A THESIS

submitted to

THE UNIVERSITY OF GLASGOW

by

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in fulfilment of the
requirements for the degree of

DOCTOR OF PHILOSOPHY

April 1956

The School of Pharmacy
Royal Technical College
Glasgow.

SOME POTENTIAL TUBERCULOSTATIC AGENTS

The author wishes to thank Professor J. P. Todd for useful advice, and Dr. J. B. Stenlake under whose guidance this work was carried out, and whose wealth of helpful suggestions and criticisms has proved invaluable.

CONTENTS

PAGE

HISTORICAL.

Introduction ... ... 1.
Sulphones ... ... 2.
Streptomycin and related compounds ... 9.
para-Aminosalicylic Acid ... ... 13.
Thiosemicarbazones ... ... 16.
*iso*Nicotinic Acid Hydrazide ... ... 20.

DISCUSSION OF THE SYNTHESES UNDERTAKEN.

INTRODUCTION ... ... 26.

BISDIALKYLAMINOALKYL SULPHONES.

Reactions with diethyl malonate ... ... 32.
Preparation of bis-3-diethylaminopropyl sulphone ... ... 37.
Preparation of long-chain bis-dialkylaminoalkyl sulphides and sulphones ... ... 41.

UNSATURATED SULPHONES.

Experiments with lithium alkenyls ... 46.
Bromination of saturated sulphones ... 48.
Bis-3-diethylaminoprop-1-enyl sulphone ... ... 48.
Attempted preparation of bis-3-diethylaminoprop-1-enyl sulphide ... ... 51.

THE OXIDATION OF ALKYL SULPHIDES. ... 66.

PAGE

EXPERIMENTAL.

Experiments with diethyl malonate ... ... 72.

Preparation of bis-3-diethyl-aminopropyl sulphone ... ... 78.

Preparation of long-chain bis-dialkylaminoalkyl sulphides and sulphones ... ... 84.

Experiments with lithium alkenyls ... ... 96.

Attempted bromination of di-n-butyl sulphone ... ... 100.

Bis-3-diethylaminoprop-1-enyl sulphone ... ... 101.

Experiments connected with the attempt to prepare bis-3-diethyl-aminoprop-1-enyl sulphide ... ... 104.

Oxidation experiments ... ... 119.

BACTERIOLOGICAL RESULTS.

General methods of testing tuberculostatic agents ... ... 128.

Testing of bis-dialkylamino-alkyl sulphides and sulphones ... ... 131.

BIBLIOGRAPHY. ... ... 134.

APPENDIX

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HISTORICAL

Introduction

The discovery and development of penicillin as a successful antibacterial agent has focussed attention on the production and examination of other antibiotics. Systematic screening of these antibiotics for antibacterial activity has led to the discovery of a number of such substances, possessing *in vitro* activity against *Mycobacterium tuberculosis*, of which only streptomycin and certain of its closely related derivatives have proved to be of value clinically.

In addition to antibiotics, large numbers of synthetic compounds have been prepared and tested for activity against *M. tuberculosis*. As with the antibiotics, many of these compounds have marked tuberculostatic properties *in vitro*, but when tested in experimental animals, they have been found to be either inactive or too toxic for clinical trials. Frequently, however, modifications in the structure of such molecules have led to the production of therapeutically valuable compounds.

The more successful of the synthetic compounds obtained in this way are 4:4'-diaminodiphenyl sulphone (Dapsone)** and related sulphones, *p*-aminosalicylic acid, *p*-acetylaminobenzaldehyde thiosemicarbazone (Thiacetazone), and isonicotinic acid hydrazide (Isoniazid). At the present time

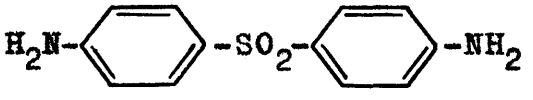
** A table giving the systematic chemical names of proprietary and official substances is to be found in Appendix I.

the sulphones are used chiefly in the treatment of leprosy, and they have been superseded in the treatment of tuberculosis by streptomycin, dihydrostreptomycin, p-aminosalicylic acid, and isonicotinic acid hydrazide.

The discovery of these compounds and their development as chemotherapeutic agents is now reviewed in more detail.

The Sulphones.

The sulphones, which have been found to be active against M. tuberculosis, are mainly derivatives of 4:4'-diaminodiphenyl sulphone (Dapsone) (I). This compound was first prepared in 1908 by Fromm and Wittmann[1], but its



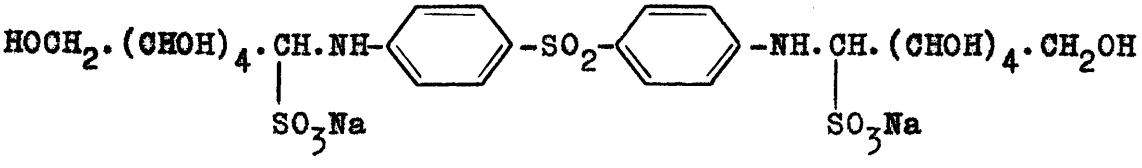
(I)

valuable antibacterial properties were not discovered until 1937[2]. Thereafter, it was shown to be active against M. tuberculosis both in vitro and in experimental animals[3,4]. Recently (1953), it has been reported by Francis[5] that it is more effective in combination with streptomycin than either Thiacetazone, p-ethylsulphonylbenzaldehyde thiosemicarbazone or p-aminosalicylic acid, in similar combination with streptomycin, for the treatment of tubercle infected guinea-pigs.

Despite its great activity Dapsone is too toxic for

general use as an antituberculosis agent. This toxicity, however, has not prevented its use in the treatment of leprosy, a field in which it has proved to be of very great value[6]. The successful treatment of leprosy by oral administration of Dapsone, in doses which are gradually increased over a period of several months, was first described by Lowe[7]. In this way, patients are eventually given large and effective doses, which would previously have been considered to be too toxic. As a result, Dapsone is now firmly established as an agent in the treatment of leprosy.

A number of more soluble and less toxic derivatives of Dapsone for the treatment of tuberculosis have been prepared by substitution in the amino groups. Of these, disodium 4:4'-diaminodiphenyl sulphone-N:N'-diglucosesulphonate (Promin) (II), which was introduced by Feldman, Hinshaw, and Moses[8],

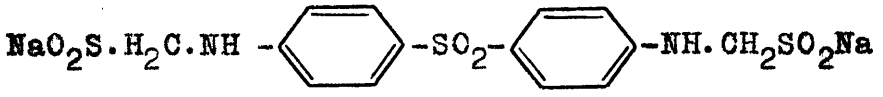


(II)

has been extensively investigated in America. From the results of experiments in animals, it was shown that, although Promin produced satisfactory results during treatment, when the treatment was stopped the animals eventually died from tuberculosis[9,10,11]. Owing to its toxic effects in man, a

form of medication was introduced in which Promin was administered during alternate weeks[12]. This form of treatment did produce favourable results in human pulmonary tuberculosis[13,14], but Dancey, Schmidt, and Wilkie also reported[15] that Promin was only beneficial in lesions of recent origin, and that it was only suitable as an adjunct to other modes of treatment.

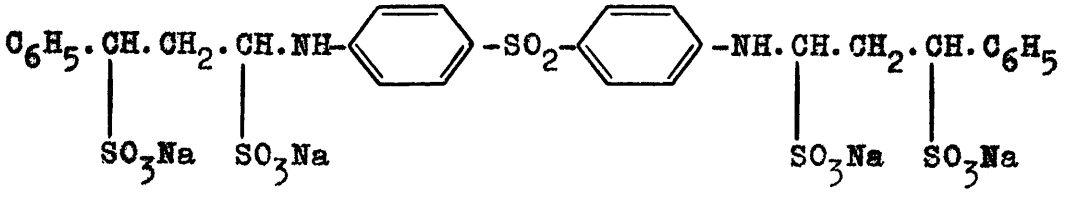
The related compound, 4:4′-diaminodiphenylsulphone disodium formaldehyde sulphoxylate (Diasone) (III), was synthesised independently by Raiziss, Clemence, and



(III)

Freifelder[16], and by Bauer and Rosenthal[17]. It was reported to be rather less toxic than Promin in experimental animals[18,19].

In this country, tetrasodium 4:4′-bis-γ-phenyl-n-propylaminodiphenyl sulphone tetrasulphonate (Solapsone; Sulphetrone)(IV), which was prepared by Gray and Henry[20] in



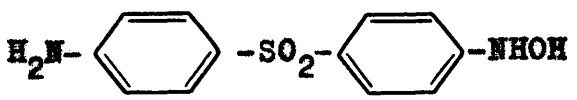
(IV)

1937 and shown in the same year to have antibacterial properties[21], was not developed as a tuberculostatic agent until

1944. Its activity in experimental tuberculosis in guinea-pigs was demonstrated by Brownlee and Kennedy[22], and it was found to have low toxicity. In clinical trials, too, Solapsone has shown definite improvements in certain cases, but some toxic symptoms have also been noted[23,24,25].

Numerous other N-substituted derivatives of 4:4'-diamino-diphenyl sulphone have been described, but few have proved even as promising as the earlier sulphones. Smith, McClosky, and Jackson reported[26] that 4-amino-4'-galacturonylamino-diphenyl sulphone and 4-amino-4'-ureidodiphenyl sulphone were as effective as Promin in experimental tuberculosis, but both 4-amino-4'-ß-carboxyethylaminodiphenyl sulphone (V) and 4-amino-4'-hydroxylaminodiphenyl sulphone (VI) were less active[27]. 4:4'-ß-Carboxyethylaminodiphenyl sulphone, however, was later found to be active *in vitro*[28] and to show promising results in experimental tuberculosis. 4-Amino-4'-succinimidodiphenyl sulphone (VII) and 4-amino-4'-γ-carbethoxypropionamidodiphenyl sulphone (VIII) were also reported[29] to be as effective as Promin in the treatment of experimental tuberculosis, although inferior to 4-amino-4'-*n*-propylaminodiphenyl sulphone. Youmans and Doub[30] tested *in vitro* a series of N-alkyl and N-alkenyl derivatives of 4:4'-diaminodiphenyl sulphone, and found that only one, 4-amino-4'-allylaminodiphenyl sulphone was more active than the parent sulphone.

(V)



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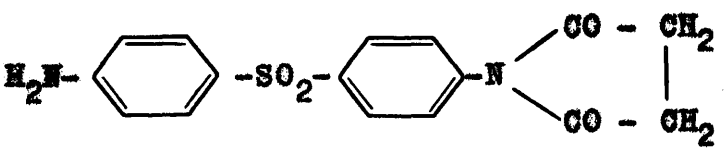

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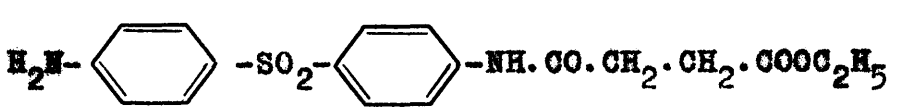
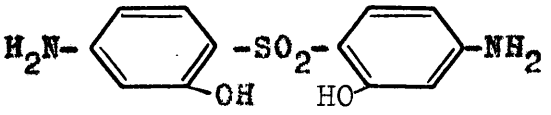


(VIII)

Fuller and Banks[31] considered the question of orientation of amino and sulphone groups, and showed that to maintain activity at least one amino group must be retained in the <u>para</u> position to the sulphone group. A series of nuclear substituted derivatives were prepared by Youmans and Doub[30],

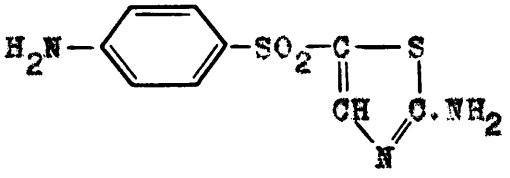
and Freedlander and French[32], and found to be less active than Dapsone. More promising results were obtained with 2:2'-dihydroxy-4:4'-diaminodiphenyl sulphone (IX) which was



(IX)

reported by Linnell and Stenlake[33,34] to be much less toxic than Dapsone, although equally active.

Replacement of one of the benzene nuclei by a heterocyclic ring has been effected in 4-aminophenyl 2'-amino-5'-thiazolyl sulphone (X). This compound produced favourable

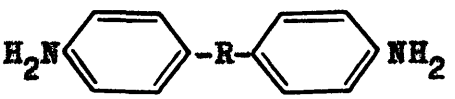


(X)

results against M.tuberculosis in experimental animals at half the dose required for Promin[35], but was later reported to be more toxic than Dapsone[36].

The in vitro examination[30] of a series of compounds of structure (XI) revealed only one substance (R = SO_2S) which

was more active than 4:4'- diaminodiphenyl sulphone, as



(XI)

shown in Table 1. Wojahn and Lerch[37] too found that 4:4'- diaminodiphenyl disulphide (XI, R=S_2) and some of its derivatives were active against M. tuberculosis, but they showed high toxicity in mice and could only be used for local application.

TABLE 1.

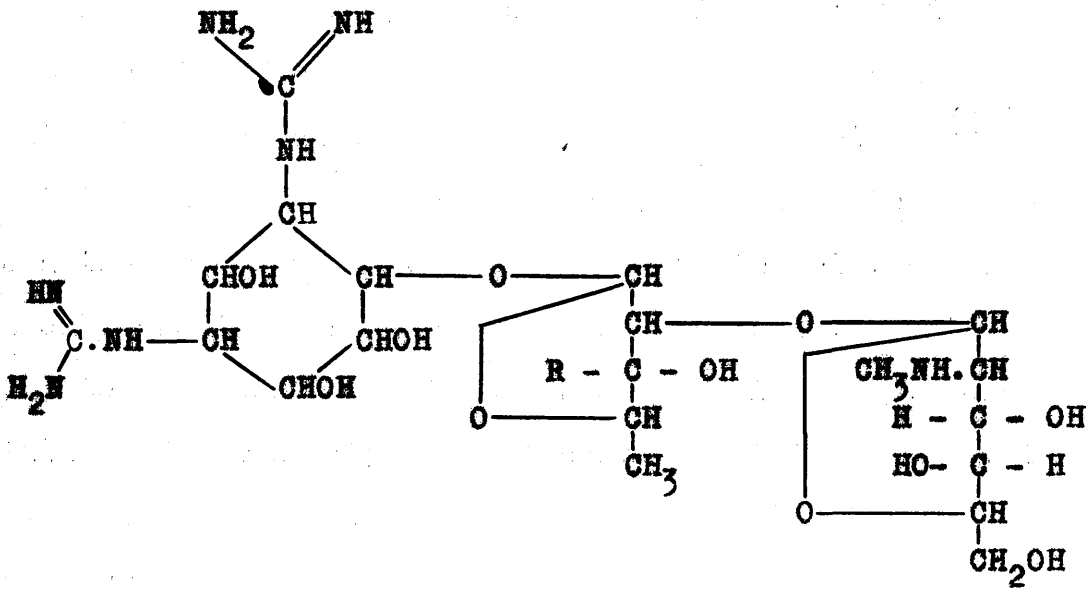
Compound XI Linking Group R=	Percentage Activity as compared with 4:4'-Diaminodiphenyl Sulphone (100)
$-SO_2-$	100
-SO-	5.6
-S-	22
$-SO_2S-$	220
$-SO_2(CH_2)_3SO_2-$	21
-CO-CO-	6.0

Until recently, all the evidence pointed to the fact that nitrogen substituted derivatives of Dapsone were converted into the parent compound in the body, and that these derivatives owed there activity to this breakdown[38,39]. It has now been shown by Francis and Spinks[39] that Dapsone is not excreted unchanged, although they were unable to identify the products. However, Bushby and Woiwod [40] identified the main product as a conjugate in which one of the free amino groups was blacked by glycuronic acid, and showed that only about 5% Dapsone was present as such. This conjugate was also found in the blood. Similarly, Solapsone administered parentally was not converted into Dapsone, the mono-substituted derivative (semi-solapsone) being identified as an excretion product. In view of the fact that certain mono-substituted derivatives of Dapsone, which have anti-tuberculosis activity, are excreted unchanged, Bushby and Woiwod suggested that the activity of Dapsone was in fact due to the mono-substituted derivative formed in the body. Similarly, it was considered that the activity of Solapsone was due to the semi-solapsone present in the commercial substance, and also formed in the body. No further investigation of mono-substituted derivatives of 4:4'-diaminodiphenyl sulphone has so far been reported.

Streptomycin.

Streptomycin (XII, R=CHO) was discovered by Schatz, Bugie

and Waksman in 1944[41] after testing a large number of actinomycetes, fungi, and bacteria for tuberculostatic activity. It is a product of the metabolism of the mould



(XII)

Streptomyces griseus and was found to show high tuberculostatic activity both in vitro[42,43] and in experimental animals[44]. Early clinical reports[45,46,47] were equally satisfactory, and later reports confirmed that it was the most effective substance known for treating tuberculous meningitis[48,49,50,51,52], pulmonary[53,54,55] and miliary tuberculosis[49].

It is poorly absorbed from the intestines, and hence suffers from the disadvantage that it has to be administered parentally. Two other serious disadvantages were found to attend its use. In the first place, the tubercle bacillus

(and other strains of bacteria) initially sensitive to streptomycin becomes resistant to the antibiotic[56,57,58,59] making prolonged courses of treatment impossible. The other undesirable feature is that toxic symptoms develop in many cases[60,61]. These symptoms result from damage to the labyrinth of the ear, but they gradually disappear when administration of the drug is stopped. An attempt to avoid or delay the emergence of streptomycin-resistant tubercle bacilli by intermittent dosage was considered to offer no advantage over daily dosage treatment[62]. On the other hand, James, Sides, Dye, and Dyke reported[63] that doses of streptomycin, administered every third day, gave results comparable with daily dosage treatment, and that the former method not only markedly reduced the toxic symptoms but also delayed the emergence of streptomycin-resistant strains of M. tuberculosis. It was observed that resistant strains generally appeared most readily in patients who had the most extensive infections.

With the introduction of p-aminosalicylic acid for the treatment of tuberculosis, it was found that a combination with streptomycin delayed the emergence of streptomycin-resistant strains of bacteria[64,65], and this is now an established method of treatment. Streptomycin is also given with Isoniazid, but daily administration is essential since strains of M. tuberculosis resistant to Isoniazid are more liable to emerge with intermittent administration[66,67].

Dihydrostreptomycin

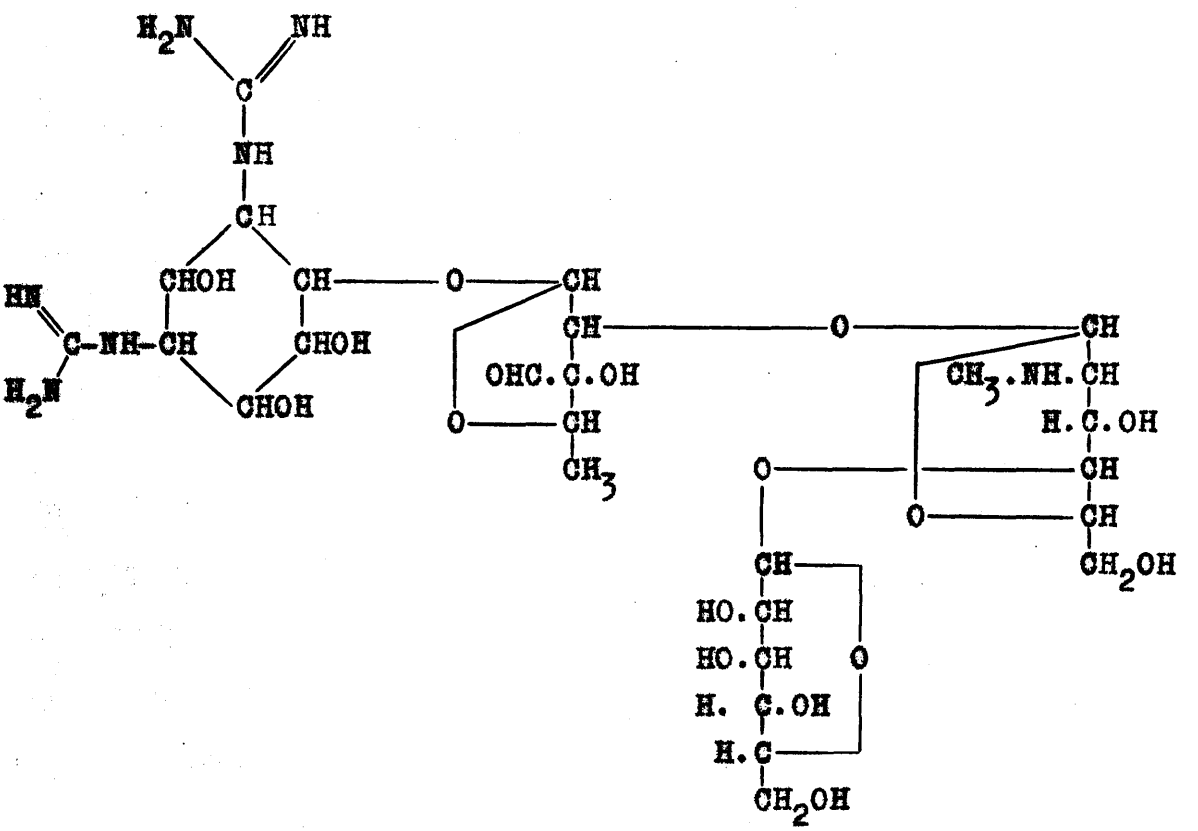
Hydrogenation of streptomycin hydrochloride in aqueous solution in the presence of a platinum or palladium catalyst yields dihydrostreptomycin hydrochloride. *In vitro*[68] and *in vivo*[69,70,71,72] tests, and also later clinical reports[73,74,75] showed dihydrostreptomycin (XII, R=CH_2OH) to be just as effective as streptomycin against the tubercle bacillus. This activity was somewhat unexpected since previous observations had shown that reagents which block the carbonyl group, such as hydroxylamine and cysteine, inactivated the molecule[73].

The incidence of strains of *M. tuberculosis* resistant to dihydrostreptomycin was reduced to an insignificant level by combined treatment with p-aminosalicylic acid[76]. Toxic symptoms produced by dihydrostreptomycin do not appear as frequently, but when observed are more serious than with streptomycin[76,77]. Unlike streptomycin, dihydrostreptomycin causes nerve deafness which is irreversible, and may become worse after treatment is stopped.

Mannosidostreptomycin

Mannosidostreptomycin (XIII), isolated from crude streptomycin concentrates by Fried and Titus[78], was originally known as streptomycin B, until its structure was determined[79]. The ratio of streptomycin to mannosidostreptomycin activity, both *in vitro* and in experimental

animals was found to vary by a factor of between 1.23 and 7.06 to 1[80]. Like streptomycin, mannosidostreptomycin is inactivated by reagents which react with the carbonyl group, and, on reduction, it forms a dihydro compound.

