·3 per cent. $C_{22}H_{46}N_2SCl_2$ requires C, 59·8; H, 10·5; N, 6·3 per cent.

Bis-10-*diethylaminodecyl sulphide* was prepared from 10-chlorodecyldiethylamine (13·7 g.) by the above method, and was obtained as a yellow oil b.pt. 275° C./3·5 mm., $n_D^{15·5}$ 1·4775 (5 g., 40 per cent.). Found: Eqiv. (titration) 227. $C_{28}H_{60}N_2S$ requires Eqiv. 228. *Dihydrochloride* (from ethanol-ether), m.pt. 141 to 142° C. Found: C, 63·4; H, 11·4; N, 5·2 per cent. $C_{28}H_{62}N_2S$ requires C, 63·5; H, 11·8; N, 5·3 per cent.

Bis-10-(1′-*piperidyl*)-*decyl sulphide* was prepared from 10-chlorodecylpiperidine (14·4 g.) by the above method, and was obtained as a pale yellow, low-melting solid (9·7 g., 73 per cent.). Found: equiv. (titration) 186·5. $C_{30}H_{60}N_2S$ requires equiv. 184·4. *Dihydrochloride* (from ethanol-ether), m.pt. 204 to 204·5° C. Found: C, 64·4; H, 10·9; N, 5·1 per cent. $C_{30}H_{62}N_2SCl_2$ requires C, 65·0; H, 11·3; N, 5·1 per cent.

Bis-6-diethylaminohexyl sulphone. Potassium permanganate (3 per cent.) in acetic acid (50 per cent.) was slowly added (20 min.) to an ice cold solution of bis-6-diethylaminohexyl sulphide (1·8 g.) in acetic acid (50 per cent.; 3 ml.), until present in slight excess. After a further 20 minutes the solution was decolourised with sulphur dioxide, and evaporated to dryness under reduced pressure. Sodium carbonate solution was added to make alkaline and the solution again evaporated to dryness. The solid residue after continuous extraction with ether and distillation gave *bis-6-diethylaminohexyl sulphone* as a colourless liquid, b.pt. 220° C./3 mm., n_D^{20} 1·4743 (1·75 g., 90 per cent.). Found: C, 63·4; H, 11·6; N, 7·4 per cent. $C_{20}H_{44}O_2N_2S$ requires C, 63·8; H, 11·8; N, 7·4 per cent. *Dihydrochloride* (from ethanol-ether), m.pt. 139 to 140° C. Found: C, 53·1; H, 10·3; N, 6·2; Cl, 15·8 per cent. $C_{20}H_{46}ON_2SCl_2$ requires C, 53·4; H, 10·3; N, 6·2; Cl, 15·8 per cent.

Bis-6-(1′-*piperidyl*)-*hexyl sulphone* was prepared from bis-6-(1′-piperidyl)-hexyl sulphide (1·87 g.), and was obtained as colourless plates (from ether-petroleum), m.pt. 50·5 to 51° C. (1·75 g., 86 per cent.). Found: C, 65·9; H, 10·8, 11·3; N, 6·9 per cent. $C_{22}H_{44}O_2N_2S$ requires C, 65·9; H, 11·1; N, 7·0 per cent. *Dihydrochloride* (from ethanol-ether) m.pt. 191·5 to 192·5° C. Found: Cl, 14·96 per cent. $C_{22}H_{46}O_2N_2SCl_2$ requires Cl, 14·94 per cent.

Bis-10-*diethylaminodecyl sulphone* was prepared from bis-10-diethylaminodecyl sulphide (1·51 g.), and was obtained as a low melting solid (1·6 g., 97 per cent.), which gave a *dihydrochloride* (from ethanol), m.pt. 142·5° C. Found: C, 59·7; H, 10·8; N, 4·9; Cl, 12·7 per cent. $C_{28}H_{62}O_2N_2SCl_2$ requires C, 59·8; H, 11·1; N, 5·0; Cl, 12·6 per cent.

Bis-10-(1′-*piperidyl*)-*decyl sulphone* was prepared from bis-10-(1′-piperidyl)-decyl sulphide (2·2 g.), and was obtained as colourless flakes (from ether), m.pt. 74·5 to 75° C. (2·4 g. crude, 100 per cent.). Found: C, 70·1; H, 11·6; N, 5·4 per cent. $C_{30}H_{60}O_2N_2S$ requires C, 70·2; H, 11·8; N, 5·5 per cent. *Dihydrochloride* (from ether), m.pt. 182° C. Found: C, 61·3; H, 10·9; N, 4·5; Cl, 12·1 per cent. $C_{30}H_{62}O_2N_2SCl_2$ requires C, 61·5; H, 10·7; N, 4·8; Cl, 12·1 per cent.