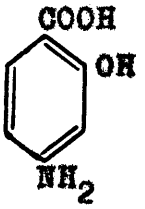


(XIII)

para-Aminosalicylic Acid.

The observations of Bernheim[81,82], that addition of benzoates and salicylates increased the oxygen uptake of the tubercle bacillus, led to the discovery of p-aminosalicylic

acid (XIV) as a useful drug in the treatment of tuberculosis.



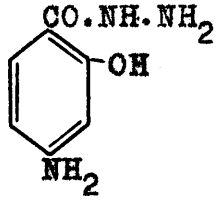
(XIV)

Lehmann[83], on repeating the experiments, noted that benzoates and salicylates were only capable of influencing the oxygen metabolism of pathogenic strains of M. tuberculosis, the non-pathogenic strains being unaffected. Examination of a large number of derivatives of these acids revealed that p-aminosalicylic acid was tuberculostatic[84,85], and subsequently it was found to be effective in the treatment of tuberculosis in experimental animals[85,86], and man[87,88,89]. It is now well established as a chemotherapeutic agent in the treatment of tuberculosis, since it has a low toxicity to human beings[90]. It has the disadvantage of being rapidly absorbed and excreted, so that large daily doses (about 20g.) are required. It is not surprising therefore that nausea, vomiting, and diarrhoea are some of the unpleasant side-effects associated with its use.

Many other derivatives and compounds similar to p-amino-salicylic acid have been prepared and tested in the search for a more active and more suitable compound. Phenyl-4-amino-salicylate was reported[91,92,93] to have in vitro and in vivo

tuberculostatic activity many times greater than that of p-aminosalicylic acid, but it has since been reported[94] that both this and other aryl esters have *in vivo* activities which are only of the same order as the parent compound. The alkyl esters were shown[94,95] to have only a low order of activity.

4-Amino-2-hydroxybenzhydrazide (XV) has been tested both



(XV)

in vitro and *in vivo* and its activity was found to be low[94,96,97,98], although it has been reported elsewhere[99] to have an activity *in vitro* of a similar order to that of p-aminosalicylic acid.

Büchi, Lieberherr, and Flury[100] prepared a series of derivatives involving substitution or replacement of the carbonyl group, substitution of the amino group, or replacement of the hydroxy group. None of these compounds was of the same level of activity as p-aminosalicylic acid *in vitro*.

These reports and many others have confirmed the original conclusions of Lehmann[84] that:-

(1) the hydroxyl group in the 2 position is essential; replacement by amino or chlorine abolishes all activity, whilst removal to the 3 position causes a marked fall in activity,

(2) replacement of the 4-amino group by a nitro or other group, or removal to the 3 or 5 position, causes a marked fall in activity,

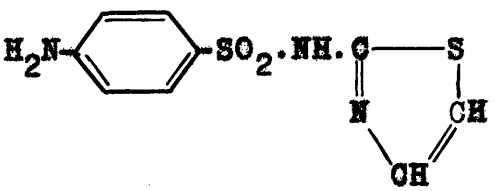
(3) alkylation of the amino group or esterification of the carboxyl group causes only a slight reduction of activity.

The use of p-aminosalicylic acid is now well established in the treatment of tuberculosis, but owing to the development of strains of M. tuberculosis resistant to the drug, and to the fact that p-aminosalicylic acid itself delays emergence of strains resistant to streptomycin or Isoniazid, it is normally given with one or other of these substances. The dose of p-aminosalicylic acid when given with streptomycin is still about 20g. daily, smaller doses being found to be less effective [101]. Combination with Isoniazid is more valuable from the point of view of avoiding bacterial resistance, and as little as 10g. of the sodium salt may then be given daily along with 200mg. of Isoniazid [66,67].

Thiosemicarbazones.

The discovery that sulphonamides such as sulphathiazole (XVI) and sulphathiadiazole (XVII) showed activity against the tubercle bacillus [102], led to the examination of compounds having similar structures. Domagk described 4-acetylaminobenzaldehyde thiosemicarbazone (Thiacetazone; conteben; TB1/698; tibione)(XVIII) as being the most active

of a series of substances examined. This compound has since



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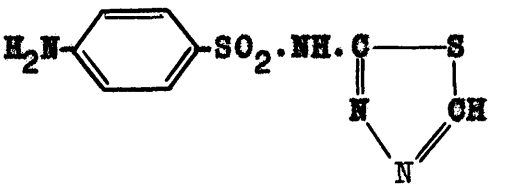

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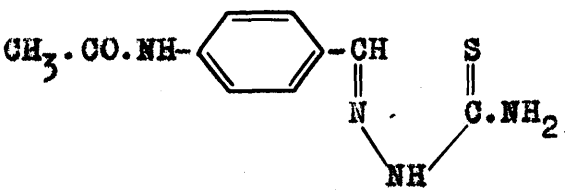


(XVIII)

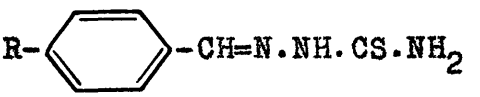
been thoroughly examined by several research groups. Preliminary tests indicated that it was superior to p-aminosalicylic acid in tuberculosis of experimental animals[103,104], and Domagk also confirmed this[105]. Hinshaw and McDermott[106] and Mertens and Bunge[107] described the results of large-scale clinical tests in Germany, and stated that in certain cases, improvement was noticed within a few days of the commencement of treatment. The dosage varied from 12.5 to 200 mg. daily. It was found that certain toxic effects, mainly in the form of gastro-intestinal disturbances, were frequent.

According to Domagk[104] and Levaditi[105], Thiacetazone is superior to p-aminosalicylic acid, but inferior to strepto-

mycin in experimental tuberculosis in animals. However, Spain, Childress, and Fishler[108] found that Thiacetazone and streptomycin were equally active in experimental animals, and that combination of the two drugs in half doses was just as effective as Thiacetazone alone, and probably more so than streptomycin. Simultaneous administration of the two drugs was also found[109] to delay the emergence of Thiacetazone-resistant organisms. Similarly, Thiacetazone given with a sub-effective dose of dihydrostreptomycin was found to be more effective in the treatment of tuberculosis in experimental animals[110] than Thiacetazone alone, or the combination of p-aminosalicylic acid and a sub-effective dose of dihydrostreptomycin.

The effect of structural modifications in the Thiacetazone molecule was examined by Behnisch, Mietzch, and Schmidt[111], who showed that the sulphur atom was important for tuberculostatic activity. Thiosemicarbazones of related aromatic ketones were found to be less effective than those of the aldehydes, and substitution of the hydrogen atoms of the thiosemicarbazide residue also led to a reduction in activity. Activity was increased by substitution in the aromatic ring, particularly so for substituents containing nitrogen, sulphur, and oxygen. Positional isomerism was also important, and the general order of decreasing activity was *para*, *meta*, *ortho*. p-Nitrobenzaldehyde thiosemicarbazone (XIX, R=NO_2) was more active than p-aminobenzaldehyde thiosemicarbazone, (XIX, R=NH_2)

but the latter was the parent compound for numerous derivatives (for example, R=C_6H_5CONH-, $(CH_3)_2N$-, $CH_3OC_6H_4CN=N$- , as well as CH_3CO-) all considerably more active than itself.



(XIX)

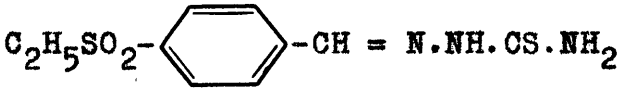
Similarly, oxygen substituted derivatives of p-hydroxybenzaldehyde thiosemicarbazone (for example XIX, R=CH_3O- and R=CH_3COO-) were found to be more active than the parent compound. p-Ethoxybenzaldehyde thiosemicarbazone has also been reported[112] to show appreciable activity in experimental animals.

p-Aminosalicylaldehyde thiosemicarbazone was reported to possess in vitro activity about ten times that of Thiacetazone[96], but according to Goldberg and Walker both p-aminosalicylaldehyde thiosemicarbazone and some of its N-substituted derivatives proved to be less effective than p-aminosalicylic acid in the treatment of tuberculosis in experimental animals[113].

Hagenbach and Gysin[114] reported that nicotinaldehyde thiosemicarbazones showed a relatively high tuberculostatic effect, but that replacement of the pyridine nucleus by furan, thiophene, thiazole, pyrrole, 4-methylpyrrole, or imidazole led to a complete loss of activity.

Although numerous other thiosemicarbazones have been

prepared and tested for activity against the tubercle bacillus, they are, almost without exception, as toxic as Thiacetazone[115,116]. p-Ethylsulphonylbenzaldehyde thiosemicarbazone (XX) for example showed marked activity[117,118]

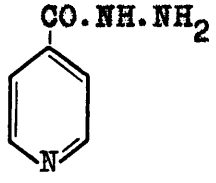


(XX)

but the report of a clinical trial[119] indicated that its toxicity was of a similar order to that of Thiacetazone. This high toxicity has restricted the introduction of the thiosemicarbazones into general use in the treatment of tuberculosis. They are, however, of value occasionally when special indications may advocate their use.

isoNicotinic Acid Hydrazide (Isoniazid).

isoNicotinic acid hydrazide (XXI) has recently been introduced as a chemotherapeutic agent for the treatment of



(XXI)

tuberculosis, and in many ways it is the most satisfactory substance available. Preliminary experiments showed that it

possesses an exceptionally high antitubercular activity[120, 121,122] and after the first encouraging report on its clinical use[123] there seemed to be good reason to believe that an effective treatment for tuberculosis had at last been found.

Isoniazid has the advantage of being comparatively free from any toxic effects in man when normal doses are given[124, 125] although Biehl and Nimitz reported[126] that peripheral neuritis became increasingly common as the daily dose was increased to 24 mg./kg. Toxic symptoms have also been reported in the case of experimental animals which received exceptionally large doses of Isoniazid[124,127,128]. Sullivan, Barclay, and Karnofsky, however, found no serious adverse reactions when patients were given daily doses of 20-37.5 mg./kg. for periods of from six to sixty days[129].

It soon became obvious that in the treatment of patients with Isoniazid, initial improvement was invariably followed by relapse, due to the development of strains of M.tuberculosis resistant to the drug[126,130,131]. Fortunately this relapse can be prevented or delayed by giving Isoniazid and streptomycin together[132]. The Medical Research Council reports that streptomycin, 1g. daily, with Isoniazid, 200mg.daily, is effective both clinically and in producing a low incidence of both streptomycin and Isoniazid resistance[66,67]. The action of the two is synergistic, thus showing that they must act by a different mechanism against the tubercle bacillus.

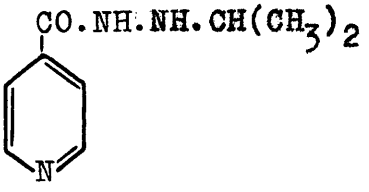
A combination of Isoniazid and p-aminosalicylic acid is

also effective in the treatment of tuberculosis[133,134,135,136] but here again it has been reported[137,138] that the initial recovery is followed by relapse, due to emergence of Isoniazid-resistant strains of M. tuberculosis. A variation in this method of treatment in which the patients are treated for short periods with, successively, Isoniazid and streptomycin, streptomycin and p-aminosalicylic acid, and p-aminosalicylic acid and Isoniazid, was considered to be an improvement[139].

Recently, it has been demonstrated[140,141,142,143], that strains of the tubercle bacillus which are highly resistant to Isoniazid, show a loss of virulence for experimental animals. Mycobacteria possessing lower levels of resistance than are normally found clinically, do not show this lack of virulence. Middlebrook, Cohn and Schaefer found[144] this highly resistant strain in the sputum of patients whose treatment with Isoniazid had been started at a dosage of not less than 8 mg./kg. daily, and they claimed that treatment with Isoniazid alone should be started at this dosage, since all the resistant strains which emerged would then be avirulent. It is not known yet whether strains, attenuated in this way, do or do not revert once again to the virulent form, and clearly the adoption of this method of medication depends on this very point.

Following upon the success of Isoniazid in the treatment of tuberculosis, many other acid hydrazides and derivatives

have been prepared and tested for activity against M.tuberculosis. Favourable results have been obtained with 1-isonicotinoyl-2-isopropylhydrazine (XXII) in experimental



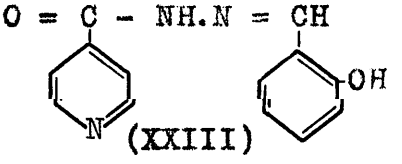
(XXII)

animals[121,145,146,147]. isoNicotinoyl hydrazide methanesulphonate[148,149] has also been found to possess activity similar to that of Isoniazid in experimental animals, and, being much less toxic than Isoniazid, it could be used in larger doses with a correspondingly more favourable result.

Bernstein and his colleagues reported[150] that introduction of a substituent into the pyridine ring resulted in a loss of both in vitro and in vivo activity. On the other hand, alkylation or acylation of the hydrazine nitrogen, or condensation of Isoniazid with aldehydes and ketones yielded active derivatives, but none of them was more active than Isoniazid. They also described[151] the activity of several heterocyclic carboxylic acid hydrazides. The most active of these were 2-furoic acid hydrazide, thiophen-2-carboxylic acid hydrazide, and glyoxaline-5-carboxylic acid hydrazide, but none of these compounds was as active as Isoniazid.

Among the many other derivatives of Isoniazid, which

possess *in vivo* and *in vitro* activity against *M. tuberculosis*, are 1,1'- methylenebis(2-*iso*nicotinoyl hydrazide)[152] and D-galacturonic acid *iso*nicotinylhydrazone[153], both of which have been reported as being less toxic than the parent compound. *o*-Hydroxybenzal *iso*nicotinylhydrazone (XXIII)



(XXIII)

has also been reported[154] to have activity of the same order as Isoniazid, and its toxicity towards experimental animals is low, being between one fifth and one tenth of that of the parent compound. The two compounds were found to act together, delaying development of strains of *M. tuberculosis* resistant to either substance.

In the aliphatic series, cyanacetic acid hydrazide was found by Hartl[155] to possess high *in vivo* activity, and a preliminary report by Scheu[156] claimed that it was comparable to Isoniazid in the treatment of human pulmonary tuberculosis. Later reports, however, showed that the drug was less active than Isoniazid *in vitro* and *in vivo* against *M. tuberculosis*, and that it was usually inactive against Isoniazid-resistant strains, although the toxicities of the two compounds were of the same order[157,158]. *In vitro* experiments on the tuberculostatic activities of a number of cyano-aliphatic hydrazides and related compounds indicated

that some of them possessed similar or increased activity over that of cyanacetic acid hydrazide[159].

The mode of action of Isoniazid against the tubercle bacillus has not been explained, but recent experimental work may give a lead which will eventually provide this information. *In vitro* tests against the tubercle bacillus with Isoniazid in the presence of copper were claimed to enhance the activity of the drug[160] and it was suggested that the tuberculostatic activity of Isoniazid was due to its ability to form chelate compounds[161]. It was found that 1-*iso*nicotinoyl-1-methylhydrazine showed no activity against *M. tuberculosis*, and since this compound cannot form a chelate with copper, it supports the view that chelation is an essential step in the action of the drug[162]. However, Albert has since shown[163] that of the two isomers of *iso*-nicotinic acid hydrazide, nicotinic acid hydrazide has the same affinity for metals and is inactive against *M. tuberculosis*, whilst picolinic acid hydrazide has a very much greater affinity for metals but is much less active than Isoniazid against the tubercle bacillus. He concludes that some other factor apart from the ability to form chelates must be of importance in the functioning of Isoniazid as a tuberculostatic agent. It would appear, therefore, that positional isomerism in this series somehow plays an important part in determining the level of activity.

DISCUSSION OF THE

SYNTHESES UNDERTAKEN

INTRODUCTION

Although the known substances most effective in the treatment of tuberculosis are those already described, the search continues for more active yet less toxic compounds. The diversity of structure amongst known active compounds presents no common pattern which might lead to the discovery of more active compounds. Certain observations, however, do provide fresh points from which to attack the problem. Thus, for example, long-chain fatty acids and bases are both known to have a marked inhibitory effect on the growth of Mycobacterium tuberculosis, and it is conceivable that this activity is bound up with the all-important fat metabolism of the organism.

Stanley, Coleman, Greer, Sacks and Adams[164], in examining a series of long-chain fatty acids, showed that the maximum effect was produced by those acids containing 16 or 17 carbon atoms. They also found that the activity increased as the carboxyl group was displaced towards the centre of the molecule, whilst replacement of the carboxyl group by a dialkylaminomethyl group also produced active compounds. Robinson[165] described the preparation of a branched-chain fatty acid which was more active than the straight-chain compounds of Adams and Stanley. Other normal and branched-chain acids, including derivatives of chaulmoogric and

hydnocarpic acids, have been examined[166,167,168,169], and found to exhibit activity against M. tuberculosis in vitro. Bailey and Cavallito[170] have shown that combinations of streptomycin and aliphatic acids of chain length 10 to 18 carbon atoms are more active in vitro than streptomycin alone. On the other hand, Dubos and Davis[171] and Dubos and Middlebrook[172] found that the esters of certain long-chain fatty acids such as oleic acid favoured the growth of the bacillus.

The natural acids of the tubercle bacillus itself, which have been isolated by Anderson[173] and others, have been shown to promote tubercle formation, the typical lesion of the disease, in experimental animals. One of these acids, phthioic acid, which exhibited this property and which was originally thought to be saturated because of its failure to react with halogens, has since been shown to be a mixture mainly of $\alpha\beta$ -unsaturated acids[174,175,176].

The antibacterial properties of aliphatic ω -mono- and di-amines, amidines, guanidines, and quaternary bases were first examined by Fuller[177] in a series of in vitro tests against a number of micro-organisms. As with the aliphatic acids, antibacterial activity of these bases generally increased with chain length up to a maximum and thereafter decreased with further lengthening of the chain. Similar tests were carried out by Borrows, Hargreaves, Page, Resuggan, and Robinson[178] on a series of primary, secondary, and

tertiary amines containing between 8 and 30 carbon atoms. In all cases, these compounds with between 17 and 20 carbon atoms in the chain were most active against the micro-organisms tested, which included M. tuberculosis.

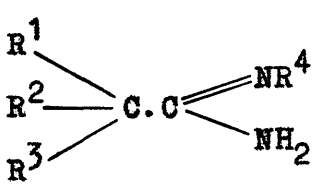
Ames and Bowman[179] prepared and tested a series of bisdialkylaminoalkanes (XXIV) against M. tuberculosis, and the compounds (XXIV), in which n = 16 or 18; R = CH_3, were found to exhibit considerable activity.

$$(R)_2N.(CH_2)_n.N(R)_2$$

(XXIV)

They also showed that similar long-chain substituted piperidines, although rather less active, were much less toxic than the corresponding dialkylaminoalkanes.

The long-chain aliphatic monoamidines (XXV) prepared by Newbery and Webster[180] were also found to possess anti-bacterial properties, and some showed marked in vitro activity



Where R^4 = n alkyl and $R^1 = R^2 = R^3 = H$

or $R^1 = R^2 = R^3 = R^4$ = alkyl

(XXV)

against M. tuberculosis. However, they were considered to be too toxic for the prolonged administration likely to be

required to treat animals infected with tuberculosis.

The effect of introducing a sulphone group into the carbon chain of aliphatic amines was examined by Peak and Watkins[181]. A series of compounds (XXVI, R=C_4H_9, C_8H_{17}, and $C_{16}H_{33}$) and (XXVII) were shown to exhibit only low <u>in vitro</u> activity, although in many cases the corresponding sulphides were appreciably active. The only example of an

$(C_2H_5)_2N.CH_2.CH_2.SO_2.R$ (XXVI)

$CH_3N(CH_2.CH_2.SO_2.C_8H_{17})_2$ (XXVII)

$(C_2H_5)_2N.CH_2.CH_2.SO_2.CH_2.CH_2.N(C_2H_5)_2$

(XXVIII)

$\alpha\omega$-bisdialkylaminoalkyl sulphone examined was the short chain compound (XXVIII) which showed little activity. <u>In vitro</u> activity against <u>M. tuberculosis</u> and other bacteria has also been reported by Nambara[182] for a number of aryl and aryl-alkyl sulphones, including the compounds (XXIX) (R^1 = CH_3 or C_6H_5; R^2 = C_6H_5O, $C_4H_9SO_2$, or 1-piperidyl).

$R^1.SO_2.CH_2.CH_2.R^2$

(XXIX)

In view of the high tuberculostatic activities which have been reported for $\alpha\omega$-bisdialkylaminoalkanes, and of

the known potentiating effect of polyoxyethylene substituents in the aromatic amino sulphones[183], it was planned to examine in detail the effect of introducing the sulphone group into a series of aliphatic molecules. Four main lines of investigation were envisaged:-

1. The synthesis of a series of $\alpha\omega$-bisdialkylaminoalkyl sulphones, in which not only the effect of the sulphone group but also that of varying chain length on tuberculostatic activity could be studied.
2. The examination of a parallel series of sulphides in those cases where the choice of synthetic route to the sulphone was through these intermediates.
3. The preparation and testing of analogous $\alpha\omega$-bis-(1'-piperidyl)-alkyl sulphides and sulphones, on the grounds that such compounds should be markedly less toxic than their bis-dialkylaminoalkyl analogues.
4. The synthesis of a series of bis-ω-dialkylamino-β-hydroxyalkyl sulphides and sulphones, with the object of assessing the influence of hydroxyl substituents on the toxicity of such compounds.

The inclusion of a study of the influence of hydroxyl substituents in this series was felt to be important, since it has been shown that the introduction of the hydroxyl group into the molecule of aromatic amino sulphones markedly reduces the toxicity, without affecting the level of activity[33,34].

It was considered that a series of β -hydroxy sulphones would be analogous to 2:2'-dihydroxy-4:4'-diaminodiphenyl sulphone, in respect of the relative positions of the hydroxyl and sulphone groups. Moreover, one route to such a series of compounds, via the corresponding $\alpha\beta$ -unsaturated sulphones was particularly attractive, since many of the acids which have been isolated from the tubercle bacillus are themselves $\alpha\beta$ -unsaturated. Although little is known of the function of these acids in the metabolism of the organism, they are known to be largely responsible for tubercle formation, and it was felt that the study of unsaturated sulphones might provide a useful means of probing the importance of unsaturation.

The first three lines of investigation were accomplished successfully, but attempts to obtain a route to the fourth series of compounds were less successful, since only one intermediate $\alpha\beta$ -unsaturated sulphone was obtained. The methods of synthesis are discussed in the succeeding parts of this section, and the bacteriological results of the compounds tested are shown and analysed fully in the appropriate part of the thesis.

BISDIALKYLAMINOALKYL SULPHONES

Although numerous methods for the synthesis of sulphones have been reported from time to time[184,185,186,187,188,189], the route most generally adopted is the classical one via the corresponding sulphides. Examination of a number of examples of the condensation of alkyl halides to yield sulphides, showed that yields in these reactions are often only of the order of 50% or less. Losses of this order, after the preparation of intermediates, which quite possibly involve several stages, are serious, and it was therefore decided to examine the possibility of devising a method which would allow the formation of this link at an earlier stage in the reaction sequence. A synthesis based on the use of diethyl malonate appeared to offer the possibility of achieving this end.

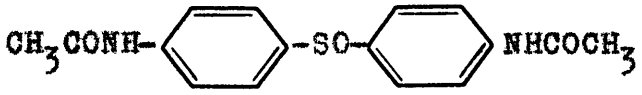
Reactions with diethyl malonate.

Naik, Desai, and Parekh[190] have described reactions between thionyl chloride and various active methylene derivatives to yield sulphoxides. Of particular interest from the point of view of the present work, were the reactions between thionyl chloride and malon-dimethylamide and malon-diethylamide to yield the sulphoxides (XXX, R = CH_3 or C_2H_5).

$$(R.NH.CO)_2CH.SO.CH(CO.NH.R)_2$$

(XXX)

Similarly in the aromatic series, Sugasawa and Sakurai[191] prepared 4:4'-diacetamidodiphenyl sulphoxide (XXXI) from acetanilide and thionyl chloride.



(XXXI)

A series of reactions as indicated below was therefore envisaged, in which the first step was the condensation of diethylmalonate (XXXII, R = H) or of a substituted diethylmalonate (XXXII, R = alkyl) with thionyl chloride.

$$R.CH(CO_2C_2H_5)_2 \xrightarrow{SOCl_2} (C_2H_5CO_2)_2\ R.C.SO.C.R(CO_2C_2H_5)_2$$

(XXXII) (XXXIII)

$$\xrightarrow[\text{decarboxylation}]{\text{hydrolysis and}} R.CH_2.SO.CH_2.R$$

Reaction of ethoxymagnesiomalonic ester, prepared by the method of Bowman[192], with thionyl chloride under varying conditions gave the expected bisdiethoxycarbonylmethyl sulphoxide (XXXIII, R = H). Initially thionyl chloride in solution in benzene was added to the ethoxymagnesiomalonic ester, but in subsequent experiments it was found that improved yields, and smaller quantities of by-product were obtained by reversing the method of addition. When the

reaction was complete, excess diethyl malonate was removed by distillation under reduced pressure, whilst the bulk of the tetraethyl ethanetetracarboxylate, formed as a by-product in the reaction, crystallised after a few days, and was removed by filtration. The product occurred as a yellowish-to reddish-brown oil, with a slight green fluorescence, soluble in most organic solvents, sparingly soluble in light petroleum, and insoluble in water. It was found to be soluble in alkali hydroxide solutions, due to hydrolysis and formation of the corresponding salts.

At this stage, the refractive index of the product, due to the presence of impurity, chiefly tetraethyl ethanetetracarboxylate, was always in the region of 1.46. This impurity was difficult to remove completely, as its solubility was similar to that of the required product in all solvents tested.

Attempts to purify the sulphoxide by distillation under reduced pressure using normal methods were unsuccessful. Bath temperatures of over 190°C. were required and decomposition occurred rapidly, as shown by darkening of the compound, and the accompanying distillation of diethyl malonate. Chromatographic separation of bisdiethoxycarbonylmethyl sulphoxide from its impurities was attempted by passing a benzene solution through a column of Whatman's cellulose pulp, but the refractive index of the recovered material was practically unchanged. Pure samples were finally obtained by molecular

distillation under high-vacuum, although distillation proceeded only very slowly. In this way diethyl malonate came over first at 90-95°C., followed by tetraethyl ethane-tetracarboxylate, whilst at temperatures of 100°C. (increasing to 115°C. as the level of the liquid fell in the distillation flask) a pale straw-coloured liquid distilled, darkening slightly as the temperature was raised. Redistillation gave a liquid of refractive index, $n_D^{13.5}$ 1.4630, in small yield, which was shown by analysis to be reasonably pure bisdiethoxy-carbonylmethyl sulphoxide.

A final attempt to speed this process by steam-distillation showed that separation of the sulphoxide from its impurities could not be effected by this means.

Attempts to characterise bisdiethoxycarbonylmethyl sulphoxide.

In view of the difficulty which had been experienced in obtaining pure samples of the required sulphoxide, it was considered desirable to characterise the product further, if possible by the preparation of crystalline derivatives. Most of these experiments were unsuccessful, the only products which were obtained being liquids of uncertain composition. These experiments are now briefly described.

An attempt to form a crystalline diethylamide by refluxing with diethylamine was abortive and the starting

ester was recovered. The preparation of the SS-dialkyl-N-toluene-p-sulphonylsulphidimine by condensation with p-toluenesulphonamide in acetic anhydride following the method of Tarbell and Weaver[193] was similarly unsuccessful, the only products being N-acetyl-p-toluenesulphonamide and unchanged sulphoxide. Neither could the reaction be induced using phosphorus pentachloride in chloroform, or aluminium chloride in benzene as dehydrating agents. This lack of reactivity provides a further example of a heavily substituted sulphoxide failing to form a sulphidimine. Thus, Mann and Pope[194] were unable to prepare sulphidimines from derivatives of diethyl sulphide containing more than two chlorine atoms, whilst Tarbell and Weaver[193] were similarly unable to condense bis-2-hydroxyethyl sulphoxide with toluene-p-sulphonamide.

Hydrolysis of bisdiethoxycarbonylmethyl sulphoxide to thionyldiacetic acid (biscarboxymethyl sulphoxide, XXXIV)

$$HOOC.CH_2SO.CH_2COOH$$

(XXXIV)

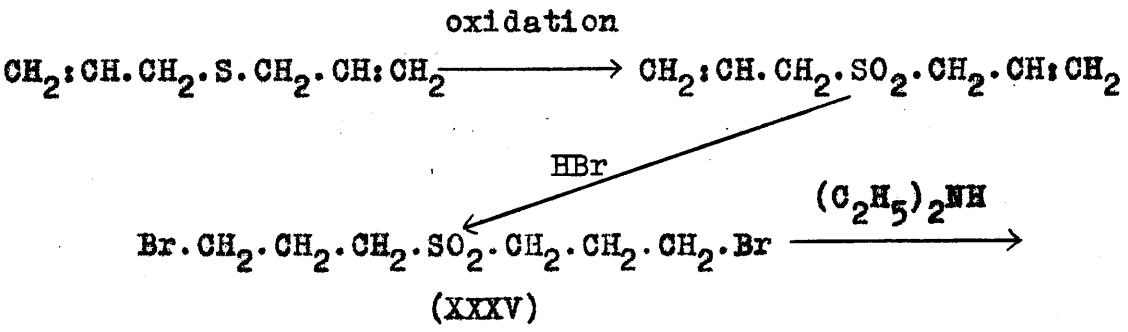
was only partially successful despite numerous modifications of the experimental technique. Saponification with both aqueous and ethanolic potassium hydroxide, followed by acidification and decarboxylation, was not profitable, the difficulty being to separate the water-soluble product from the salts formed in the reactions. Ethanolic hydrochloric

acid failed to bring about hydrolysis, but refluxing with concentrated hydrochloric acid gave the expected biscarboxymethyl sulphoxide. The latter failed to undergo further decarboxylation to dimethyl sulphoxide when heated above its melting-point.

Oxidation of bisdiethoxycarbonylmethyl sulphoxide followed by treatment with concentrated hydrochloric acid failed to yield the expected biscarboxymethyl sulphone. Because of the failures with these reactions, and the low yields of bisdiethoxycarbonylmethyl sulphoxide, further work on this route appeared to be unprofitable, and attention was turned to alternative methods of obtaining the required compounds.

The preparation of bis-3-diethylaminopropyl sulphone.

In considering possible methods for the synthesis of bis-3-diethylaminopropyl sulphone it was felt that methods involving the direct condensation of diethylaminopropyl chloride with sodium sulphide should be avoided. Slotta and Behnisch[195] have shown that diethylaminobutyl chloride readily quaternises to 1:1-dimethylpyrrolideum chloride, and 1-dimethylamino-2-chloropropane is also known to form ethyleneiminium compounds[196]. The possibility of a similar cyclisation with 3-diethylaminopropyl chloride under the conditions necessary for sulphide formation influenced the choice in favour of the following route, which was adopted.



$(C_2H_5)_2N.CH_2.CH_2.CH_2.SO_2.CH_2.CH_2.CH_2.N(C_2H_5)_2$

(XXXVI)

It was subsequently shown at a later date that 3-diethylaminopropyl chloride can be condensed with sodium sulphide quite readily to yield bis-3-diethylaminopropyl sulphide, and that the corresponding sulphone could be obtained from the latter by oxidation.

The addition of hydrogen bromide to diallyl sulphone in the presence of benzoyl peroxide was expected to produce the required intermediate compound, bis-3-bromopropyl sulphone (XXXV), the normal addition of halide based on the Markownikoff rule being reversed under the combined influence of the peroxide and the polarity of the sulphone group.

Following the method described for the preparation of methyl ß-bromopropionate in Organic Syntheses[197], diallyl sulphone was treated with hydrogen bromide in ice-cold ethereal solution. Practically no increase in weight occurred under these conditions. Similarly, using carbon tetrachloride as solvent there was little increase in weight after

treating the solution at room temperature with hydrogen bromide for 26 hours. Reaction of diallyl sulphone with constant-boiling hydrobromic acid under reflux for 3.5 hours, followed by neutralisation of the acid and extraction with chloroform, was equally unsuccessful.

Experiments in which carbon tetrachloride solutions of diallyl sulphone were refluxed for varying periods, while hydrogen bromide was passed in, were more successful. After removal of the solvent a reddish-brown tarry liquid was obtained, from which a liquid fraction was obtained after extraction with benzene, ether, and alcohol. Further addition of hydrogen bromide to this extract in carbon tetrachloride, yielded, on removal of solvent, a reddish-brown solid, which, after chromatography in benzene on a column of mixed activated charcoal and powdered cellulose, gave crystalline material. Further chromatography of this material in benzene on a column of alumina, followed by repeated recrystallisation of the fractions from ether yielded, in one experiment, crystals melting at 102.5°C. in very small yield, and larger amounts of crystals melting at 72-74°C. From other experiments a third crystalline substance, melting at 85-86°C. was obtained in addition to that melting at 72-74°C. Analyses showed that the sample melting at 85-86°C. was the required bis-3-bromopropyl sulphone, and that the other two compounds were monobromo compounds. The compound, m.p. 72-74°C., was converted to a mono-diethylaminopropyl propenyl sulphone by reaction

with diethylamine.

Bis-3-bromopropyl sulphone was finally obtained in improved and consistent yields by a modification of the reaction, in which hydrogen bromide was passed into the solution of diallyl sulphone in carbon tetrachloride continuously for 20 hours, the reaction mixture being raised to boiling point initially and periodically every three hours. Using this method of adding hydrogen bromide, a sample of monobromo compound, m.p. 72-74°C., was also partially converted to bis-3-bromopropyl sulphone, indicating that it must be 3-bromopropyl prop-2'-enyl sulphone (XXXVII). The corresponding diethylamino derivative described above is on this basis 3-diethylaminopropyl prop-2'-enyl sulphone (XXXVIII). The

$Br\ CH_2CH_2CH_2SO_2CH_2CH{:}CH_2$ (XXXVII)

$(C_2H_5)\ N.CH_2CH_2CH_2SO_2CH_2CH{:}CH_2$ (XXXVIII)

$CH_3.CHBrCH_2SO_2CH_2CH{:}CH_2$ (XXXIX)

other unsaturated monobromo compound, m.p. 102.5°C., is assumed to be 2 bromopropyl prop-2'-enyl sulphone (XXXIX).

Bis-3-diethylaminopropyl sulphone (XXXVI) was readily prepared by the reaction of bis-3-bromopropyl sulphone with diethylamine. The crude base was not isolated, but converted directly into the crystalline dihydrochloride, which was readily obtained in a high state of purity. A pure sample

of bis-3-diethylaminopropyl sulphone was subsequently prepared by the alternative route already mentioned (p.38). The preparation is described in detail in the next section.

The preparation of long-chain bisdialkylaminoalkyl sulphides and sulphones.

The method described in the previous section for the preparation of bis-3-diethylaminopropyl sulphone was adopted to avoid the possibility of self-quaternisation of 3-diethylaminopropyl chloride in the alternative more general route via bis-3-diethylaminopropyl sulphide. In the synthesis of longer chain compounds of the general type (XL), where

$$(C_2H_5)_2N(CH_2)_nSO_2(CH_2)_nN(C_2H_5)_2$$

(XL)

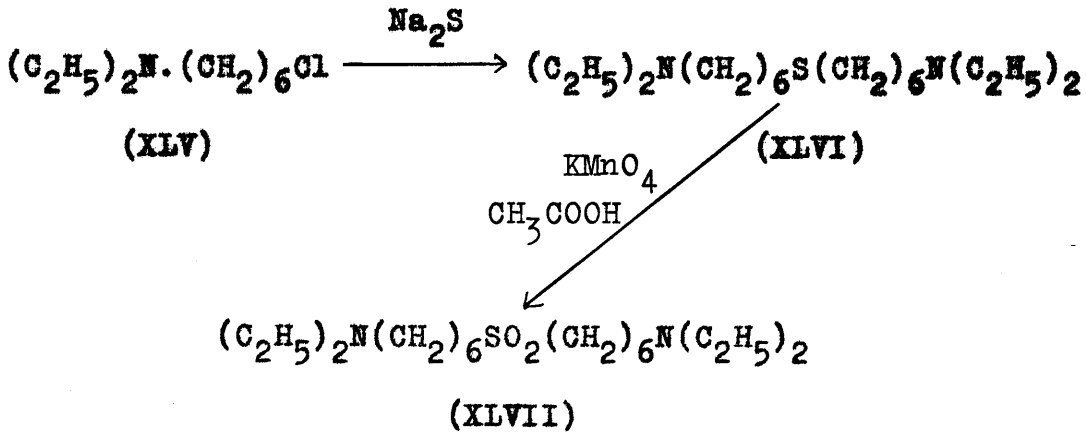
n = 6 and 10, this difficulty no longer applied. A general method of synthesis was therefore used, based on the method described by Andrews, Bergel, and Morrison[198] for the preparation of analogous $\alpha\omega$-trimethylalkylammonium sulphides, as outlined below.

$$C_2H_5OOC(CH_2)_4COOH \xrightarrow{SOCl_2} C_2H_5OOC(CH_2)_4COCl \xrightarrow{(C_2H_5)_2NH}$$

(XLI) (XLII)

$$C_2H_5OOC(CH_2)_4CON(C_2H_5)_2 \xrightarrow{LiAlH_4} (C_2H_5)_2N.(CH_2)_6OH \xrightarrow[2.\ NaOH]{1.\ SOCl_2}$$

(XLIII) (XLIV)



Ethyl hydrogen adipate (XLI) was prepared in 27.9 per cent yield from adipic acid and diethyl adipate by the method described in Organic Syntheses[199] for the preparation of ethyl hydrogen sebacate. A yield of 71-75 per cent was reported for the latter compound. Dibutyl ether was omitted in the preparation of ethyl hydrogen adipate, but a subsequent preparation using dibutyl ether failed to increase the yield. It was found more convenient to separate the mixed distillate of diethyl adipate and ethyl hydrogen adipate by extraction of the latter compound with aqueous alkali, followed by acidification and extraction with organic solvent, rather than to separate the two esters by fractional distillation.

Ethyl hydrogen adipate was converted to ethyl adipyl chloride (XLII) by refluxing with excess thionyl chloride. After removal of excess reagent, the ethyl adipyl chloride, without further purification, was condensed with diethylamine to give ethyl N N-diethyladipamate (XLIII). Reduction of the latter with lithium aluminium hydride in ether gave 6-hydroxyhexyldiethylamine (XLIV) in good yield.

6-Hydroxyhexyldiethylamine in benzene solution was converted into 6-chlorohexyldiethylamine hydrochloride by the slow addition of thionyl chloride. It was found that the presence of solvent was essential since direct reaction was so vigorous that charring occurred. After removal of benzene and excess thionyl chloride, the hydrochloride was converted to the free base (XLV) by treating it with cold aqueous sodium hydroxide solution. Extraction with ether gave the crude base which was very dark in colour, and distillation gave pure 6-chlorohexyldiethylamine.

6-Chlorohexyldiethylamine was converted to bis-6-diethylaminohexyl sulphide (XLVI) by refluxing with sodium sulphide in aqueous ethanolic solution. The product was readily isolated, after distilling off most of the ethanol, by extraction with ether, and, after purification by distillation, was oxidised with potassium permanganate in 50% acetic acid to bis-6-diethylaminohexyl sulphone (XLVII).

The dihydrochlorides of the sulphide and sulphone were obtained by dissolving the respective bases in dilute hydrochloric acid, evaporating to dryness under reduced pressure, treating with charcoal as necessary, and recrystallising to constant melting-point from ethanol-ether.

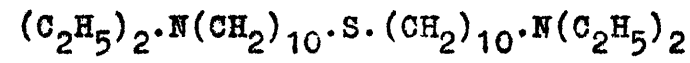
The corresponding piperidyl derivatives, bis-6-(1'-piperidyl)-hexyl sulphide (XLVIII) and bis-6-(1'-piperidyl)-hexyl sulphone (XLIX) were obtained by treating ethyl adipyl chloride with piperidine, and following the subsequent stages

of the synthesis described above. The sulphide, which was

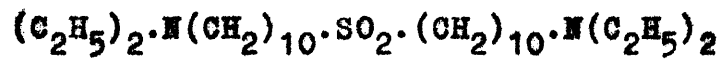
(XLVIII) (XLIX)

a liquid, was purified by distillation, and the sulphone by recrystallisation from ether-light petroleum. The corresponding dihydrochlorides were prepared and purified in the usual way.

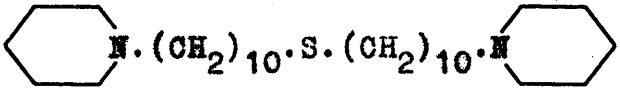
Bis-10-diethylaminodecyl sulphide (L) and sulphone (LI), and bis-10-(1'-piperidyl)-decyl sulphide (LII) and sulphone (LIII) were obtained in an analogous manner from



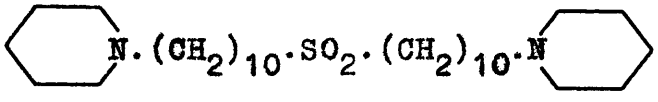
(L)



(LI)



(LII)



(LIII)

ethyl hydrogen sebacate. Bis-10-diethylaminodecyl sulphide, obtained as a colourless oil, was purified by distillation.

Bis-10-diethylaminodecyl sulphone and bis-10-(1'-piperidyl)-decyl sulphide were both low-melting solids which could not be purified by recrystallisation. Bis-10-(1'-piperidyl)-decyl sulphone, on the other hand, was readily obtained in a high state of purity by recrystallisation from ether. Crystalline dihydrochlorides were easily prepared from all these compounds.

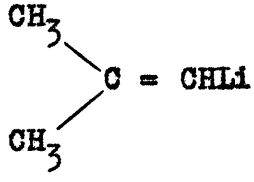
It was shown that the same general method was applicable to the synthesis of bis-3-diethylaminopropyl sulphide and that cyclisation of the intermediate 3-diethylaminopropyl chloride does not occur. Formation of the corresponding sulphone, bis-3-diethylaminopropyl sulphone (XXXVI) by this route provided proof that addition of hydrogen bromide to diallyl sulphone under the conditions already described did in fact give bis-3-bromopropyl sulphone, and not the alternative bis-2-bromopropyl sulphone.

Ethyl-ß-diethylaminopropionate, prepared by the method of Adamson[200] from diethylamine and ethyl acrylate, was converted by a series of reactions analogous to those described above to bis-3-diethylaminopropyl sulphide and bis-3-diethylaminopropyl sulphone. The latter, as the dihydrochloride, was identical in every respect (m.p. and mixed m.p.) with the dihydrochloride of bis-3-diethylaminopropyl sulphone obtained by the route from diallyl sulphone.

$\alpha\beta$- UNSATURATED SULPHONES.

Experiments with lithium alkenyls.

The preparation of sulphoxides, which are themselves readily oxidised to the corresponding sulphones, by the reaction of Grignard reagents has been reported on a number of occasions. Sulphoxides have been formed in this way by reaction with thionyl chloride[201,202,203], also with alkyl sulphites and thionyl chloride[194]. E. A. Braude and his collaborators have described in recent years a number of condensations using alk-1-enyl lithium derivatives[204,205, 206,207,208,209,210] as intermediates in the preparation of unsaturated compounds. It was decided, therefore, to examine the reaction between isobutenyl lithium (LIV) and



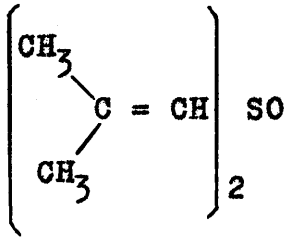
(LIV)

ethyl sulphite as a model for a general route for the formation of bis- $\alpha\beta$ -unsaturated sulphoxides.

isoButenyl bromide, prepared from tertiary butyl alcohol by the method of Braude and Timmons[205] was converted into isobutenyl lithium by reaction with lithium metal in dry ether under nitrogen. The conversion to isobutenyl lithium, as determined by decomposing an aliquot portion with water

and titrating with standard acid, was found to be in the region of 70% of the theoretical yield. An attempt to increase the yield of lithium alkenyl by the use of lithium sand[211] was unsuccessful.

In the attempted preparation of diisobutenyl sulphoxide (LV), ethyl sulphite was slowly run into a cold stirred



(LV)

solution of isobutenyl lithium in an atmosphere of nitrogen. Decomposition of the reaction mixture by means of cold saturated ammonium chloride, followed by ether extraction, yielded a reddish-brown liquid in poor yield. In a repeat experiment, the mixture was refluxed for 1.5 hours after the addition of ethyl sulphite was complete. Extraction as above gave the same poor yield of liquid product, insufficient for characterisation.