Summary

1. A series of bisdialkylaminoalkyl sulphides and sulphones have been prepared for testing as antituberculosis agents.

2. The preliminary bacteriological examination reveals that none of the compounds is of the same order of activity as streptomycin or isoniazid. Compounds with long chains are more active than short chain compounds, whilst sulphides are more active than the corresponding sulphones.

3. The short chain unsaturated sulphone, bis-3-diethylamino-prop-1-enyl sulphone, shows a surprisingly high level of activity.

We wish to thank Dr. S. R. M. Bushby of the Wellcome Research Laboratories for testing the compounds described, and Mr. W. McCorkindale, Dr. A. C. Syme and Mr. W. Gardiner for the microanalyses.

References

1. Rist, Block and Hamer, *Ann. Inst. Pasteur*, 1940, **64**, 203.
2. Gray and Henry, *Br. Pat.* 491,265.
3. Buttle, Dewing, Foster, Gray, Smith and Stephenson, *Biochem. J.*, 1938, **32**, 1101.
4. Brownlee, Green and Woodbine, *Brit. J. Pharmacol.*, 1948, **3**, 15.
5. Brownlee, *Lancet*, 1948, **255**, 131.
6. Lowe, *ibid.*, 1950, **258**, 145.
7. Linnell and Stenlake, *J. Pharm. Pharmacol.*, 1950, **2**, 736.
8. Linnell and Stenlake, *ibid.*, 1950, **2**, 937.
9. Amstutz, *J. Amer. chem. Soc.*, 1950, **72**, 3420.
10. Julia, *C.R. Acad. Sci., Paris*, 1950, **231**, 621.
11. Stanley, Greet, Sachs and Adams, *J. Pharmacol.*, 1932, **45**, 121.
12. Borrows, Hargreaves, Page, Resuggan and Robinson, *J. chem. Soc.*, 1947, 179.
13. Bowman and Fordham, *ibid.*, 1951, 2753.
14. Ames and Bowman, *ibid.*, 1952, 1057.
15. Grundland and Ratsimamanga, *C.R. Acad. Sci., Paris*, 1950, **230**, 1701.
16. Barry, Belton, Kelly and Twomey, *Nature, Lond.*, 1950, **166**, 303.
17. Newbery and Webster, *J. chem. Soc.*, 1947, 738.
18. Block, Lehr, Erlenmeyer, *Helv. Chim. Acta*, 1945, **28**, 1046.
19. Eiseman, *J. exp. Med.*, 1948, **88**, 189.
20. Peak and Watkins, *J. chem. Soc.*, 1951, 3292.
21. Andrews, Bergel and Morrison, *ibid.*, 1953, 2998.
22. Chanley and Polgar, *Nature, Lond.*, 1950, **166**, 693.
23. Cason and Sumbrel, *J. Amer. chem. Soc.*, 1950, **72**, 4837.
24. Cason and Sumbrel, *J. biol. Chem.*, 1951, **192**, 405, 415.
25. Chanley and Polgar, *J. chem. Soc.*, 1954, 1003.
26. Polgar, *ibid.*, 1954, 1008.

27. Rothstein, *ibid.*, 1937, 311.
28. Dubos and Davies, *J. exp. Med.*, 1946, **83**, 409.
29. Peizer and Schecter, *Amer. J. clin. Path.*, 1950, **20**, 682.
30. Lewin, *J. Prakt. Chem.*, 1930, **127**, 77.
31. *Org. Synth.*, **19**, 45.
32. Avison, *J. appl. Chem.*, 1951, **1**, 469.
33. Work, *J. chem. Soc.*, 1942, 426.
34. Sauer and Adkins, *J. Amer. chem. Soc.*, 1938, **60**, 402.
35. Schinzel and Benoit, *Bull. Soc., Chim. Fr.*, 1939, [5], **6**, 501.
36. Price, Guthrie, Herbrandson and Peel, *J. org. Chem.*, 1946, **11**, 281.

DISCUSSION

The paper was presented by MR. D. EDWARDS.

DR. R. F. TIMONEY (Dublin) suggested, with reference to the failure to prepare bis-3-diethylamino-2-hydroxypropyl sulphone by the route found to give bis-3-diethylamino-prop-1-enyl sulphone, that the authors might try to prepare the sultone, which was comparable to a lactone, and hydrolyse it.

DR. J. B. STENLAKE, in reply, thanked Dr. Timoney for his suggestion.