In order to determine whether or not the failure of the reaction lay in the use of an alkenyl lithium derivative, a further experiment was carried out in an attempt to prepare di-n-butyl sulphoxide from n-butyllithium. Reaction of n-butyllithium, prepared from n-butyl bromide, with ethyl sulphite in the cold and extraction as above yielded a golden-yellow liquid in very poor yield. This showed some signs of

crystallising after standing for several days in a vacuum desiccator, and was probably the required sulphoxide, but since the yields were so poor, this method of synthesising the required compounds was not investigated further.

Bromination of saturated sulphones.

Bromination of fatty acids in the presence of red phosphorus (Hell-Volhard-Zelinsky method) gives the corresponding α-bromo acids[212]. The application of a similar reaction to saturated sulphones would be expected to yield $\alpha\alpha'$-dibromo sulphones, which by dehydrobromination would lead to the corresponding bis-$\alpha\beta$-unsaturated sulphones.

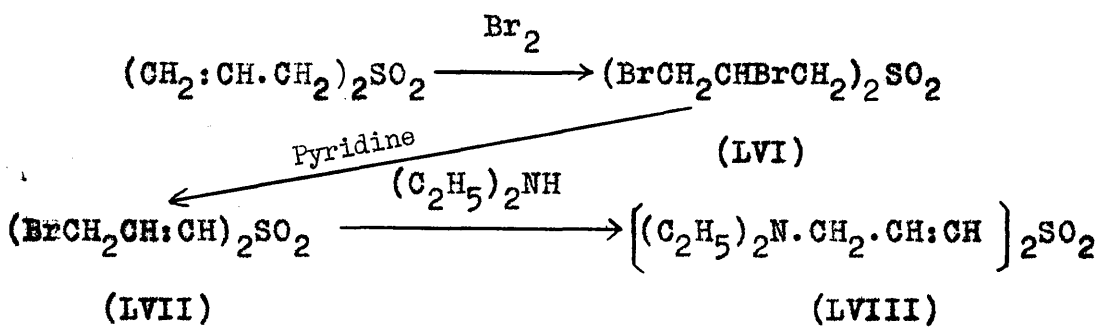
The bromination of di-n-butyl sulphone with red phosphorus and bromine was examined under similar conditions to those used in the preparation of α-bromoisobutyryl bromide[213]. After refluxing the sulphone in carbon tetrachloride solution for six hours with bromine and red phosphorus, and subsequent extraction, the bulk of the unchanged di-n-butyl sulphone was recovered. It would appear that the preparation of α-bromo sulphones cannot be effected by this method.

Bis-3-diethylaminoprop-1-enyl sulphone.

With the failure of the above attempt to find a general method for the preparation of $\alpha\beta$-unsaturated sulphones, attention was turned to the synthesis of bis-3-diethylaminoprop-1-enyl sulphone for which a specific route appeared to

be available from diallyl sulphone. The method adopted was based on the preparation by Rothstein[214] of benzyl 3-bromoprop-1-enyl sulphone from benzyl allyl sulphone by successive bromination and dehydrobromination.

The reaction scheme starting from diallyl sulphone and outlined below was envisaged. Bromination of diallyl sulphone in carbon tetrachloride solution gave bis-2:3-dibromopropyl sulphone (LVI) in good yield. In the initial



dehydrobromination experiments in which pyridine was added rapidly to the solution of bis-2:3-dibromopropyl sulphone with slow stirring of the reaction mixture viscous liquids were obtained which crystallised only very slowly. Under these conditions, high concentrations of pyridine may have been temporarily localised, so that the extent of dehydrobromination varied considerably and mixed products resulted.

Bis-2:3-dibromopropyl sulphone was satisfactorily dehydrobrominated in hot benzene solution by slowly adding the theoretical amount of pyridine and refluxing for 30 minutes. Pyridine hydrobromide was removed by extracting with water, and bis-3-bromoprop-1-enyl sulphone (LVII) was

obtained after removing the solvent, and crystallising from carbon tetrachloride.

Bis-3-diethylaminoprop-1-enyl sulphone (LVIII) was readily obtained by dissolving bis-3-bromoprop-1-enyl sulphone in benzene and adding excess diethylamine. A precipitate of diethylamine hydrobromide separated immediately, but the mixture was usually heated for a short time to complete the reaction. Purification of the base was attempted by distillation under reduced pressure, but decomposition occurred. It was therefore converted directly into the dihydrochloride, the latter being readily obtained in a high state of purity.

Both bis-3-bromoprop-1-enyl sulphone and bis-3-diethylaminoprop-1-enyl sulphone dihydrochloride showed complete lack of reactivity at the double bonds. They did not decolourise bromine water, nor did they give a yellow colour with tetranitromethane in carbon tetrachloride. Iodine values using both the iodine monochloride and pyridine bromide methods of the British Pharmacopoeia gave negative results. An experimean was set up to see if lithium bromide[215] would catalyse the uptake of bromine by bis-3-bromoprop-1-enyl sulphone, but after 5 hours the amount of free bromine in the solution remained unchanged. A similar lack of reactivity to halogens at the double bond is also a characteristic of $\alpha\beta$-unsaturated acids.

The only evidence of unsaturation was obtained from the fact that both compounds decolourised alkaline potassium

permanganate solution. Hydrogenation of bis-3-diethylamino-prop-1-enyl sulphone dihydrochloride using platinum oxide as catalyst was unsuccessful, and unchanged starting material was recovered. Hydrogenation of bis-3-bromoprop-1-enyl sulphone was more successful, but four molecules of hydrogen were taken up on complete hydrogenation and not two as expected, thus indicating that hydrobrominolysis had also occurred. This was confirmed by the evolution of hydrogen bromide fumes. The product, isolated as a reddish-brown rather viscous liquid was expected to be dipropyl sulphone, which is a low-melting solid. The residue, however, failed to crystallise on standing in a vacuum desiccator, and attempts to crystallise it from ether were equally unsuccessful. Partial hydrogenation similarly failed to yield bis-3-bromopropyl sulphone, the product being isolated as an oil which could not be characterised. It must be concluded therefore that hydrogenation and hydrobrominolysis, in all probability, proceed simultaneously.

The lack of reactivity of the double bond and the method of preparation of bis-3-diethylaminoprop-1-enyl sulphone together provide strong evidence for placing the double bond in the $\alpha\beta$ position.

Attempted preparation of bis-3-diethylaminoprop-1-enyl sulphide

Before this section was started the bacteriological results of the compounds prepared in the previous sections

had been obtained. These results are discussed later on in this thesis and are enumerated in Table 2, but they seemed to indicate that bis-3-diethylaminoprop-1-enyl sulphide would be more active against M. Tuberculosis than any of the compounds tested, and this particular work was started with the object of preparing the compound, and comparing its activity with that of bis-3-diethylaminoprop-1-enyl sulphone.

A route similar to that used in the preparation of bis-3-diethylaminoprop-1-enyl sulphone was envisaged, namely, bromination of diallyl sulphide followed by dehydrobromination and condensation of the product with diethylamine. Rothstein[216] has shown that 2-bromo-1:1-bisethylthiopropane (LIX) readily dehydrobrominates to give 1:1-bisethylthioprop-1-ene (LX) in accordance with the usual Saytzeff elimination

$$CH_3.CHBr.CH(SCH_2CH_3)_2 \longrightarrow CH_3.CH{:}C(SCH_2CH_3)_2$$

(LIX) (LX)

rule[217]. However application of the rule to the dehydrobromination of bis-2:3-dibromopropyl sulphide gives no guidance as to the direction in which elimination might be expected to occur, and by analogy with the corresponding sulphone, it seemed probable that $\alpha\beta$-elimination would also occur with the sulphide.

Bis-2:3-dibromopropyl sulphide (LXI) was readily obtained by direct bromination of diallyl sulphide, but attempts to

dehydrobrominate it with pyridine failed completely. It

$$BrCH_2.CHBr.CH_2.S.CH_2.CHBr.CH_2Br$$

(LXI)

was assumed that attack at the α positions was inhibited by electron accession from the lone pairs on the adjacent sulphur atom. These conditions do not apply in the corresponding sulphone, and the dehydrobromination proceeds smoothly and in good yield. Rothstein[218], too, has shown that whilst benzyl 2-chloropropyl sulphone undergoes dehydrochlorination in pyridine, the isomeric benzyl 3-chloropropyl sulphone, which, because of the more remote sulphone group is similarly not activated for elimination, is not dehydrochlorinated in pyridine.

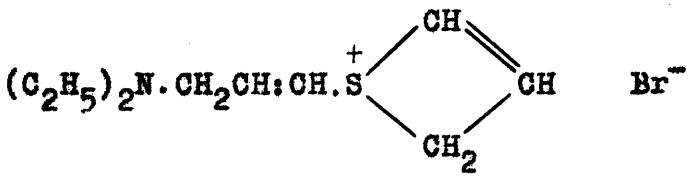
As expected, stronger bases, such as potassium hydroxide in aqueous or absolute ethanol, readily promoted dehydrobromination, the first experiments giving rise to a mixture of a tribromosulphide and a dibromosulphide, which were easily separated by fractional distillation. More careful control of the reaction conditions in subsequent experiments, gave only the dibromosulphide, thought to be bis-3-bromoprop-1-enyl sulphide.

However, it was soon apparent that this structure could not be correct on account of its behaviour when reacted with diethylamine. Heat was required to promote the reaction,

and the product proved not to be the expected bis-3-diethylaminoprop-1-enyl sulphide, but a base which conformed in analysis and molecular weight to a bromopropenyl diethylaminopropenyl sulphide. Reaction with diethylamine was not complete, since a second unsaturated dibromosulphide was recovered from the reaction mixture. This latter compound failed to react with diethylamine both under reflux in benzene solution, and when heated under pressure in the absence of solvent. The base which was obtained from the reaction mixture also failed to react further with diethylamine.

Two explanations of this anomaly seemed possible:-

(a) The formation of an intramolecular halide (LXII)



(LXII)

(b) The formation of a vinylic bromide during dehydrobromination.

Structure (LXII), however, is untenable, since formation of sulphonium halides has been observed only in δ -haloalkyl sulphides, and not with the corresponding γ -haloalkyl sulphides[219,220,221]. Moreover, the solubility properties of the base were the reverse of those expected of a sulphonium halide. The presence of a vinylic bromide, on the other hand,

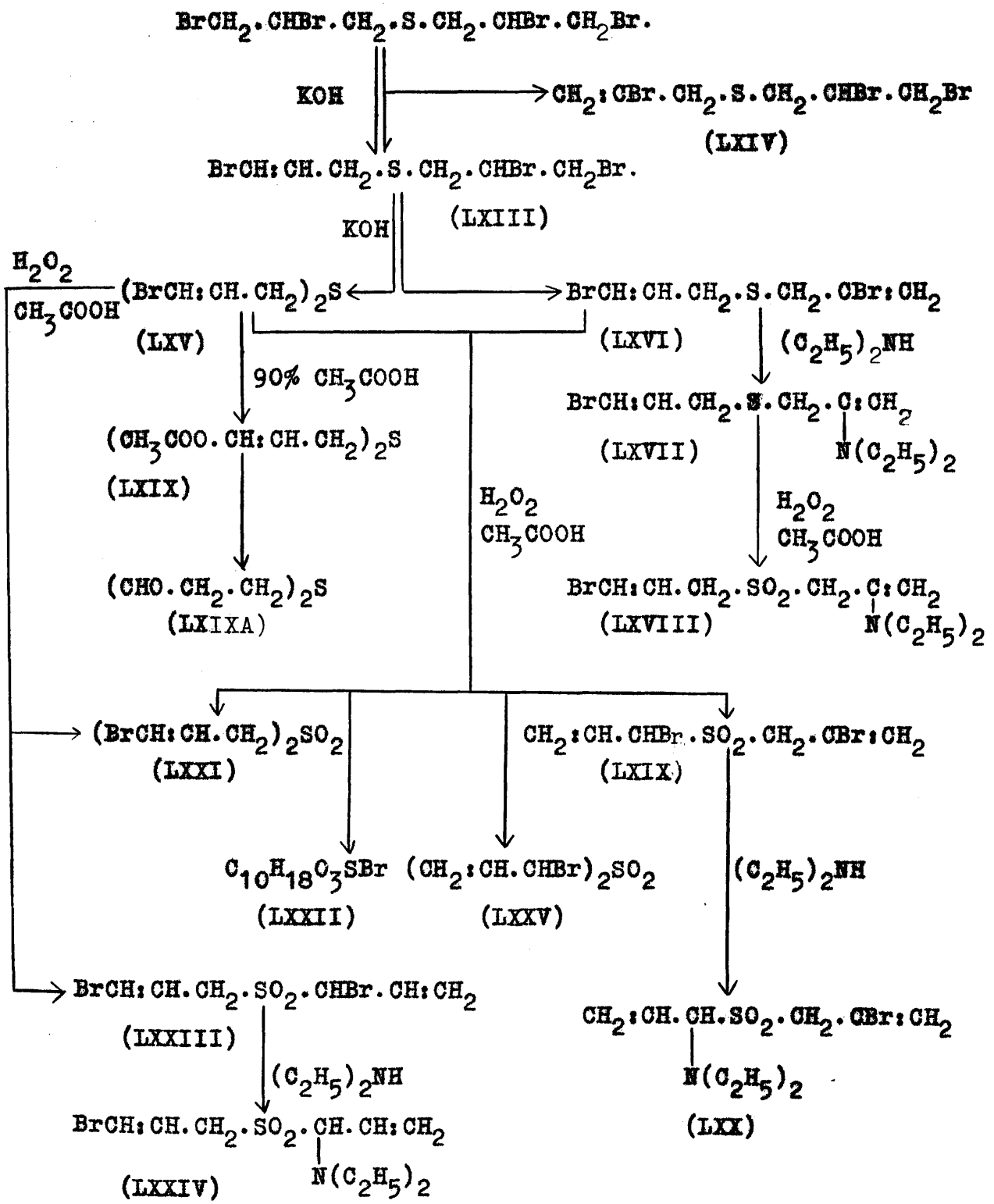
provided a more satisfactory explanation of the unreactive bromine in the dibromosulphide and the derived base. Furthermore, this agrees with the postulate that attack is inhibited in the α position of bis-2:3-dibromopropyl sulphide by the presence of the sulphide electrons.

Dehydrobromination of bis-2:3-dibromopropyl sulphide with potassium hydroxide occurs stepwise with the formation in the first instance of a tribromosulphide for which either structure (LXIII) or (LXIV) is possible. Ozonolysis of the compound, however, gave only trace amounts of formaldehyde, but hydrobromic acid was liberated in almost theoretical yield for one vinylic bromide group, indicating that the structure is correctly represented by 2:3-dibromoprop 3'-bromoprop-2'-enyl sulphide (LXIII). Thus the initial dehydrobromination appears to follow a route analogous to that found in the dehydrobromination of $\alpha\beta$-dibromoisobutyraldehyde diethyl acetal (LXXVI), which yields ß-bromo-α-methylacraldehyde diethyl acetal (LXXVII) by $\beta\gamma$-elimination[222]. The small yield of formaldehyde is probably due to contamination

$$CH_2Br.CBr(CH_3).CH(OC_2H_5)_2 \longrightarrow CHBr{:}C(CH_3).CH(OC_2H_5)_2$$

(LXXVI) (LXXVII)

by traces of 2:3-dibromoprop 2'-bromoprop-2'-enyl sulphide (LXIV), rather than to anomalous ozonolysis[223,224] which might well be expected to occur with a bromopropenyl sulphide of structure (LXIII). Anomalous ozonolyses have been


BrCH2.CHBr.CH2.S.CH2.CHBr.CH2Br.
KOH
CH2:CBr.CH2.S.CH2.CHBr.CH2Br
(LXIV)
BrCH:CH.CH2.S.CH2.CHBr.CH2Br.
(LXIII)
KOH
H2O2
CH3COOH
(BrCH:CH.CH2)2S
(LXV)
BrCH:CH.CH2.S.CH2.CBr:CH2
(LXVI)
(C2H5)2NH
90% CH3COOH
(CH3COO.CH:CH.CH2)2S
(LXIX)
BrCH:CH.CH2.S.CH2.C:CH2
N(C2H5)2
(LXVII)
H2O2
CH3COOH
H2O2
CH3COOH
(CHO.CH2.CH2)2S
(LXIXA)
BrCH:CH.CH2.SO2.CH2.C:CH2
N(C2H5)2
(LXVIII)
(BrCH:CH.CH2)2SO2
(LXXI)
CH2:CH.CHBr.SO2.CH2.CBr:CH2
(LXIX)
C10H18O3SBr
(LXXII)
(CH2:CH.CHBr)2SO2
(LXXV)
(C2H5)2NH
BrCH:CH.CH2.SO2.CHBr.CH:CH2
(LXXIII)
(C2H5)2NH
CH2:CH.CH.SO2.CH2.CBr:CH2
N(C2H5)2
(LXX)
BrCH:CH.CH2.SO2.CH.CH:CH2
N(C2H5)2
(LXXIV)

observed with analogous substances such as 4-ethoxybut-2-ene (LXXVIII), but they were considered unlikely in the

$$CH_3CH = CH.CH_2OC_2H_5$$

(LXXVIII)

present experiments, since no formaldehyde was detected in the ozonolysis of bis-3-bromoprop-2-enyl sulphide (LXV). Formation of 2:3-dibromoprop 2'-bromoprop-2'-enyl sulphide even in low yield, suggested that the dibromosulphide formed by the further action of potassium hydroxide on the tribromosulphide mixture was in fact a mixture of bis-3-bromoprop-2-enyl sulphide and 3-bromoprop-2-enyl 2'-bromoprop-2'-enyl sulphide (LXVI). Careful fractionation, however, failed to effect a separation of the two compounds. This conclusion is based on:-

(a) the structures assigned to the tribromosulphides,

(b) ozonolysis of the mixed dibromosulphides and of the dibromosulphide which failed to react with diethylamine, and

(c) the reactions of the mixed dibromosulphides and of the bromopropenyl diethylaminopropenyl sulphide isolated from the mixture after reaction with diethylamine.

Structure (LXV) for the unreactive dibromo sulphide was confirmed by ozonolysis, which gave no formaldehyde but

liberated hydrobromic acid in high yield for two vinylic bromide groups. Ozonolysis of the mixed dibromosulphides, on the other hand, gave formaldehyde in a yield of 19% of the theoretical for one vinylidine group (29% allowing for the presence of (LXV) to the extent of 33% in the mixture) in agreement with structure (LXVI) for the second component of the mixture. The alternative compound formulated as 3-bromoprop-2-enyl 1'-bromoprop-2'-enyl sulphide (LXXIX) was

$$BrCH{:}CH.CH_2SCHBr.CH{:}CH_2$$

(LXXIX)

rejected, since this would require a thiotropic rearrangement during preparation, and this is unlikely under the alkaline conditions of the dehydrobromination. Comparable thiotropic[225] and oxotropic[226] rearrangements are known to occur only under acid conditions. Finally the high yield of hydrobromic acid obtained on ozonolysis of the mixed dibromosulphides confirmed that structures (LXV) and (LXVI) were correct.

It follows from this that the base obtained by reacting diethylamine with the mixed dibromosulphides must be 3-bromoprop-2-enyl 2'-diethylaminoprop-2'-enyl sulphide (LXXII). In retrospect, formation of a base by reaction of a vinylic halide with diethylamine seemed improbable, since vinylic chlorides are known to be unreactive towards secondary amines[227]. There is some evidence, however, that some

vinylic bromides are more reactive than the corresponding chlorides. For example, Hamer and Rathbone[222] have shown that ß-bromo-∝-methylacraldehyde diethyl acetal (LXXX) reacts readily with aniline, undergoing substitution. On

$$BrCH{:}C(CH_3).CH(OC_2H_5)_2$$

(LXXX)

the other hand Parcell and Pollard[228] found that only the allylic bromide of 2:3-dibromoprop-1-ene was replaced in reaction with diethylamine. The only general replacement reaction of vinylic bromide appears to be the formation of lithium alkenyls[205] and replacement by metal alkoxides[229, 230] and metal thioalkoxides[231].

It was found that bis-3-bromoprop-2-enyl sulphide undergoes almost complete solvolysis in 90% acetic acid, hydrobromic acid being liberated in 91% of the theoretical yield after heating for one hour on a boiling water bath. The product bis-3-acetoxyprop-2-enyl sulphide (LXIX) was unstable and could not be completely characterised. It gave no colour with Schiff's reagent or Fehling's solution, but was rapidly resinified by sodium hydroxide solution, presumably due to formation of bis-2-formylethyl sulphide (LXIXA). Tollen's reagent also was reduced instantly on addition of bis-3-acetoxyprop-2-enyl sulphide.

Reactivity in vinylic bromides is not completely general, being governed by the nature of adjacent substituents. For

example Dufraisse and Netter[232] found that whilst ∝-bromo-ß-ethoxybenzalacetophenone (LXXXI) reacted with piperidine it did so only by replacement of the ethoxy group to give ∝-bromo-ß-piperidinobenzalacetophenone (LXXXII), the vinylic bromide taking no part in the reaction. Similarly it was found that

$$C_6H_5CO.CBr{:}C(OC_2H_5).C_6H_5 \xrightarrow{C_5H_{10}NH} C_6H_5CO.CBr{:}C(NC_5H_{10})C_6H_5$$

(LXXXI) (LXXXII)

bis-3-bromoprop-2-enyl sulphone (LXXI), unlike the corresponding sulphide did not undergo solvolysis when treated with 90% acetic acid. Thus, replacement of an electron donating (sulphide) group by an electron attracting (sulphone) group in the 1-position exerts a profound effect on the reactivity of the halogen in 3-bromoprop-2-ene. In the same way the difference in reactivity of the bromo-substituents in 3-bromoprop-2-enyl 2'-bromoprop-2'-enyl sulphide could be explained by the presence of the thiomethyl group $-SCH_2-$, immediately adjacent to the vinylic halogen in the 2'-bromoprop-2'-enyl fragment.

The retention of the vinylidene group in 3-bromoprop-2-enyl 2'-diethylaminoprop-2'-enyl sulphide was confirmed by the liberation of formaldehyde on ozonolysis. The low yield (13% of theoretical for 1 mole) was attributed to the small scale of the reaction. Comparable yields were obtained under similar conditions with test compounds of known structure.

Oxidation of the sulphide base with hydrogen peroxide gave 3-bromoprop-2-enyl 2'-diethylaminoprop-2'-enyl sulphone (LXVIII), which similarly on ozonolysis gave hydrobromic acid, and formaldehyde (12% of theoretical for 1 mole).

Oxidation of the mixed dibromosulphides with hydrogen peroxide in acetic acid gave an oily product which reacted with diethylamine, permitting separation into two fractions, basic and non-basic respectively. Distillation of the basic fraction gave a base $C_{10}H_{18}O_2NSBr$ in 40% yield. This was not identical with 3-bromoprop-2-enyl 2'-diethylaminoprop-2'-enyl sulphone and is formulated as 1-diethylaminoprop-2-enyl 2'-bromoprop-2'-enyl sulphone (LXX). The latter is derived from 1-bromoprop-2-enyl 2'-bromoprop-2'-enyl sulphone (LXIX) which is formed by the combined thiotropic rearrangement and oxidation of 3-bromoprop-2-enyl 2'-bromoprop-2'-enyl sulphide. Rothstein has reported[225] that oxidation of acraldehyde diethyl thioacetal (LXXXIII) is similarly accompanied by migration of an ethylthio group to yield $\alpha\gamma$-bisethylsulphonyl propene (LXXXIV). Rearrangement of vinylic to allylic

$$CH_2{:}CH.CH(SC_2H_5)_2 \longrightarrow C_2H_5SO_2.CH_2CH{:}CH.SO_2C_2H_5$$

(LXXXIII) (LXXXIV)

bromide is supported in the present case by the ease with which the rearranged and oxidised product reacted with diethylamine. Reaction was immediate at room temperature,

being comparable in ease with that between bis-3-bromoprop-1-enyl sulphone and diethylamine. Ozonolysis was not completely satisfactory, owing to the small amount of material available. Formaldehyde was obtained, but only in 8% of the theoretical yield for two vinylidene groups, but this is comparable on a weight basis with the yields obtained from 3-bromoprop-2-enyl 2'-diethylaminoprop-2'-enyl sulphide and sulphone.

The oil from the above oxidation, which did not react with diethylamine, was separated by distillation into two fractions. The fraction with the lower boiling-point crystallised as a solid, m.p. 65.5-66.5°C., on cooling, identical with the oxidation product of bis-3-bromoprop-2-enyl sulphide, and was therefore bis-3-bromoprop-2-enyl sulphone (LXXI). This was confirmed by the fact that it did not react with diethylamine, and by the absence of formaldehyde and liberation of hydrobromic acid (82.6% of theoretical for two vinylic bromines) on ozonolysis.

The higher boiling fraction also solidified on cooling, and was recrystallised from ether as large prisms, m.p. 73-74°C., but did not react with diethylamine. Ozonolysis gave no formaldehyde but gave hydrogen bromide in good yield for one vinylic bromine. It also slowly reduced Tollen's reagent on heating. The possibility that the compound might be an acetoxypropenyl bromopropenyl sulphide was shown to be wrong, since analysis indicated a molecular formula $C_{10}H_{18}O_3SBr$, and

since the compound was non-basic and no nitrogen could be detected, the high percentage of carbon and hydrogen could not be explained. The structure of the compound (LXXII) was not further investigated, owing to lack of material.

Oxidation of bis-3-bromoprop-2-enyl sulphide also was accompanied by some rearrangement, presumably to 1-bromoprop-2-enyl 3'-bromoprop-2'-enyl sulphide (LXXIII), since the oxidation product reacted with diethylamine in the cold to give small yields of a base, of equivalent weight 293.3, insufficient for characterisation, but probably 1-diethylaminoprop-2-enyl 3'-bromoprop-2'-enyl sulphide (LXXIV). Crystalline bis-3-bromoprop-2-enyl sulphone was isolated from the reaction mixture. Further evidence of rearrangement was obtained by a re-examination of the oxidation products from the mixed dibromosulphides. The crude base obtained by the action of diethylamine on the oxidation product gave significantly low values for equivalent weight, indicating the presence of a di-acid base, assumed to be bis-1-diethylaminoprop-2-enyl sulphone derived from bis-1-bromoprop-2-enyl sulphone (LXXV). Evidently this base is thermolabile and decomposes during the distillation of the crude product, in the same way as bis-3-diethylaminoprop-1-enyl sulphone decomposed when attempts were made to distil it, as reported earlier. None of the mono-acid bases investigated in this section yielded crystalline hydrochlorides, but a small amount of crystalline hydrochloride was isolated from the

mixture of crude bases, sufficient to show that it was derived from a di-acid base and was not the dihydrochloride of bis-3-diethylaminoprop-1-enyl sulphone, but insufficient to characterise it.

In order to elucidate the complex changes occurring in the reactions described above, it was felt necessary in the early stages of this work to compare the reactivities of the unsaturated bromosulphides with that of the corresponding saturated sulphide. Although this latter proved unnecessary, the results of two unsuccessful attempts to prepare bis-3-bromopropyl sulphide are now recorded.

Peroxide catalysed addition of hydrogen bromide to diallyl sulphide, under the conditions used in the preparation of bis-3-bromopropyl sulphone, did not yield bis-3-bromopropyl sulphide, but instead another dibromosulphide which is assumed to be bis-2-bromopropyl sulphide. That the required compound was not obtained was confirmed by its reaction with diethylamine to form the corresponding base, and formation of its dihydrochloride. The latter differed from bis-3-diethylaminopropyl sulphide dihydrochloride (prepared earlier on in this work). It was thought that the catalytic effect of benzoyl peroxide on the addition of hydrogen bromide is neutralised by the sulphide link. On the other hand, Jones and Reid[233] have demonstrated the marked catalytic effects of even trace amounts of peroxides in the addition of thiols to unsaturated compounds, the abnormal additions being obtained

in the same way as with hydrogen bromide.

The second method employed in an attempt to prepare bis-3-bromopropyl sulphide was by condensing 1:3 dibromopropane (2 moles) with sodium sulphide (1 mole). However, instead of the required compound, bis-3-bromopropyl tetrasulphide (LXXXV) was obtained in 17% yield. Its

$$Br.(CH_2)_3.S_4.(CH_2)_3.Br$$

(LXXXV)

constitution was confirmed by conversion to the crystalline bis-3-diethylaminopropyl tetrasulphide dihydrochloride (LXXXVI), m.p. 245.5-246.5°C.

$$HCl.(C_2H_5)_2N.(CH_2)_3S_4.(CH_2)_3.N(C_2H_5)_2.HCl$$

(LXXXVI)

THE OXIDATION OF ALKYL SULPHIDES

The oxidation of sulphides to sulphones can be brought about by many reagents, including 30% hydrogen peroxide[234], nitric acid[235], potassium permanganate[186,236], chromic acid[237], perbenzoic acid[238], monoperphthalic acid[239] and sodium hypochlorite[240]. Potassium permanganate in acetic acid or hydrogen peroxide (30%) in acetic acid are the reagents most usually employed.

The state of oxidation achieved depends largely on the reaction conditions. In general, oxidation to the sulphone can be achieved by using excess reagent, although the formation of mixtures of sulphoxides and sulphones has been reported from time to time, especially when hydrogen peroxide has been used as the oxidant[241]. Chromic acid in acetic acid, alone appears to be specific for the oxidation of sulphides to sulphoxides, with complete cessation of oxidation at this stage. Gazdar and Smiles[234] also have reported controlled oxidation to the sulphoxide stage in good yield using the calculated amount of hydrogen peroxide in aqueous or acetone solution.

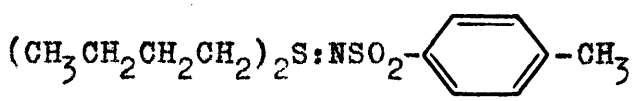
The direct oxidation of $\alpha\beta$-unsaturated sulphides as described by Price and Gillis[240] is unsatisfactory and yields are poor, presumably due to concurrent oxidation at the centre of unsaturation. With sodium hypochlorite, methyl

vinyl sulphoxide was obtained in only 17% yield from the corresponding sulphide, whilst hydrogen peroxide in acetic acid gave only 16% of the sulphone. In general, indirect methods involving dehydrohalogenation of ß-halosulphones offer a more satisfactory route to $\alpha\beta$ -unsaturated sulphones, the intermediate halo-sulphones being readily available in good yield by oxidation of the corresponding sulphides[242]. On the other hand, $\beta\gamma$ -unsaturated sulphides such as diallyl sulphide have been oxidised to the sulphone in high yield (94%) with hydrogen peroxide[243]. Similar yields have been obtained in the present work

The uncertainty surrounding the value of the above methods for oxidation of $\alpha\beta$ -unsaturated sulphides, suggested a general investigation of these and possibly other methods. This was carried out concurrently with the work previously described, in order to establish a method for the oxidation of unsaturated amino-sulphides to sulphones. The successful oxidation of unsaturated alcohols by chromic acid in pyridine by Poos, Arth, Beyler, and Sarett[244] and by manganese dioxide in light petroleum[245,246] prompted investigation of their use as reagents for the oxidation of unsaturated sulphides.

In a preliminary experiment, the oxidation of the saturated di-n-butyl sulphide by means of chromic acid in pyridine was studied. Di-n-butyl sulphoxide was obtained somewhat unexpectedly in 49% yield, despite serious difficulty

with emulsions during the extraction process. It was found, however, that these experimental difficulties could be minimised by filtering the emulsion through paper, and with ether as the extraction solvent, by the application of gentle heat. Repetition of the oxidation using a large excess of chromic acid both at room temperature and at 100° for four hours, again gave only the sulphoxide with no trace of sulphone. The di-n-butyl sulphoxide so obtained was characterised by its known physical constants, and by conversion into SS-di-n-butyl-N-toluene-p-sulphonylsulphidimine (LXXXV) by condensation with toluene-p-sulphonamide, using phosphorus pentoxide in chloroform. The product was identical with that obtained



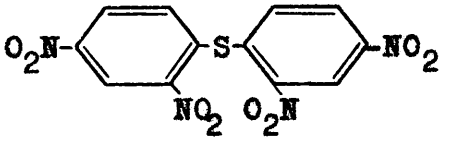
(LXXXV)

from di-n-butyl sulphide and Chloramine T.

Similar oxidations were carried out on dibenzyl sulphide, and again only the sulphoxide was obtained. A slightly increased yield was obtained when the reaction mixture was allowed to stand for five days. The oxidation of diallyl sulphide by this method, however, proved abortive. Products containing sulphur were isolated in only minute amounts, insufficient for identification. Failure to recover the starting material was probably due to co-distillation with extraction solvent.

In general, more success was obtained in oxidations with manganese dioxide in light petroleum. In these experiments the sulphide, dissolved in light petroleum, was shaken with freshly prepared manganese dioxide for varying periods of time. The best yields were obtained after 3-4 days; longer shaking did not appear to increase the yield of product. In the oxidation of di-n-butyl sulphide by this method, filtration and evaporation of the light petroleum gave only a small yield of di-n-butyl sulphoxide. The bulk of the product was adsorbed on the manganese dioxide, but was readily isolated by extracting this in a continuous extraction apparatus. Adsorption of the product appeared to be general as, in the oxidations of both dibenzyl and diallyl sulphides, evaporation of the filtrate gave only unchanged starting material, whilst the sulphoxides were obtained by extraction of the manganese dioxide. The yield of diallyl sulphoxide using this method was poor, being only 13% after 76 hours. Longer reaction times and heating the reaction mixture did not improve the yield.

The only aromatic sulphide examined was 2:2′:4:4′-tetranitrodiphenyl sulphide (LXXXVI), which was prepared by the action of sodium thiosulphate on 1-chloro-2:4-dinitrobenzene.



(LXXXVI)

This sulphide was practically insoluble in light petroleum, so the oxidation was attempted in acetone solution. Unchanged 2:2':4:4'-tetranitrodiphenyl sulphide was recovered quantitatively. It is interesting to observe that this compound failed to yield a sulphidimine with Chloramine T.

An attempt was made to prepare dicinnamyl sulphide by the action of sodium thiosulphate on cinnamyl chloride, as in the preparation of the previous sulphide, with the intention of using it in the oxidation experiments. However, isolation of the products and separation by chromatography through a column of alumina led only to the identification of dicinnamyl trisulphide (LXXXVII), as a crystalline solid

$$(C_6H_5 \cdot CH{:}CH \cdot CH_2)_2S_3$$

(LXXXVII)

from the earlier fractions. From the last fraction was obtained a liquid which may have been impure dicinnamyl sulphide, but the analytical figures were unsatisfactory and the experiments were discontinued.

It was clear from the results of the oxidation experiments that oxidation of sulphides by chromic acid in pyridine or by manganese dioxide in light petroleum led only to the formation of the corresponding sulphoxides, and that the latter method of oxidation was more satisfactory than the former. Attention was therefore turned to an

appraisal of the conventional oxidation methods.

Here, it was confirmed that chromic acid in acetic acid, like chromic acid in pyridine, gave rise only to sulphoxides, diallyl sulphoxide being obtained in 68% yield in this way. The oxidation of diallyl sulphide to diallyl sulphone with hydrogen peroxide[243] gave the product in 91% yield. Application of this method to the oxidation of the unsaturated bromo-sulphides gave the corresponding sulphones in good yield, whilst oxidation of the bisdialkylaminoalkyl sulphides by means of potassium permanganate in 50% acetic acid also gave the appropriate sulphones in satisfactory yields.

EXPERIMENTAL

Melting points are uncorrected.

The author wishes to thank the Chemistry Department for the use of apparatus, and Dr. A. G. Syme, Mr. W. McCorkindale, and Mr. W. Gardiner for the microanalyses.

EXPERIMENTS WITH DIETHYL MALONATE

Ethoxymagnesiomalonic Ester.

Magnesium turnings (12.15g.) were covered with a mixture of benzene (120 ml.) and absolute ethanol (3.75 ml.). A crystal of iodine and carbon tetrachloride (1 ml.) were added and a solution of diethyl malonate (80g.) in benzene (100 ml.) and ethanol (26.25 ml.) was run in slowly. The mixture was warmed gently to start off the reaction, and then the heat was removed while the diethyl malonate solution was added (30 min.). The mixture was then refluxed until most of the magnesium had dissolved. The excess ethanol was then removed by azeotropic distillation.

Bisdiethoxycarbonylmethyl Sulphoxide.

Redistilled thionyl chloride (30g.) was placed in a flask fitted with a stirrer, and the solution of ethoxymagnesiomalonic ester in benzene was slowly added (15 min.) with constant stirring. The mixture was heated for 5 minutes, cooled in an ice-water bath, and decomposed by the addition of 10% hydrochloric acid (200 ml.) and ice. When the complex had been decomposed (about 45 min.) the contents of the flask were transferred to a separating funnel, washed first with dilute hydrochloric acid, and then with water. After drying (Na_2SO_4), benzene and unchanged diethyl malonate were removed

by distillation under reduced pressure. The residual yellow liquid, after standing for several days, was filtered free from crystals of tetraethyl ethanetetracarboxylate. Molecular distillation yielded a fairly pure sample of bis-diethoxycarbonylmethyl sulphoxide (22.9g., 25%) $n_D^{13.5}$ 1.4630.

Found.	C, 47.7;	H, 5.8;	S, 8.4 per cent.
$C_{14}H_{22}O_9S$ requires	C, 45.9;	H, 6.1;	S, 8.75 per cent.

Attempted Preparation of Bistetraethyldiamidomethyl Sulphoxide.

Bisdiethoxycarbonylmethyl sulphoxide (0.7g.) and diethylamine (1 ml.) were refluxed for 1 hour. Removal of excess reagent under reduced pressure yielded a dark brown oil and some crystalline material. Recrystallisation from ethanol yielded yellow needles, m.p. 118°C. in poor yield. The reaction was not further investigated since the required bistetraethyldiamidomethyl sulphoxide has m.p. 176°C., and the refractive index of the residue indicated it to be chiefly unchanged bisdiethoxycarbonylmethyl sulphoxide.

Attempted Preparation of SS-bis-(diethoxycarbonylmethyl)-N-toluene-p-sulphonylsulphidimine.

Method (1). Bisdiethoxycarbonylmethyl sulphoxide (0.386g.) and toluene-p-sulphonamide (0.17g.) in acetic anhydride (5 ml.) were refluxed gently for 20 min. Removal of excess reagent under reduced pressure yielded a brown oil from which

crystalline material separated on standing for two days. Filtration and repeated crystallisations from benzene yielded white crystals m.p. 132-134°C., confirmed as being N-acetyl toluene-p-sulphonamide by a mixed melting point with an authentic sample.

Method (2). Bisdiethoxycarbonylmethyl sulphoxide (0.421g.), toluene-p-sulphonamide (0.197g.), and phosphorus pentoxide (0.12g.) in chloroform (2 ml.) were refluxed for 30 min. Phosphorus pentoxide (0.12g.) was then added and refluxing continued for a further 30 min. The hot chloroform solution was then decanted from the sludge, washed twice with sodium hydroxide solution (5%, 3 ml.) and then with water. Evaporation of the chloroform layer yielded unchanged bisdiethoxycarbonylmethyl sulphoxide (confirmed by refractive index), and acidification of the aqueous extract followed by extraction with ether yielded unchanged toluene-p-sulphonamide (confirmed by m.p. and mixed m.p. with starting material).

Method (3). Bisdiethoxycarbonylmethyl sulphoxide (0.66g.), toluene-p-sulphonamide (0.31g.),and aluminium chloride (0.2g.) in benzene (4 ml.) were refluxed for 30 min. The reaction mixture darkened considerably and hydrochloric acid was evolved. Aluminium chloride (0.1g.) was added and refluxing continued for a further 30 min. On cooling, the thick black oil was made alkaline with sodium hydroxide

solution (20%) and extracted with ether. The latter solution, after washing with water, drying (Na_2SO_4) and removal of solvent yielded a brownish solid, which was purified by recrystallisation from benzene as white crystals. These were identified as unchanged toluene-p-sulphonamide (m.p. and mixed m.p. with starting material).

Attempted Preparation of Thionyldiacetic Acid.

Method (1). Bisdiethoxycarbonylmethyl sulphoxide (1.459g.) was refluxed with aqueous solution of potassium hydroxide (20%, 7 ml.) for 40 min. Unchanged sulphoxide was extracted with ether from the cold mixture, and the aqueous solution, after acidification with hydrochloric acid, was evaporated to dryness. Extraction of the solid residue with ethanol and evaporation yielded a brown oil in poor yield along with some crystalline material, neither of which was further investigated.

Method (2). Bisdiethoxycarbonylmethyl sulphoxide (1.04g.) in ethanolic (90%) solution of potassium hydroxide (26 ml.N/2) was allowed to stand at room temperature for 6 days. A yellow oil and crystalline material separated out. After refluxing the mixture for 1 hour, the bulk of the ethanol was removed by distillation and the residual liquid was extracted with ether (to remove any water-insoluble material). Acidification of the aqueous liquid followed by extraction with ether

yielded no product, so the aqueous layer was evaporated to dryness. Extraction of the solid residue with ether and ethanol also failed to give the required thionyldiacetic acid.

Method (3). Bisdiethoxycarbonylmethyl sulphoxide (1.73g.) in ethanolic hydrochloric acid (7%, 12 ml.) was allowed to stand at room temperature for 3 days, followed by a further two days at 40°C. Evaporation of the solution yielded unchanged bisdiethoxycarbonylmethyl sulphoxide, as confirmed by refractive index.

Thionyldiacetic Acid.

Bisdiethoxycarbonylmethyl sulphoxide (1.379g.) was refluxed with hydrochloric acid (15 ml.) for 1.5 hours, by which time most of the oily layer had disappeared. The reaction mixture, on cooling, was extracted with benzene (to remove unchanged sulphoxide) and the acid solution was evaporated to dryness under reduced pressure. The residue was dissolved in water and the solution decolourised by boiling with activated charcoal Evaporation of the filtrate, and finally drying in a vacuum desiccator, yielded a white solid (0.460g., 73.5%), m.p. 115-117°C.

Found: equiv. (titration) 80; $C_4H_6O_5S$ requires equiv. 83.

Washing the thionyldiacetic acid with a small amount of dry ether raised the m.p. to 119-121°C. Oddy and Dodson report[247] m.p. 119°C. (decomp.)

Attempted Decarboxyation of Thionyldiacetic Acid.

Thionyldiacetic acid (0.2g.) was heated to 150°C. for 1 hour. Some evolution of gases occurred, indicating decarboxylation, but charring occurred simultaneously and no crystalline product could be isolated from the charred residual mass.

Attempted Preparation of Biscarboxymethyl Sulphone.

Bisdiethoxycarbonylmethyl sulphoxide (2.874g.) and solution of hydrogen peroxide (30%, 5 ml.) in glacial acetic acid (7 ml.) were refluxed for 45 min. After evaporation of the liquid under reduced pressure, the residual colourless oil was refluxed with hydrochloric acid (20 ml.) for 1.25 hours, filtered, and evaporated over a water-bath. The reddish-brown viscous residue (0.9g.) failed to crystallise after standing for several days in a vacuum desiccator and was not investigated further.

PREPARATION OF BIS-3-DIETHYLAMINOPROPYL SULPHONE

Diallyl Sulphide.

Sodium sulphide (70g.) and ethanol (200 ml.) were placed in a 3-neck flask fitted with stirrer, reflux condenser, and dropping funnel, and the stirred mixture was heated to boiling. Allyl bromide (114g.) was slowly added (30 min.) and the mixture then refluxed for 5.5 hours. On cooling, the mixture was poured into water (2 l.) and extracted with ether. The ethereal extracts were washed, dried (Na_2SO_4) and the solvent removed by distillation. The diallyl sulphide boiled at 136 - 140°C. (40.28g., 75%). Lewin[248] gives b.p. 137°C./750 mm.

Diallyl Sulphone.

Diallyl sulphide (28g.) was dissolved in glacial acetic acid (160 ml.) and the solution cooled to below 5°C. in a freezing mixture. To the solution 30% hydrogen peroxide (117 ml.) was added slowly, the temperature being maintained below 5°C. After the hydrogen peroxide was added, the solution was allowed to stand at room temperature overnight, and then heated to 80-85°C. for 1 hour. On cooling, it was poured into water (700 ml.) and extracted with chloroform. The chloroform extracts were washed with water, dried (Na_2SO_4), and the solvent removed by distillation. The

residue was distilled under reduced pressure, and diallyl sulphone (32.80g., 91.5%) was collected, b.p.120-130°C. (bath)/3.5 mm., n_D^{15} 1.4913. Lewin[248] gives b.p. 109°C. /3 mm., n_D^{20} 1.4893.

Attempted Hydrobromination of Diallyl Sulphone.

Method (1). Diallyl sulphone (3.385g.) was dissolved in ether (10 ml.), a crystal of benzoyl peroxide was added, and the solution cooled in an ice-water bath. Dry hydrogen bromide was passed into the cold solution for 13 hours. Removal of the solvent under reduced pressure yielded an oil (3.577g.). The small increase in weight and the refractive index of the liquid indicated that it was chiefly unchanged diallyl sulphone.

Method (2). Diallyl sulphone (6g.) was dissolved in carbon tetrachloride (60 ml.) and a crystal of benzoyl peroxide was added. Dry hydrogen bromide was passed into the solution (at room temperature) for 26 hours. Removal of the solvent under reduced pressure yielded an oil (6.7g.), the refractive index of which in addition to the very small increase in weight, showed it to be chiefly unchanged diallyl sulphone.

Method (3). Diallyl sulphone (6.8g.) in constant boiling hydrobromic acid (15 ml.) was refluxed for 3.5 hours. To the cold solution, sodium bicarbonate was added in slight

excess and the liquid extracted with chloroform. The chloroform extracts were washed with water, dried (Na_2SO_4), and the solvent removed under reduced pressure. The residual oil (6.832g.) was again confirmed as being chiefly unchanged starting material.

2-Bromopropyl prop-2'-enyl Sulphone and 3-Bromopropyl prop-2'-enyl Sulphone.

Diallyl sulphone (6.5g.) 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 while the solution was refluxed. Removal of the solvent gave a tarry residue which, when extracted with hot ether, benzene, and ethanol, yielded a liquid (1.48g.). This liquid, on further reaction with hydrogen bromide for 7 hours, followed by chromatography in benzene solution on a mixture of activated charcoal and powdered cellulose (equal parts), gave a crystalline solid (1.67g.). Chromatography of this solid from benzene on alumina gave two fractions. The first small fraction, crystallised from ether, gave 2-bromopropyl prop-2'-enyl sulphone, m.p. 102.5-103.5°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 repreated recrystallisations from ether, gave 3-bromopropyl prop-2'-enyl sulphone, m.p. 72-74°C.

Found. C, 31.8; H, 4.9 per cent

$C_6H_{10}O_2SBr$ requires C, 32.1; H, 5.3 per cent

3-Diethylaminopropyl prop-2'-enyl Sulphone.

3-Bromopropyl prop-2'-enyl sulphone (1g.) in benzene (15 ml.) was refluxed with diethylamine (1 ml.) for 1 hour. The reaction mixture, on cooling, was washed with water (to remove diethylamine hydrobromide) and then extracted with dilute hydrochloric acid. On making alkaline with sodium hydroxide solution, the free base was liberated and extracted with benzene. The benzene extracts, after washing with water, drying (Na_2SO_4) and removal of the solvent under reduced pressure, yielded a red oil, $n_D^{17.5}$ 1.4832. Distillation yielded 3-diethylaminopropyl prop-2'-enyl sulphone (0.45g., 46.6%), b.p.200-205°C.(bath)/2.25 mm., $n_D^{17.5}$ 1.4812, as a straw-coloured oil.

Found: equiv. (titration) 217.1

$C_{10}H_{21}O_2NS$ requires equiv. 219.3

Bis-3-bromopropyl Sulphone.

Diallyl sulphone (4.2g.) was dissolved in carbon tetrachloride (100 ml.) and a crystal of benzoyl peroxide was added. The solution was heated to boiling and dry hydrogen bromide was passed in whilst the solution cooled, and thereafter for 20 hours. The solution was brought to the boil at 3-hourly intervals, being allowed to cool to room tempera-

ture during the intervening periods. The product separated as a yellow oil which formed a solid crystalline mass on standing overnight. Evaporation of the solvent and crystallisation of the residue from ether gave bis-3-bromopropyl sulphone as colourless plates, m.p. 85-86°C. (3.7g., 43%).

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 passed in for only 8 hours gave the same product in 39% yield.

Addition of Hydrogen Bromide to 3-Bromopropyl prop-2'-enyl Sulphone.

3-Bromopropyl prop-2'-enyl sulphone (2g.) was dissolved in carbon tetrachloride (40 ml.) and a crystal of benzoyl peroxide was added. The solution was heated to boiling and dry hydrogen bromide was passed in for 7 hours, with alternate heating and cooling of the solution as described above. On removal of the solvent, the residue in benzene was chromatographed on alumina. The earlier fractions, after recrystallisation from ether, yielded bis-3-bromopropyl sulphone, m.p. 85-86°C. (confirmed by mixed m.p. with previously prepared material). The later fractions, on recrystallisation from ether, yielded unchanged 3-bromopropyl prop-2'-enyl sulphone, m.p. 72-74°C. (confirmed by mixed m.p. with starting material).

Bis-3-diethylaminopropyl Sulphone.

Method (1). Bis-3-bromopropyl sulphone (4.64g.) 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 (crude 4.22g., 96%) was dissolved in dilute hydrochloric acid (10%, 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.p. 186.5-187°C.

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.

Method (2). See p. 95.

PREPARATION OF LONG-CHAIN BISDIALKYLAMINOALKYL SULPHIDES AND SULPHONES

Diethyl Adipate.

Diethyl adipate was prepared by an adaptation of the method described for the preparation of diethyl sebacate in Organic Syntheses[199]. Adipic acid (40g.) was refluxed with stirring for 2.5 hours with ethanol (133 ml.) and sulphuric acid (10.5 ml.). Most of the ethanol was then removed by distillation and the residue was poured into brine (200 ml.). Sodium carbonate was added to neutralise the mixture, and the ester which separated was washed with water. The aqueous washings were extracted with ether and the ester and ethereal extracts were mixed and dried (Na_2SO_4). The ether was distilled off and the diethyl adipate came over at b.p. 123°C.(bath)/8.5 mm., n_D^{14} 1.4300 (40.26g., 73%).

Ethyl Hydrogen Adipate.

Ethyl hydrogen adipate was prepared from diethyl adipate by an adaptation of the method described for the preparation of ethyl hydrogen sebacate in Organic Syntheses[199]. Diethyl adipate (47.67g.), adipic acid (59.44g.) and hydrochloric acid (10.25 ml.) were heated with stirring to 160-170°C. until a clear homogeneous solution was obtained. The temperature was allowed to fall to 120-130°C., ethanol (95%, 25 ml.) was added, and the temperature of the mixture was maintained

at 130-140°C. for a further 2 hours. The liquid was then distilled, and the fraction boiling between 133° and 168°C./ 10 mm. was collected. This was taken up in ether and extracted with sodium carbonate solution. Unchanged diethyl adipate was recovered from the ethereal solution. The aqueous solution was acidified, extracted with ether and washed. Ethyl hydrogen adipate was obtained from the ethereal extracts after drying (Na_2SO_4) and removal of solvent, as a liquid which solidified on standing (39.51g., 27.9%), m.p. 26-28°C.

Ethyl NN-diethyladipamate.

Ethyl hydrogen adipate (26.25g.) 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 unchanged ethyl hydrogen adipate), and finally washed with water. The resulting ethereal solution was dried (Na_2SO_4), evaporated, and the residual liquid distilled to yield ethyl NN-diethyladipamate, b.p. 144°C./ 3 mm., $n_D^{17.5}$ 1.4572 (27.9g., 81%).

Found. N, 5.9 per cent.

$C_{12}H_{23}O_3N$ requires N, 6.1 per cent.

Ethyl NN-pentamethyleneadipamate was prepared from ethyl hydrogen adipate (22.07g.), excess thionyl chloride, and then piperidine (24g.) following the above method. Ethyl NN-pentamethyleneadipamate was obtained as a colourless oil, b.p. 169-172°C./3 mm., n_D^{19} 1.4778 (21.56g., 70.5%).

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.

Avison[249] reports b.p. 148-152°C./0.5 mm.

Ethyl Hydrogen Sebacate was prepared from diethyl sebacate and sebacic acid by the method described under ethyl hydrogen adipate, in 36% yield.

Ethyl NN-diethylsebacamate was prepared from ethyl hydrogen sebacate (31.7g.) by the method described for ethyl NN-diethyladipamate. Ethyl NN-diethylsebacamate was obtained as a colourless oil, b.p. 183-190°C./3 mm., n_D^{19} 1.4571 (22.3g., 57%).

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 (23.6g.) by the method described for ethyl NN-diethyladipamate. Ethyl NN-pentamethylenesebacamate was obtained as a colourless oil, b.p. 208-211°C./3.5 mm., $n_D^{18.5}$ 1.4757 (20.1g., 66%).

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 (27.9g.) in dry ether (60 ml.) was slowly run into a stirred hot suspension of lithium aluminium hydride (9g.) in dry ether (400 ml.). The addition was continued at a rate which was just sufficient to keep the solution refluxing, addition being complete within approximately 15 minutes. The reaction mixture was cooled in ice, and water was added dropwise, sufficient to decompose the excess lithium aluminum hydride. After treatment with sodium hydroxide solution (20%, 200 ml.), the ethereal extracts were washed, dried (Na_2SO_4) and evaporated. The residual oil distilled to give 6-hydroxyhexyldiethylamine, b.p. 110°C/5.5 mm., n_D^{15} 1.4575 (18.9g., 90%). Work[250] gives b.p. 96-99°C./2 mm.

6-Hydroxyhexylpiperidine was prepared from ethyl NN-pentamethyleneadipamate (21.1g.) by the method described for 6-hydroxyhexyldiethylamine, and was obtained as a colourless oil, b.p. 123°C./3.5 mm., n_D^{19} 1.4781 (14.4g., 89%). Sauer and Adkins[251] give b.p. 96°C./1 mm., n_D^{25} 1.4730.

10-Hydroxydecyldiethylamine was prepared from ethyl NN-diethylsebacamate (22g.) by the method described for 6-hydroxyhexyldiethylamine, and was obtained as a colourless

oil, b.p. 146°C./3 mm., $n_D^{19.5}$ 1.4602 (15.5g., 88%). Schinzel and Benoit[252] give b.p. 178-183°C./16 mm.

10-Hydroxydecylpiperidine was prepared from ethyl NN-pentamethylenesebacamate (19.6g.) by the method described for 6-hydroxyhexyldiethylamine, as colourless platelets (from ether) m.p. 59.5°C. (14.3g., 90%). Price, Guthrie, Herbrandson and Peel[253] give m.p. 60-61°C.

6-Chlorohexyldiethylamine.

Thionyl chloride (8 ml.) in benzene (30 ml.) was slowly added to a solution of 6-hydroxyhexyldiethylamine (18.9g.) in benzene (100 ml.). The solvent was removed under reduced pressure to yield a greyish crystalline mass. This was dissolved in water (20 ml.), cooled to 0°C., and basified by the addition of sodium hydroxide solution (20%, 30 ml.). Extraction with ether, washing, drying (Na_2SO_4), evaporation of the solvent, and distillation of the residual oil gave 6-chlorohexyldiethylamine, b.p. 102.5°C./11 mm., n_D^{16} 1.4513 (19.8g., 95%).

Found.	C, 63.1;	H, 11.8 per cent.
$C_{10}H_{22}NCl$ requires	C, 62.6;	H, 11.6 per cent.

Work[250] gives b.p. 118-120°C./19 mm.

6-Chlorohexylpiperidine was prepared from 6-hydroxyhexylpiperidine (13.8g.) by the method described for 6-chlorohexyldiethylamine, and was obtained as a colourless oil,

b.p. 131°C./2.5 mm., $n_D^{17.5}$ 1.4752 (10g., 66%). 6-Chlorohexylpiperidine hydrochloride was obtained in the usual way as colourless plates, m.p. 154.5-155°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 (15.1g.) by the method described for 6-chlorohexyldiethylamine, and was obtained as a colourless oil, b.p. 161°C./12 mm., n_D^{20} 1.4562 (14g., 86%). Schinzel and Benoit[252] give b.p. 173-176°C./17 mm.

10-Chlorodecylpiperidine was prepared from 10-hydroxydecylpiperidine (14.2g.) by the method described for 6-chlorohexyldiethylamine, and was obtained as a colourless oil, b.p. 151-152°C./5 mm., n_D^{18} 1.4753 (14.5g., 95%).

Price, Guthrie, Herbrandson, and Peel[253] give analytical figures for this compound, but no constants except for the hydrochloride, m.p. 135-136°C.

Found: equiv. (titration)	263.
$C_{15}H_{30}NCl$ requires equiv.	260.

Bis-6-diethylaminohexyl Sulphide.

6-Chlorohexyldiethylamine (19.8g.) in ethanol (10 ml.) was slowly added to a hot solution of anhydrous sodium

sulphide (5.5g.) in water (6 ml.) and ethanol (10 ml.), and the mixture was refluxed for 3.25 hours with continuous stirring. The residual liquor, after removing the bulk of the ethanol by distillation, was poured into water (400 ml.) and extracted with ether. The ethereal solution was washed, dried (Na_2SO_4) and evaporated, and the residual oil fractionally distilled. After the forerun of unchanged 6-chlorohexyldiethylamine, bis-6-diethylaminohexyl sulphide was obtained as a pale straw-coloured oil, b.p. 208-209°C./5.5 mm., n_D^{19} 1.4757 (13g., 72.5%).

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.p. 130.5-131°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 (9.8g.) by the method described for bis-6-diethylaminohexyl sulphide, and was obtained as a yellow oil, b.p. 230-231°C./3 mm., $n_D^{16.5}$ 1.5022 (5.7g., 64%).

Dihydrochloride (from ethanol-ether), m.p. 226.5-227.5°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 (13.79g.) by the method described for bis-6-diethylaminohexyl sulphide, and was obtained as a yellow oil, b.p. 275°C./3.5 mm., $n_D^{15.5}$ 1.4775 (5g., 40%)

Found. equiv. (titration) 227.

$C_{28}H_{60}N_2S$ requires equiv. 228.

Dihydrochloride (from ethanol-ether), m.p. 141-142°C.

Found. C, 63.4; H, 11.4; N, 5.2 per cent.

$C_{28}H_{62}N_2SCl_2$ requires C, 63.5; H, 11.8; N, 5.3 per cent.

Bis-10-(1'-piperidyl)-decyl Sulphide was prepared from 10-chlorodecylpiperidine (14.4g.) by the method described for bis-6-diethylaminohexyl sulphide, and was obtained as a pale yellow low-melting solid (9.7g., 73%).

Found. equiv. (titration) 186.5.

$C_{30}H_{60}N_2S$ requires equiv. 184.4

Dihydrochloride (from ethanol-ether), m.p. 204-204.5°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%) in acetic acid (50%) was slowly added (20 min.) to an ice-cold solution of bis-6-diethylaminohexyl sulphide (1.8g.) in acetic acid (50%. 3 ml.) until present in slight excess. After a further 20 minutes the

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 was again evaporated to dryness. The solid residue after continuous extraction with ether and removal of solvent, gave on distillation bis-6-diethylaminohexyl sulphone as a colourless liquid, b.p. 220°C./3 mm., n_D^{20} 1.4743 (1.75g., 90%).

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.p. 139-140°C.

Found. C, 53.1; H, 10.3; N, 6.2; Cl, 15.8 per cent.

$C_{20}H_{46}O_2N_2SCl_2$ 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-(1'-piperidyl)-hexyl sulphide (1.87g.) by the method described for bis-6-diethylaminohexyl sulphone and was obtained as colourless plates (from ether-petrol), m.p. 50.5-51°C. (1.75g., 86%).

Found. C,65.9; H, 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.p. 191.5-192.5°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 (1.51g.) by the method described for bis-6-diethylaminohexyl sulphone as a low-melting solid (1.6g., 97%) which gave a dihydrochloride (from ethanol), m.p. 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 (2.2g.) by the method described for bis-6-diethylaminohexyl sulphone, and was obtained as colourless flakes (from ether), m.p. 74.5-75°C. (2.4g. crude, 100%).

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 ethanol-ether), m.p. 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.

Ethyl-ß-diethylaminopropionate.

Ethyl acrylate (75g.) and diethylamine (54.75g.) were mixed and left at room temperature for four days. The liquid was then distilled and ethyl-ß-diethylaminopropionate, b.p. 87°C./15 mm., $n_D^{17.5}$ 1.4290 (118g., 91%) was collected.

Adamson[200] reports b.p. 87-88°C./15 mm.

3-Hydroxypropyldiethylamine was prepared by reduction of ethyl-ß-diethylaminopropionate (82g.) with lithium aluminium hydride, as described under 6-hydroxyhexyldiethylamine. 3-Hydroxypropyldiethylamine was obtained as a colourless oil, b.p. 81°C./15 mm., $n_D^{17.5}$ 1.4430 (50.8g., 81.8%).
v. Braun[254] reports b.p. 84°C./20 mm.

3-Chloropropyldiethylamine was prepared from 3-hydroxypropyldiethylamine (50.8g.) by the method described under 6-chlorohexyldiethylamine. 3-Chloropropyldiethylamine was obtained as a colourless oil, b.p. 62-65°C./16 mm., $n_D^{16.5}$ 1.4417 (49.22g., 84.9%).
v. Marxer[255] reports b.p. 53-57°C./12 mm.

Bis-3-diethylaminopropyl Sulphide was prepared from 3-chloropropyldiethylamine (36.51g.) by the method described under bis-6-diethylaminohexyl sulphide. Bis-3-diethylaminopropyl sulphide was obtained as a colourless oil, b.p. 133-136°C./2.5 mm., n_D^{18} 1.4758 (21.71g., 68.4%). Andrew, Bergel, and Morrison[198] give b.p. 80-81°C./0.03 mm., n_D^{21} 1.4731.

Found. equiv. (titration) 131.1 .

Calc. for $C_{14}H_{32}N_2S$, equiv. 130.1 .

Dihydrochloride (from ethanol), m.p. 222.5-223.5°C.

Found. N, 8.5; Cl, 21.4 per cent.

$C_{14}H_{34}NSCl_2$ requires N, 8.4; Cl, 21.3 per cent.

Bis-3-diethylaminopropyl Sulphone.

Method (2). Bis-3-diethylaminopropyl sulphide (3.52g.) was oxidised using potassium permanganate in acetic acid (50%) by the method described under bis-6-diethylaminohexyl sulphone. Bis-3-diethylaminopropyl sulphone was obtained as a colourless oil, b.p. 186°C./3.5 mm., $n_D^{24.5}$ 1.4707, (3.56g., 90%).

Found.	C, 57.75;	H, 10.8;	N, 9.5 per cent.
$C_{14}H_{32}O_2N_2S$ requires	C, 57.5 ;	H, 11.0;	N, 9.6 per cent.

Dihydrochloride, m.p. 186.5-187°C. Mixed melting point with bis-3-diethylaminopropyl sulphone dihydrochloride, prepared by method (1), 186.5-187°C.

EXPERIMENTS WITH LITHIUM ALKENYLS.

1:2-Dibromoisobutane

1:2-Dibromoisobutane was prepared by the method of Braude and Timmons[205]. Tertiary butyl alcohol (200 ml., 2.15 mole.) was refluxed over a water-bath with oxalic acid dihydrate (75g., 0.6 mole.). The isobutylene thus produced was led off from the top of the reflux condenser and bubbled through bromine (344g.) contained in two vessels connected in series. After 7 hours the colour of the bromine had been discharged and both liquids were only faintly yellow in colour. They were mixed and distilled. The fraction boiling between 146° and 160°C. was collected (205g., 32%), $n_D^{19.5}$ 1.5145, and used without further purification in the next section.

Braude and Timmons[205] report b.p. 152°C., n_D^{20} 1.5078 for 1:2-dibromoisobutane.

isoButenyl Bromide.

1:2-Dibromoisobutane (112g.) was added to a stirred hot solution of potassium hydroxide (32.5g.) in a mixture of ethanol (156 ml.) and water (12.5 ml.) at a rate sufficient to maintain gently refluxing. The mixture was then refluxed for a further 7 hours and allowed to cool overnight.

After filtering off the potassium bromide, the liquid was poured into water (1 l.) and extracted with ether. The ethereal extracts were washed, dried ($CaCl_2$) and distilled using a Fenske column (6"), the fraction boiling between 91° and 92°C. being collected. A small piece of sodium was added to the distillate which was then redistilled, and the fraction boiling at 91-92°C. was collected, (22.85g., 33.2%), n_D^{17} 1.4590.

Braude and Timmons report[205] b.p. 91-91.3°C.

isoButenyl Lithium.

Ether (100 ml., sodium dried) was placed in a 3-neck flask (500 ml.) fitted with stirrer, reflux condenser and dropping funnel. Lithium (1.7g.), cut into small pieces was then added. isoButenyl bromide (18g.) in ether (10 ml.) was placed in the dropping funnel and about one tenth of the solution was run into the flask and the mixture stirred. The reaction started in about 20 min. and the ethereal solution was then refluxing gently. The remainder of the solution of isobutenyl bromide was then added slowly (1 hour) at a rate sufficient to maintain refluxing, and the mixture refluxed for a further 2 hours. The solution was filtered by suction into a graduated vessel under an atmosphere of nitrogen, and the amount of isobutenyl lithium estimated by the following method. The solution (1 ml.) was pipetted into water (10 ml.) and the lithium hydroxide thus produced

was estimated by titrating against standard (N/10) hydrochloric acid, using methyl orange as indicator.

Attempted Preparation of Diisobutenyl Sulphoxide.

Ethyl sulphite (8g.) was added slowly (1 hour) to a stirred solution of iso-butenyl lithium (5.25g.) in ether (500 ml.). The solution turned an orange colour. After stirring for a further 30 min., the mixture was decomposed by the addition of ammonium chloride (20g.) as a saturated ice-cold solution. The ethereal layer, after washing and drying (Na_2SO_4), was evaporated under reduced pressure to yield a reddish-brown liquid (2.3g.), n_D^{22} 1.5370. Distillation at 130-140°C.(bath)/2 mm. yielded a small quantity of yellow liquid, n_D^{25} 1.4960, insufficient for characterisation.

n-Butyllithium was prepared from n-butyl bromide by the method described under isobutenyllithium.

Attempted Preparation of Di-n-butyl Sulphoxide.

Ethyl sulphite (1.4g.) in ether (40 ml.) was added slowly (20-30 min.) to a stirred ice-cold solution of n-butyllithium (1.28g.) in ether (100 ml.). Stirring was then continued with the solution at room temperature for 3 hours. The mixture was decomposed by the addition of ammonium chloride (4g.) as a saturated ice-cold solution.

The ethereal layer, after washing and drying (Na_2SO_4), was evaporated under reduced pressure to yield one or two drops of golden-yellow liquid. This showed some signs of crystallising on standing in a vacuum desiccator, and may have been the required sulphoxide, but the yield was too poor and the product was not further investigated.

ATTEMPTED BROMINATION OF DI-n-BUTYL SULPHONE

Di-n-butyl Sulphone.

Di-n-butyl sulphoxide (1.487g.) was dissolved in acetic acid (5 ml.), and an excess of 30% hydrogen peroxide (2 ml.) was added. The solution was heated to 100°C. for 2 hours, cooled, and poured into water (25 ml.). After neutralisation with sodium carbonate solution, the precipitated sulphone was extracted with benzene, washed, dried (Na_2SO_4), and the solvent removed under reduced pressure. Di-n-butyl sulphone was obtained as plates (from water), m.p. 44°C. (1.37g., 83.8%). Wood and Travers[256] report m.p. 44°C.

Attempted Bromination of Di-n-butyl Sulphone.

Di-n-butyl sulphone (1.37g.) was dissolved in carbon tetrachloride (15 ml.) in a flask fitted with a stirrer, reflux condenser, and dropping funnel. Powdered red phosphorus (0.1g.) was then added, followed by bromine (2.43g) in carbon tetrachloride (15 ml.) and the mixture was refluxed for 6 hours. On cooling, the solution was washed with sodium carbonate solution, and then with water, dried (Na_2SO_4) and evaporated to dryness. The residue was a yellowish-brown solid, which, when recrystallised from water was identified as unchanged di-n-butyl sulphone.

BIS-3-DIETHYLAMINOPROP-1-ENYL SULPHONE

Bis-2:3-dibromopropyl Sulphone.

A slight excess of bromine (36g.) was added slowly to a hot stirred solution of diallyl sulphone (16.3g.) in carbon tetrachloride (250 ml.). The solution remained colourless during the addition of the bromine until the end, when it was reddish in colour. The solvent was distilled off under reduced pressure, and the residue recrystallised from carbon tetrachloride as whitish crystals (47g., 92.5%). It was further recrystallised to give colourless needles, m.p. 99-100°C. Lewin reports[248] m.p. 98-100°C.

Bis-3-bromoprop-1-enyl Sulphone.

Bis-2:3-dibromopropyl sulphone (46.6g.) was dissolved in hot benzene (160 ml.). Pyridine (17 ml.) was slowly added to the stirred hot solution (15 min.), and the mixture refluxed for a further 30 minutes. When cold, the benzene solution was washed with water, dried (Na_2SO_4), and evaporated under reduced pressure to yield a mass of yellowish crystals (crude yield 18.6g., 61%). Recrystallisation from carbon tetrachloride gave colourless needles of bis-3-bromoprop-1-enyl sulphone, m.p. 73-74°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 (3.65g.) 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 (to remove diethylamine hydrobromide), dried (Na_2SO_4), and evaporated under reduced pressure. The residual oily base was dissolved in dilute hydrochloric acid, and the solution cautiously evaporated under reduced pressure. The semi-crystalline residue, recrystallised from ethanol, gave colourless needles of bis-3-diethylaminoprop-1-enyl sulphone dihydrochloride (2.3g., 53%), m.p. 192-193°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.p. 188-189°C. (decomp.)

Found. C, 42.2; H, 4.3 per cent.

$C_{26}H_{34}O_{16}N_8S$ requires C, 41.8; H, 4.6 per cent.

Attempt to Catalyse the Uptake of Bromine by Bis-3-bromoprop-1-enyl Sulphone by means of Lithium Bromide.

Solutions of bromine (25 ml. M/40), lithium bromide (25 ml. M/20) and bis-3-bromoprop-1-enyl sulphone (25 ml. M/80) in glacial acetic acid were mixed in a stoppered flask. An aliquot portion (10 ml.) was pipetted into a titration

flask, excess potassium iodide solution was added, and the liberated iodine was titrated against standard (N/80) sodium thiosulphate solution. Repeat estimations were carried out at intervals over a period of 5 hours. The results showed that no uptake of bromine by bis-3-bromoprop-1-enyl sulphone had taken place.

Hydrogenation of Bis-3-bromoprop-1-enyl Sulphone.

Bis-3-bromoprop-1-enyl sulphone (1.011g.) was dissolved in dry ethanol (30 ml.), platinum oxide (0.1005g.) was added, and hydrogenation carried out for 21 hours. The uptake of hydrogen was equivalent to four moles, indicating that hydrogenation was accompanied by hydrobrominolysis. The reaction mixture was filtered, and treated with activated charcoal to remove the colloidal precipitate of platinum. Evaporation under reduced pressure yielded a reddish-brown liquid which did not crystallise in a vacuum desiccator. Attempts to recrystallise it from ether were unsuccessful.

EXPERIMENTS CONNECTED WITH THE ATTEMPT TO PREPARE BIS-3-DIETHYLAMINOPROP-1-ENYL SULPHIDE

Bis-2:3-dibromopropyl Sulphide.

Diallyl sulphide (14.33g.) was dissolved in carbon tetrachloride (100 ml.). A slight excess of bromine (41g.) in carbon tetrachloride (30 ml.) was slowly added to the stirred solution. Heat was evolved. The solvent was removed under reduced pressure, and the residue was recrystallised twice from carbon tetrachloride as white needles, m.p. 92-93.5°C. (31g., 56.8%). McKittrick[257] gives m.p. 94-95.5°C.

Found. Br, 73.9 per cent.

Calc. for $C_6H_{10}SBr_4$, Br, 73.7 per cent.

Dehydrobromination of Bis-2:3-dibromopropyl Sulphide.

Method (1). Bis-2:3-dibromopropyl sulphide (15g.) was dissolved in a mixture of ether (100 ml.) and ethanol (40 ml.) and the solution warmed. Potassium hydroxide (4g.; theoretical 3.87g.) dissolved in a mixture of water (3 ml.) and ethanol (20 ml.) was added slowly with swirling. On cooling, the mixture was poured into water (400 ml.) and extracted with ether. The ethereal extracts, after washing, and drying (Na_2SO_4), yielded on removal of solvent a golden-brown liquid (10.22g.).

Distillation of a portion of this liquid (8.13g.) yielded two fractions:-

(a) A mixture of bis-3-bromoprop-2-enyl sulphide and 3-bromoprop-2-enyl 2'-bromoprop-2'-enyl sulphide as a straw-coloured liquid, b.p. 125-130°C.(bath)/4 mm., $n_D^{18.75}$ 1.5990 (3.6g.). n_D^{25} 1.5975 after redistillation.

Found. Br, 58.5 per cent.

$C_6H_8SBr_2$ requires Br, 58.8 per cent.

The mixed dibromosulphides (1.0215g.) in chloroform (25 ml.) were ozonised for 1 hour, the solvent removed under reduced pressure at low temperature, and the oily product hydrolysed by refluxing for 30 mins. with water (40 ml.). Steam distillation and treatment of the steam-distillate with dimedone yielded the formaldehyde dimedone derivative (.2110g., 19.3% of theoretical for 1 vinylidene group). Treatment of the residue after steam distillation with nitric acid (1 ml.) and an excess of silver nitrate solution yielded silver bromide (0.92g., 65.2% of theoretical for 2 vinylic bromides).

(b) 2:3-dibromopropyl 3'-bromoprop-2'-enyl sulphide as a yellow liquid, b.p. 118-119°C./0.75 mm., $n_D^{18.75}$ 1.6123 (3.5g.).

Found. Br, 69.3 per cent.

$C_6H_9SBr_3$ requires Br, 67.9 per cent.

Ozonolysis of the tribromosulphide (0.9436g.) as above yielded formaldehyde dimedone derivative in only low yield (0.0227g., 2.91% of theoretical for 1 vinylidene group), and hydrobromic acid (as silver bromide, 0.502g., 91.64% of theoretical for 1 vinylic bromide).

Method (2). Bis-2:3-dibromopropyl sulphide (11.75g.) was dissolved in a mixture of benzene (50 ml.) and ethanol (20 ml.). A slight excess of potassium hydroxide in ethanol (63 ml. of 0.8608 N/1; theoretical 62.91 ml.) was added slowly to the cold stirred solution. After stirring for a further 10 minutes, the potassium bromide was filtered off, and the bulk of the solvent removed by distillation. The residual liquid was poured into water (120 ml.) and extracted with benzene. After drying (Na_2SO_4) and removal of the solvent, there remained a mixture of bis-3-bromoprop-2-enyl sulphide and 3-bromoprop-2-enyl 2'-bromoprop-2'-enyl sulphide, n_D^{20} 1.5942 (7.086g., 95.2%), which distilled at 96-97°C./ 1.3 mm. as a straw-coloured liquid, n_D^{20} 1.5961.

Interaction of a Mixture of Bis-3-bromoprop-2-enyl Sulphide and 3-Bromoprop-2-enyl 2'-bromoprop-2'-enyl Sulphide with Diethylamine.

The mixture of dibromosulphides (9.5g.) in benzene (120 ml.) were refluxed for 1 hour with excess diethylamine (25 ml).

The mixture was evaporated to dryness, extracted with benzene, washed with water (to remove diethylamine hydrobromide), and then extracted with dilute hydrochloric acid (to separate the base). The acid aqueous extract was made alkaline with sodium hydroxide solution, extracted with benzene, washed with water, dried (Na_2SO_4), and the solvent removed under reduced pressure to yield a yellow liquid (5.42g.). This was distilled twice at 123-128°C.(bath)/3.5 mm. to give 3-bromoprop-2-enyl 2'-diethylaminoprop-2'-enyl sulphide as a colourless liquid, n_D^{19} 1.5300.

Found. equiv. (titration) 263.6; N, 5.2 per cent.

$C_{10}H_{18}NSBr$ requires equiv. 264.2; N, 5.3 per cent.

The base (0.679g.) was ozonised, as described for the mixture of dibromosulphides, and the ozonide was hydrolysed to yield formaldehyde, isolated as the dimedone derivative (0.0973g. 13.24% of theoretical for 1 vinylidene group), and hydrobromic acid (not estimated).

The benzene extract (non-basic) was washed, dried (Na_2SO_4), and evaporated under reduced pressure to yield a yellow-brown liquid (2.69g.), which distilled at 120-125°C. (bath)/3.5 mm. to yield bis-3-bromoprop-2-enyl sulphide as a straw-coloured liquid, n_D^{20} 1.5958.

Found. C, 26.5; H, 3.15 per cent.

$C_6H_8SBr_2$ requires C, 26.5; H, 3.0 per cent.

Ozonolysis of bis-3-bromoprop-2-enyl sulphide (0.962g.) yielded only a trace of formaldehyde (estimated as dimedone derivative, not weighed), and hydrobromic acid (estimated by conversion to silver bromide - 1.125g., 84.8% of theoretical for two vinylic bromine atoms).

Treatment of Bis-3-bromoprop-2-enyl Sulphide with Acetic Acid Solution.

Bis-3-bromoprop-2-enyl sulphide (1.093g.) in glacial acetic acid (15 ml.) and water (1.5 ml.) was heated for 1 hour over a boiling water-bath. The solution turned dark-red in colour. It was poured into water (60 ml.) to yield an opalescent solution. Partial neutralisation by the addition of sodium hydroxide solution (20%) made the liquid cloudy. Extraction with benzene, washing, and drying (Na_2SO_4) yielded, after removal of the solvent, a reddish-brown liquid which was distilled at 95-100°C.(bath)/0.35 mm. as a yellow oil, n_D^{14} 1.5603, (0.266g.). The substance reduced Tollen's reagent, but did not bring back the colour to Schiff's reagent. On heating with Fehling's solution any reduction was masked by the formation of a black precipitate, presumably copper sulphide produced by decomposition of the compound. With sodium hydroxide solution a pleasant odour was detected at first although the solution rapidly resinified. These reactions seemed to indicate that the substance was bis-3-acetoxyprop-2-enyl sulphide, but it

darkened in colour rapidly due to decomposition and no analytical figures could be obtained.

The aqueous liquid from the extraction yielded, on acidification with nitric acid and addition of excess silver nitrate solution, a precipitate of silver bromide (1.369g., equivalent to 90.65% theoretical for two vinylic bromine atoms).

Attempts to condense Bis-3-bromoprop-2-enyl Sulphide with Diethylamine.

Method (1). Bis-3-bromoprop-2-enyl sulphide (1g.) in benzene (20 ml.) was refluxed for 2 hours with diethylamine (2.5 ml.) and allowed to stand overnight at room temperature. The liquid was evaporated to dryness, extracted with benzene, washed with water, and then extracted with dilute hydrochloric acid. The benzene layer after washing and drying (Na_2SO_4) yielded, on removal of solvent, unchanged bis-3-bromoprop-2-enyl sulphide, n_D^{20} 1.5959. The acid aqueous extract was made alkaline with sodium hydroxide solution and extracted with benzene, and the latter solution yielded, after washing with water, drying (Na_2SO_4), and evaporation of the solvent, one or two drops of base as a red liquid, $n_D^{22.5}$ 1.5268.

Method (2). Bis-3-bromoprop-2-enyl sulphide (3.63g.) was heated with diethylamine (6 ml.) at 130-140°C. for

2.5 hours in a bomb (40 ml.). On cooling and extraction (as in method (1)) the bulk of the starting material, n_D^{20} 1.5956, was obtained together with trace amounts of base, n_D^{20} 1.5278.

3-Bromoprop-2-enyl 2'-diethylaminoprop-2'-enyl Sulphone.

3-Bromoprop-2-enyl 2'-diethylaminoprop-2'-enyl sulphide (1g.) was dissolved in glacial acetic acid (15 ml.) and the solution cooled to below 5°C. Solution of hydrogen peroxide (30%, 3 ml.) was added slowly with stirring to the semi-solid mass, and the reaction mixture was allowed to stand overnight at room temperature. The solution was then heated to 80-85°C. for 1 hour, allowed to cool, and poured into water (50 ml.). A slight excess of sodium hydroxide solution (20%) was added, and the liberated base was extracted with benzene. The benzene extracts were washed and dried (Na_2SO_4), and the solvent removed under reduced pressure to yield a yellow oil. Distillation at 160°C.(bath)/1.4 mm. yielded 3-bromoprop-2-enyl 2'-diethylaminoprop-2'-enyl sulphone as a pale yellow oil (0.32g., 29.2%), $n_D^{15.5}$ 1.5343. Wt. per ml. at 19°C. 1.284.

Found. equiv. (titration) 294.3; N, 4.6 per cent.
$C_{10}H_{18}O_2NSBr$ requires equiv. 296.2; N, 4.7 per cent.

Ozonolysis of the base (0.27g.) yielded formaldehyde (0.033g. of formaldehyde dimedone derivative; 12.38% of theoretical

for 1 vinylidene group), and hydrobromic acid (not estimated).

Oxidation of the Mixture of Bis-3-bromoprop-2-enyl Sulphide and 3-Bromoprop-2-enyl 2'-bromoprop-2'-enyl Sulphide.

The mixture of dibromosulphides (5.614g.) in glacial acetic acid (70 ml.) was oxidised, as described in the preparation of 3-bromoprop-2-enyl 2'-diethylaminoprop-2'-enyl sulphone, by means of a solution of hydrogen peroxide (30%, 14 ml.), poured into water (300 ml.), and extracted with benzene to yield a mixture which included bis-3-bromoprop-2-enyl sulphone, 1-bromoprop-2-enyl 2'-bromoprop-2'-enyl sulphone and bis-1-bromoprop-2-enyl sulphone, as a yellow oil together with some crystalline material (5.467g.), $n_D^{24.5}$ 1.5683.

Reaction of the Mixed Dibromosulphones with Diethylamine.

The mixed dibromosulphones (5.45g.) from the above reaction, in benzene (50 ml.), were treated with diethylamine (7 ml.), and warmed on a hot water-bath for 5 minutes. After removing the solvent under reduced pressure, the residue was washed with water and extracted with benzene. The basic fraction was separated by extraction with dilute hydrochloric acid, basifying the aqueous extract by means of sodium hydroxide solution, and extracting with benzene.

Basic fraction. Red oil (2.296g.), n_D^{14} 1.5110.

Found. equiv. (titration) 247.6,

$C_{14}H_{28}O_2N_2S$ requires equiv. 144.2, and

$C_{10}H_{18}O_2NSBr$ requires equiv. 296.2 .

The crude mixed bases (1.131g.) were distilled at 170-175°C. (bath)/1.7 mm. to yield 1-diethylaminoprop-2-enyl 2'-bromoprop-2'-enyl sulphone as a yellow oil (0.4533g.), n_D^{14} 1.5188. Considerable decomposition had occurred in the distillation flask. Wt. per ml. at 19°C. 1.307.

Found. equiv. (titration) 295.3; N, 4.9 per cent.

$C_{10}H_{18}O_2NSBr$ requires equiv. 296.2; N, 4.7 per cent.

Ozonolysis of the base (0.247g.) yielded formaldehyde (as dimedone derivative, 0.0386g., 7.92% of theoretical for 2 vinylidene groups), and hydrobromic acid (not estimated).

The crude mixed bases (0.2g.) were dissolved in dilute hydrochloric acid and evaporated to dryness under reduced pressure. The residue gave a small yield of whitish crystals, m.p. 189-190°C. from ethanol-ether, insufficient for recrystallisation. (Mixed melt with bis-3-diethylamino-prop-1-enyl sulphone dihydrochloride (m.p. 192-193°C.) was depressed to 176-179°C.). The low value of equivalent weight obtained from the remainder of the crude crystals indicated that the substance was possibly bis-1-diethylamino-prop-2-enyl sulphone dihydrochloride.

Non-basic fraction.

This was obtained from the benzene solution from which the base had been extracted as a reddish-brown oil containing some crystalline material (2.24g.), n_D^{14} 1.5624. Distillation of the oil yielded two fractions -

(a) A yellowish liquid, b.p. 160-165°C. (bath)/1.3 mm. (1.2g.) which solidified on cooling. It was separated from traces of oil by passing through a column of alumina in ether solution. The crystalline material was isolated from the earlier fractions and recrystallised several times from light petroleum (40-60°C.) to yield bis-3-bromoprop-2-enyl sulphone as white plates, m.p. 65.5-66.5°C.

Found C, 23.8; H, 3.0; Br, 52.15 per cent.
$C_6H_8O_2SBr$ requires C, 23.7; H, 2.7; Br, 52.6 per cent.

Ozonolysis of bis-3-bromoprop-2-enyl sulphone (0.4133g.) yielded only a trace of formaldehyde and hydrogen bromide, (0.421g. silver bromide, 82.6% of theoretical for 2 vinylic bromines).

(b) A yellow liquid, b.p. 180-200°C. (bath)/1.3 mm. (1.5g.) which solidified on cooling, and which, on recrystallisation from ether, gave prisms, m.p. 73-74°C.
Found. C,41.9; H, 6.3; Br,28.1 per cent.(S present;N absent.)
$C_{10}H_{18}O_3SBr$ requires C, 41.7; H, 6.3; Br, 27.7 per cent.
The substance did not react with diethylamine, and reduced

Tollen's reagent slowly on heating. It did not bring back the colour to Schiff's reagent. Ozonolysis of the compound (0.289g.) gave no trace of formaldehyde, but gave hydrobromic acid in good yield (not estimated).

Oxidation of Bis-3-bromoprop-2-enyl Sulphide and Reaction of the Product with Diethylamine.

Bis-3-bromoprop-2-enyl sulphide (2.331g.) in glacial acetic acid (30 ml.) was oxidised with solution of hydrogen peroxide (30%, 5.5 ml.), as described in the preparation of 3-bromoprop-2-enyl 2'-diethylaminoprop-2'-enyl sulphone. The resulting solution was then poured into water (150 ml.) and extracted with benzene. The benzene extracts, after washing and drying (Na_2SO_4), were evaporated under reduced pressure to yield a yellow oil (2.45g.) contaminated with some crystalline material. This was dissolved in benzene (20 ml.), warmed with diethylamine (2.5 ml.) for 5 minutes, evaporated to dryness, and extracted with benzene. Separation into basic and non-basic fractions was carried out as before by extracting the benzene solution with dilute hydrochloric acid. The non-basic fraction remained in the benzene layer and was obtained from the latter after washing, drying and evaporation, while the base was isolated from the acid extract by adding excess sodium hydroxide solution, and extracting with benzene.

Basic fraction.

This was obtained as a reddish-brown liquid (0.117g.), n_D^{16} 1.5123, which owing to lack of material was not characterised, although it was presumed to be 1-diethylaminoprop-2-enyl 3'-bromoprop-2'-enyl sulphone.

Found. equiv. (titration) 293.3.

$C_{10}H_{18}O_2NSBr$ requires equiv. 296.2.

Non-basic fraction.

This was a yellow oil containing some crystalline material (2.091g.), n_D^{14} 1.5649. Distillation at 145-150°C. (bath)/0.6 mm. yielded a colourless oil which solidified on cooling (1.75g.). The crystalline material was separated from traces of oil by passing it in ethereal solution through a column of alumina. It was isolated from the earlier fractions, and recrystallised several times from light petroleum as colourless plates, m.p. 65.5-66.5°C., identical (m.p. and mixed m.p.) with bis-3-bromoprop-2-enyl sulphone obtained previously (p.113).

Attempted Solvolysis of Bis-3-bromoprop-2-enyl Sulphone.

Bis-3-bromoprop-2-enyl sulphone (1.382g.) in glacial acetic acid (18 ml.) and water (2 ml.) was heated on a boiling water bath for 1.25 hours. The solution was then cooled, poured into water (150 ml.) and extracted with

benzene. Unchanged bis-3-bromoprop-2-enyl sulphone (1.232g.; confirmed by m.p. and mixed m.p. with starting material) was recovered from the benzene extracts.

Addition of Hydrogen Bromide to Diallyl Sulphide.

Diallyl sulphide (7.27g.) was dissolved in carbon tetrachloride (100 ml.) and a crystal of benzoyl peroxide was added. The solution was heated to boiling, and dry hydrogen bromide was passed in while the solution cooled. The solution was brought to the boil every 3 hours. After 22 hours the solvent was removed under reduced pressure to yield a yellow liquid (13.7g.). Fractionation of the liquid yielded two components.

(a) 2-Bromopropyl prop-2'-enyl Sulphide, b.p. 49-50°C./1.7 mm. $n_D^{17.5}$ 1.5275 (5.5g.)

Found. Br, 41.8 per cent.

$C_6H_{11}SBr$ requires Br, 41.0 per cent.

(b) Bis-2-bromopropyl Sulphide, b.p. 95°C./0.95 mm. n_D^{19} 1.5547 (7.4g.).

Found. Br, 58.3 per cent.

$C_6H_{12}SBr_2$ requires Br, 58.0 per cent.

Bis-2-diethylaminopropyl Sulphide.

Bis-2-bromopropyl sulphide (1.042g.) in benzene (12 ml.) was refluxed with diethylamine (2 ml.) for 5 hours. The base was extracted from the unreacted

material in the usual manner as a yellow oil (0.461g.), distilling at 80°C./1.2 mm., n_D^{18} 1.4747.

Found. equiv. (titration) 142.3.

$C_{14}H_{32}N_2S$ requires equiv. 130.1.

The base, without further purification, was converted to the dihydrochloride in the usual way, and recrystallised from ethanol-ether as colourless crystals m.p. 224-226°C. (decomp.). Mixed melting point with bis-3-diethylamino-propyl sulphide dihydrochloride (m.p. 222.5-223.5°C.) depressed to 211-212.5°C.

Found. Cl, 21.3; N, 8.45 per cent.

$C_{14}H_{34}N_2SCl_2$ requires Cl, 21.3; N, 8.4 per cent.

Bis-3-bromopropyl Tetrasulphide.

1:3 Dibromopropane (40.4g.), prepared by the method in Organic Syntheses[258] was added to a stirred mixture of sodium sulphide (7.8g.) in water (10 ml.) and ethanol (45 ml.). The mixture was then refluxed for 3.5 hours, cooled, and poured into water (250 ml.). It was extracted with benzene, washed with water, dried (Na_2SO_4), and the solvent removed under reduced pressure to yield a brown oil. This was distilled twice to yield bis-3-bromopropyl tetra-sulphide, b.p. 121-125°C./1.2 mm. (6.32g., 17%) as a pale yellow oil, n_D^{13} 1.5538.

Found. Br, 42.4 per cent.

$C_6H_{12}S_4Br_2$ requires Br, 42.9 per cent.

Bis-3-diethylaminopropyl Tetrasulphide Dihydrochloride.

Bis-3-bromopropyl tetrasulphide (2.313g.) in benzene (20 ml.) was refluxed with diethylamine (4 ml.) for 1.5 hours. The mixture was evaporated to dryness, extracted with benzene, and the benzene extracts were extracted with dilute hydrochloric acid. Addition of excess sodium hydroxide to the acid extract liberated the free base which was extracted with benzene. After washing with water, drying (Na_2SO_4), and removal of solvent under reduced pressure, a pale yellow oil remained (1.34g.), $n_D^{17.5}$ 1.4953, which distilled at 155-160°C.(bath)/1.6 mm., as a colourless oil, $n_D^{17.5}$ 1.4988. This was converted to the dihydrochloride in the usual way, and recrystallised twice from ethanol as colourless needles, m.p. 245.5-246.5°C.

Found. C,39.8; H,7.5; N,6.7; Cl, 17.0 per cent.

$C_{14}H_{34}N_2S_4Cl_2$ requires C,39.1; H,8.0; N,6.5; Cl, 16.5 per cent.

OXIDATION EXPERIMENTS.

Di-n-butyl Sulphide.

Anhydrous sodium sulphide (12g.) was placed in a flask with ethanol (50 ml.), and the mixture was heated to boiling with stirring. n-Butyl bromide (37g.) was then slowly added (20 min.), and the stirred mixture was refluxed for a further 7 hours. The bulk of the ethanol was distilled off and the residue, on cooling, poured into water (100 ml.) and extracted with ether. The ethereal extracts were washed, dried (Na_2SO_4), and the ether removed by distillation. The residue was distilled, and di-n-butyl sulphide, b.p. 47°C./2 mm., n_D^{16} 1.4560 (12g., 61%) was collected. Gray and Gutekunst[259] report b.p. 180-185°C./760 mm.

Dibenzyl Sulphide was prepared as above from benzyl bromide (40g.). The impure dibenzyl sulphide was purified by distilling at 160-170°C.(bath)/2 mm. It condensed as a yellow crystalline mass, m.p. 44-46°C. (10g., 40%). Shriner, Struck, and Jorison[260] report m.p. 49°C.

2:2':4:4'-Tetranitrodiphenyl Sulphide

1-Chloro-2:4-dinitrobenzene (10.1g.) was dissolved in ethanol (90 ml.). A solution of sodium thiosulphate (12.5g.) in water (50 ml.) was added, and the mixture was refluxed with stirring for 30 minutes. Sodium thiosulphate

(5g.) was then added and the mixture refluxed for a further 30 minutes. On cooling, 2:2':4:4'-tetranitrodiphenyl sulphide was filtered off, washed with ethanol and dried in a vacuum desiccator, m.p. 195-197°C. (4.7g., 51.5%). Hodgson and Dodgson[261] gave m.p. 197°C.

Attempted Preparation of Dicinnamyl Sulphide.

Cinnamyl chloride (12.14g.) was dissolved in ethanol (240 ml.), and a mixture of sodium thiosulphate (12.14g.) in water (140 ml.) was added. The mixture was refluxed with stirring for 1 hour, sodium thiosulphate (4.86g.) was added, and the mixture was refluxed for a further 30 minutes. The bulk of the ethanol was distilled off, and the residue, on cooling, was poured into water (200 ml.) and extracted with ether. The ethereal extracts, after washing with water and drying (Na_2SO_4), were evaporated to yield a yellow-coloured semi-solid mass (5.75g.). This was dissolved in light petroleum (40-60°C.) and passed through a column of alumina. It was eluted first with light petroleum, then with benzene (increasing to 40%) in light petroleum, and finally with ethanol (12%) in light petroleum. From the earlier fractions a white solid was obtained which was recrystallised from light petroleum (40-60°C.) as feathery crystals of a dicinnamyl trisulphide, m.p. 95-95.5°C.

Found. C, 64.9; H, 5.6 per cent.

$C_{18}H_{18}S_3$ requires C, 65.5; H, 5.5 per cent.

From the last fraction a reddish-brown liquid, $n_D^{14.5}$ 1.5728, was obtained which, as indicated by the analysis, was probably an impure specimen of dicinnamyl sulphide. Attempts to obtain pure material were unsuccessful.

Found. C, 85.2; H, 8.2 per cent.

$C_{18}H_{18}S$ requires C, 81.2; H, 6.8 per cent.

Oxidations with Chromic Acid in Pyridine.

(a) Di-n-butyl Sulphoxide.

Chromic acid (18.5g.) was added slowly (1 hour) to a stirred solution of di-n-butyl sulphide (5.5g.) in pyridine (180 ml.). After standing overnight the mixture was poured into water (1 l.) and extracted with ether. The ethereal extracts, after washing with water, drying (Na_2SO_4), and evaporation of the solvent, yielded a yellow liquid which crystallised in a vacuum desiccator. Distillation of the product at 115-120°C.(bath)/2 mm. gave di-n-butyl sulphoxide (3g., 49%) as a colourless liquid, which crystallised only under anhydrous conditions as white crystals, m.p. 31-32°C. Bert[203] reports m.p. 32°C.
On exposure to the air, the crystals rapidly absorb moisture and liquefy, a process which is reversed on dehydration.

(b) Dibenzyl Sulphoxide.

Chromic acid (6.2g.) was added slowly (1 hour) to a

stirred solution of dibenzyl sulphide (1.25g.) in pyridine (50 ml.). After standing for 5 days the mixture was poured into water (50 ml.) and extracted with benzene. The benzene extracts, after washing and drying (Na_2SO_4), yielded on evaporation a yellowish solid, m.p. 126-130°C. (1.1g.). This was recrystallised from light petroleum (80-100°C.) to yield almost colourless crystals of dibenzyl sulphoxide, m.p. 133-134°C. (0.95g., 71%). Bohme[239] gives m.p. 134-135°C.

(c) Attempted Oxidation of Diallyl Sulphide.

Chromic acid (23.5g.) was added slowly (1 hour) to a stirred solution of diallyl sulphide (10.3g.) in pyridine (226 ml.). After standing overnight the mixture was poured into water (1.5 l.) and extracted with benzene. The benzene extracts, after washing with water, drying (Na_2SO_4), and removal of the solvent by distillation, yielded a dark brown oil (0.8g.), n_D^{20} 1.5370 which was not further investigated. Fractionation of the benzene distillate failed to yield any diallyl sulphoxide, and evaporation of the aqueous liquid, followed by extraction, yielded only a trace of dark brown oil.

Oxidations with Manganese Dioxide in Light Petroleum.

Manganese dioxide was prepared by precipitation from manganese sulphate and potassium permanganate as described

by Ball, Goodwin and Morton[245]. Light petroleum (40-60°C.) was sodium dried.

(a) Di-n-butyl Sulphoxide.

Di-n-butyl sulphide (1.2g.) dissolved in light petroleum (120 ml.) was shaken continuously with manganese dioxide (12.7g.) for 85 hours. Filtration and evaporation yielded a small quantity of yellow liquid which crystallised in a vacuum desiccator (0.25g.). The manganese dioxide was then extracted with benzene for 13 hours in a continuous extraction apparatus. Evaporation gave a further yield of yellow liquid which crystallised under anhydrous conditions (0.75g). Distillation of the mixed products gave di-n-butyl sulphoxide (0.97g., 71%) as an oil crystallising under anhydrous conditions, m.p. 31-32°C.

(b) Dibenzyl Sulphoxide.

Dibenzyl sulphide (0.74g.) in light petroleum (75 ml.) was shaken continuously with manganese dioxide (7.5g.) for 72 hours. Filtration and evaporation gave only traces of unchanged dibenzyl sulphide. The manganese dioxide was extracted with chloroform for 10 hours in a continuous extraction apparatus to yield, on evaporation, a solid product, m.p. 93-100°C. (0.59g.). Recrystallisation from light petroleum (80-100°C.) gave dibenzyl sulphoxide, m.p. 133-134°C. (0.5g., 74%).

(c) Diallyl Sulphoxide.

Diallyl sulphide (2.5g.) dissolved in light petroleum (370 ml.) was shaken continuously with manganese dioxide (37.5g.) for 76 hours. Filtration and evaporation gave only a small quantity of unchanged sulphide. The manganese dioxide was then extracted with chloroform in a continuous extraction apparatus for 6 hours. Removal of the solvent by distillation yielded a brownish-red liquid $n_D^{15.75}$ 1.5173 (crude yield 1.28g., 45%). Distillation of the product yielded diallyl sulphoxide, b.p. 100-110°C.(bath)/3 mm., $n_D^{17.5}$ 1.5117, $d_{17.5}^{17.5}$ 1.034, (0.36g., 13%). Lewin[248] gives b.p. 89-90°C./2.6 mm., n_D^{20} 1.5115, d_4^{20} 1.0261.

Attempted Oxidation of 2:2'4:4'-tetranitrodiphenyl Sulphide with Manganese Dioxide in Acetone.

2:2'4:4'-tetranitrodiphenyl sulphide (0.79g.) dissolved in acetone (45 ml.) was shaken continuously with manganese dioxide (2.9g.) for 18 hours. The mixture was then filtered, and the manganese dioxide was extracted with acetone in a continuous extraction apparatus for 7 hours. After removal of the solvent, the yellow residue was recrystallised from ethanol, m.p. 197-198°C. (0.71g.), and found to be unchanged starting material (mixed melting point with starting material 197-198°C.).

SS-di-n-butyl-N-toluene-p-sulphonylsulphidimine.

(a) From di-n-butyl sulphide.

Di-n-butyl sulphide (0.68g.) was shaken vigorously with a cold saturated aqueous solution of Chloramine T (1.36g.). A solid separated out in a few minutes, and was filtered off after standing for 1 hour, washed with water and dried. It was recrystallised from benzene-light petroleum mixture to yield the sulphidimine as colourless needles, m.p. 77.5-78°C.

Found. S, 19.5 per cent.

$C_{15}H_{25}O_2NS$ requires S, 20.3 per cent.

(b) From di-n-butyl sulphoxide.

Di-n-butyl sulphoxide (0.55g.) and toluene-p-sulphonamide (0.56g.) were refluxed with phosphorus pentoxide (0.35g.) in chloroform (4 ml.) for 30 minutes. Phosphorus pentoxide (0.35g.) was then added and the mixture refluxed for a further 30 minutes. The hot solution was then decanted from the sludge, cooled, washed with sodium hydroxide solution (10%) and finally with water. The chloroform solution, after drying (Na_2SO_4) and evaporation, yielded a brownish mass of crystals. These were heated with charcoal in benzene solution, and filtered. The residue, after removal of solvent and recrystallisation from benzene-light petroleum, gave the sulphidimine as colourless needles, m.p. 77.5-78°C., alone or mixed with a specimen prepared as

described under (a).

The sludge from the reaction mixture was warmed with a few ml. of sodium hydroxide solution (20%), and then left standing overnight. The brownish crystals which separated from the solution were filtered off and purified as above to give a further yield of SS-di-n-butyl-N-toluene-p-sulphonylsulphidimine.

Attempted Preparation of SS-bis-(2:4-dinitrophenyl)-N-toluene-p-sulphonylsulphidimine.

2:2':4:4'-Tetranitrodiphenyl sulphide (0.332g.) in acetone (20 ml.) was shaken vigorously for 5 minutes with a cold saturated aqueous solution of Chloramine T (0.26g.), and then warmed in a water-bath at 50°C. for a further 10 minutes. The solution turned dark red in colour. After the addition of water (20 ml.), the bulk of the acetone was removed by distillation. The precipitated solid was filtered off, dried, and recrystallised from benzene, m.p. 197-198°C., and found to be unchanged starting material, (mixed m.p. with starting material 197-198°C.).

Oxidation of Diallyl Sulphide with Chromic Acid in Acetic Acid.

Chromic acid (1.875g.) in water (2 ml.) was added to a solution of diallyl sulphide (2.5g.) in acetic acid (80%,

110 ml.). The solution was heated to 70°C. for 20 minutes, left standing at room temperature for 12 hours, and poured into water (50 ml.). Extraction with chloroform, washing with water, drying (Na_2SO_4), and removal of solvent under reduced pressure yielded a yellow oil (2.254g.). Distillation under reduced pressure gave diallyl sulphoxide (1.94g., 68.1%) as a colourless oil, b.p. 103-108°C.(bath)/ 3.25 mm., $n_D^{17.5}$ 1.5140.

BACTERIOLOGICAL RESULTS

GENERAL METHODS OF TESTING TUBERCULOSTATIC AGENTS.

Before any tuberculostatic agent can be used for clinical tests, it must undergo numerous *in vitro* and *in vivo* tests. *In vitro* tests are a useful preliminary although their value is strictly limited, since there is no guarantee that substances possessing *in vitro* activity will show similar activity *in vivo*. On the other hand a substance showing practically no antibacterial activity *in vitro* may show considerable *in vivo* activity. In addition, even with compounds showing considerable *in vitro* activity, *in vivo* tests are necessary in order to establish the chemotherapeutic index by means of toxicity tests.

One of the chief advantages of reliable *in vitro* tests is that the synthesis of large quantities of substances, required for tests on experimental animals for a period of six or seven weeks, is not necessary until some idea of the antibacterial activities of the substances has been obtained. Reliable *in vitro* tests can nowadays be obtained using the special medium of Dubos[171], or Peizer and Schecter[262]. The former medium includes certain water-soluble esters of oleic acid, in addition to serum albumin, and the bacteria grow rapidly throughout the liquid medium rather than at the surface alone. The egg-agar medium of Peizer and Schecter provides more reliable results and often

shows up as inactive, compounds which have given positive results in Dubos medium. However, all compounds shown to be effective in man, have been found to be active in both of these media.

Of the in vivo methods, the guinea pig test has been used extensively and developed by Feldman and Hinshaw[263]. Guinea pigs are highly susceptible to human tuberculosis, so that any substance which produces favourable results in them, will be almost certain to be beneficial to human beings. The animals are infected by means of a subcutaneous injection of virulent human tubercle bacilli, and the disease is allowed to develop for about six weeks. Each animal should then give a positive tuberculin reaction. The maximum therapeutic dose possible, consistent with safety, is then administered sufficiently often so as to maintain adequate concentrations of the drug in the blood. A control group of animals is used for comparison with those in the test group, and the experiment is usually designed so that the proportion of survivors in the test group is compared with no survivors in the control group. Very often the survivors are kept under observation for the remainder of their lives, or treatment may be continued in a proportion of the survivors.

The mouse test was introduced by Swabacher and Wilson[264] in an attempt to cut down the time required for the test. An acute infection is established by large

injections of the tubercle bacilli and the assessment of activity is based upon the mean mortality time of a group of mice, or alternatively upon the number of organisms isolated from a weighed piece of spleen.

An *in vivo* test which makes use of the rabbit cornea as the site of infection has been described by Robson[265]. Standard tuberculous lesions are obtained within a few days and are sufficiently reliable for studying antituberculous agents. These drugs are injected into the posterior chamber of the eye and diffuse into the anterior part and the cornea. By this means, adequate chemotherapeutic levels of the drug can be maintained at the site of the infection for between 48 and 72 hours[266].

TESTING OF BISDIALKYLAMINOALKYL SULPHIDES AND SULPHONES

Preliminary assessment of the tuberculostatic activity of the compounds prepared in this work was measured against

(1) M. tuberculosis var hominis (CN 3679) in Dubos medium and in Peizer and Schecter medium, and

(2) M. tuberculosis var hominis (H 37 Rv) in Peizer and Schecter medium only.

For the tests in Dubos medium the drugs were added to the medium at a concentration of 1,000 µg. per ml., sterilised by Tyndallization at 60°C. on two successive days, and then diluted aseptically in two-fold decrements in volumes of 2 ml. in 5 ml. screw-cap bottles. For the tests in Peizer and Schecter medium, the drugs were added to physiological normal saline at ten times the desired strength, sterilised similarly, and then serially diluted in two-fold decrements. Volumes of 0.2ml. were than transferred to 5 ml. screw-cap bottles and 1.8 ml. of the medium added to each at 56°C. to give final concentrations of the same order as that used in the Dubos medium. The medium was then incubated in a sloped position.

The inoculum for the Dubos medium was one drop of a seven days old Dubos culture, centrifuged and concentrated to half of the original volume, while for the Peizer and Schecter medium about one hundredth of this inoculum was used,

namely, one drop of a four days old culture without concentration, run over the surface of the medium.

The tests in Dubos medium were read after seven and fourteen days incubation at 37°C., and those in the Peizer and Schecter medium after fourteen and twenty-one days.

For purposes of comparison the tests were also carried out on Isoniazid and on streptomycin.

Table 2 shows the results of the bacteriological tests. The key to the numbering of the compounds in the table is given below.

1. Bis-3-diethylaminopropyl sulphone dihydrochloride.
2. Bis-3-diethylaminoprop-1-enyl sulphone dihydrochloride.
3. Bis-6-diethylaminohexyl sulphone dihydrochloride.
4. Bis-6-(1'-piperidyl)-hexyl sulphone dihydrochloride.
5. Bis-10-diethylaminodecyl sulphone dihydrochloride.
6. Bis-10-(1'-piperidyl)-decyl sulphone dihydrochloride.
7. Bis-6-diethylaminohexyl sulphide dihydrochloride.
8. Bis-6-(1'-piperidyl)-hexyl sulphide dihydrochloride.
9. Bis-10-diethylaminodecyl sulphide dihydrochloride.
10. Bis-10-(1'-piperidyl)-decyl sulphide dihydrochloride.
11. Isoniazid.
12. Streptomycin.

I am indebted to Dr. S. R. M. Bushby of the Wellcome Research Laboratories for kindly undertaking these tests.

TABLE 2.

COMP. NO.	INCUBATION (DAYS)	MINIMUM INHIBITING CONCENTRATION (μg./ml.)					
		DUBOS MEDIUM STRAIN CN3679				PEIZER and SCHECTER MEDIUM H37Rv	PEIZER and SCHECTER MEDIUM CN3679
		EXP.1	EXP.2	EXP.3	EXP.4	EXP.1	EXP.2.
1	7	1000	> 1000	> 1000	> 1000	-	-
	14	1000	> 1000	> 1000	> 1000	> 1000	> 1000
	21	-	-	-	-	> 1000	> 1000
2	7	8	8	16	8	-	-
	14	8	16	62	16	500(±250)	250
	21	-	-	-	-	500	500(±250)
3	7	1000	> 1000	> 1000	> 1000	-	-
	14	> 1000	> 1000	> 1000	> 1000	> 1000	> 1000
	21	-	-	-	-	> 1000	> 1000
4	7	1000(±500)	> 1000	> 1000	> 1000	-	-
	14	> 1000	> 1000	> 1000	> 1000	> 1000	> 1000
	21	-	-	-	-	> 1000	> 1000
5	7	62(±8)	62(±31)	31(±16)	62(±31)	-	-
	14	62	62	31	62	250(+125)	125
	21	-	-	-	-	250(∓125)	250(±125)
6	7	16(±8)	31(±16)	16(±8)	31(±16)	-	-
	14	16	31	16	62(±31)	125(±62)	125(±62)
	21	-	-	-	-	125	125
7	7	> 1000	> 1000	1000	> 1000	-	-
	14	> 1000	> 1000	> 1000	> 1000	> 1000	> 1000
	21	-	-	-	-	> 1000	> 1000
8	7	500	500(±250)	250(±125)	500(±250)	-	-
	14	500	1000(±500)	500	500	1000	1000
	21	-	-	-	-	1000	1000
9	7	2	4(±2)	4(±2)	2	-	-
	14	4	8(±4)	4	4	62	125(±62)
	21	-	-	-	-	62	125(±62)
10	7	4(±2)	8(±4)	< 1	4(±2)	-	-
	14	4	8	4	8	125(± 62)	125(±62)
	21	-	-	-	-	125(± 62)	125(±62)
11	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
12	7	-	0.3	-	-	-	-
	14	-	0.3	-	-	-	2.5(±1.2)
	21	-	-	-	-	-	2.5(±1.2)

(±) SIGNIFIES CONCENTRATIONS AT WHICH THERE WAS PARTIAL INHIBITION OF GROWTH.

Conclusions.

The results of the bacteriological tests, shown in Table 2, lead to the following conclusions:-

1. None of the compounds examined possesses tuberculostatic activity of the same order as that of Isoniazid or streptomycin.

2. The long-chain compounds are more active than those with shorter chains.

3. Sulphides are more active than sulphones.

4. Unsaturation in the chain increases activity to a surprisingly high level, the short chain compound, bis-3-diethylaminoprop-1-enyl sulphone dihydrochloride being almost as active as bis-10-(1'-piperidyl)-decyl sulphone dihydrochloride, the most active of the saturated sulphones examined.

In conclusion, therefore, it can be stated that whilst no useful development can be expected from a further study of saturated aliphatic amino sulphides and sulphones, profitable advances may yet lie in a full examination of the effects of unsaturation in this series.

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APPENDIX I

Official or Proprietory Name	Systematic Name
Dapsone.	4:4′-Diaminodiphenyl sulphone.
Diasone.	4:4′-Diaminodiphenyl sulphone disodium formaldehyde sulphoxylate.
Isoniazid.	iso-Nicotinic acid hydrazide.
Promin.	Disodium 4:4′-diaminodiphenyl sulphone-N:N′-diglucose-sulphonate.
Solapsone; Sulphetrone	Tetrasodium 4:4′-bis-γ-phenyl-n-propylaminophenyl sulphone tetrasulphonate.
Thiacetazone; Conteben; TB1/698; Tibione.	4-Acetylaminobenzaldehyde thiosemicarbazone.