PART II
SYNTHESIS OF SOME BIS-(AMINOARYL) SULPHONES

INTRODUCTION

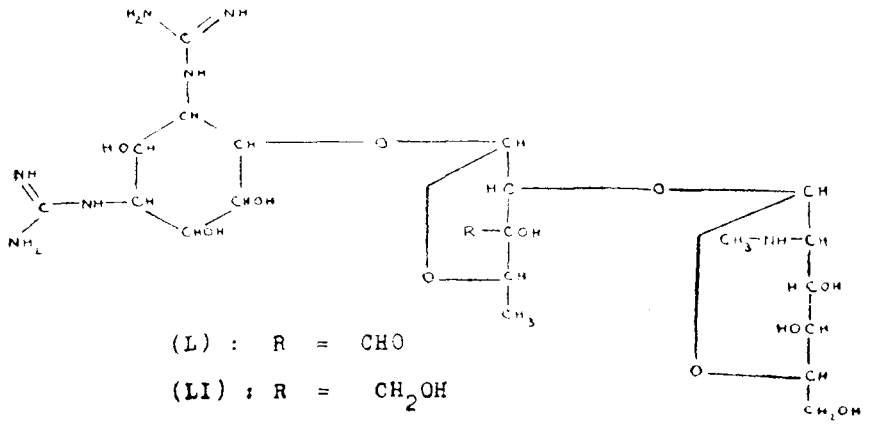
Tuberculosis stands high on the list of man-killing diseases. The disease is characterised by the formation in the tissues of nodular bodies or tubercles (hence, tuberculosis) and is manifested symptomatically in the pulmonary form by fever, cough and progressive loss of weight. The causative agent is a fungus-like bacterium known as Mycobacterium tuberculosis or the tubercle bacillus. This organism has the ability of infecting practically any tissue or organ of the body, thereby producing a variety of tuberculoses of which mention can be made of pulmonary tuberculosis, tuberculosis laryngitis, enteritis, osteomyelitis, meningitis and the most dreadful miliary tuberculosis. When the disease is well established in a patient, it offers a very high resistance to treatment. There is no short and easy cure for the disease. The chemotherapeutic agents now in use do not kill and eradicate the tubercle bacillus. At best, they are tuberculostats and merely arrest the progress of the disease.

Wells and Long[118] assembled the knowledge of tuberculosis existing upto 1932 and concluded that no known remedy modified the disease in the experimental animal or man. The discovery by Domagk[119] of the chemotherapeutic activity of prontosil, 2, 4-diaminoazobenzene-4'-sulphonamide hydrochloride, against experimental infections due to virulent streptococci provided a new impetus. The chemotherapeutic agents for tuberculosis may be divided into two main classes, the antibiotics and the synthetic tuberculostats. At present the antibiotics are clinically the most important. Only two of the several antibiotics that have been isolated and screened during the last few years have been clinically approved.

Streptomycin, a metabolic product of Streptomyces griseus, was isolated in 1944 by Schatz, Bugie and Waksman[120] and since then was shown to be the most effective agent available for the treatment of miliary tuberculosis, pulmonary tuberculosis and tuberculous meningitis. However, several side reactions are frequently encountered. Another serious disadvantage attending the use of streptomycin is the rapidity with which resistant strains develop. This effect has been partially overcome by conjoint administration of p-aminosalicylic acid. Dihydrostreptomycin was developed by Peck and his co-workers[121] in an effort to find a less toxic substitute for streptomycin. It is equally active as the parent compound and possesses practically all the disadvantages of the latter, apparently in a somewhat lesser degree. The structure of streptomycin and dihydrostreptomycin have been determined[122, 123] to be (L) and (LI) respectively.

The synthetic tuberculostats may be classified into sulphones, aminohydroxybenzoic acids, thiosemicarbazones and pyridine carboxylic acid derivatives.

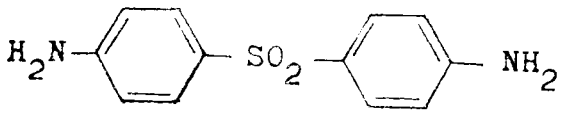
The first of the modern synthetic tuberculostats to be discovered are the sulphones. The parent compound of this group is bis-(p-aminophenyl) sulphone (LII). The compound was first synthesised by Fromm and Wittmann[124]. The chemotherapeutic activity of the sulphone was first evaluated by Buttle and his



(L) : R = CHO

(LI) : R = CH_2OH

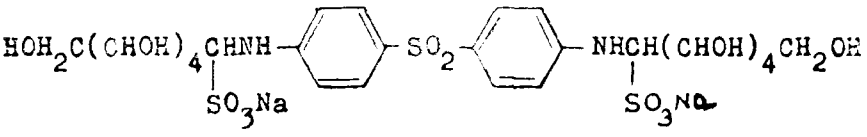
co-workers[125] and later Rist[126] demonstrated its high antibacterial activity. Buttle and his co-workers observed that it is hundred times as active as sulphanilamide. Though the com-



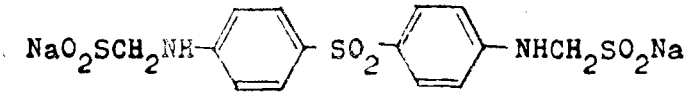
(LII)

pound is highly tuberculostatic, it is highly toxic and hence it is not clinically favoured in tuberculosis. But it has been used with some success in leprosy[127]. Another disadvantage of the compound is its high insolubility. The hydrochloride is hydrolysed in water. These disadvantages prompted the preparation of numerous derivatives of the parent sulphone in order to reduce the toxicity and increase the solubility and activity.

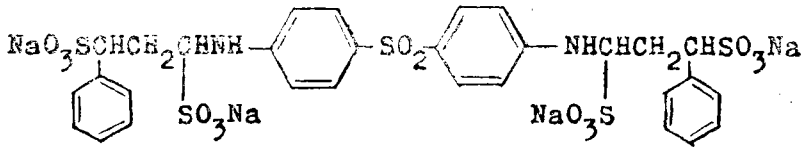
Compounds such as promin (LIII), diasone (LIV), sulphetrone (LV) and promizole (LVI) are some of the more promising ones. In these cases, though the solubilities are increased and the toxicities are decreased, the activities are also somewhat decreased.



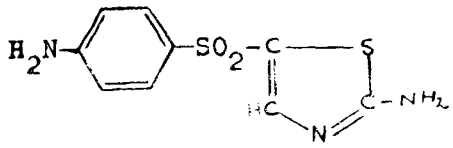
(LIII)



(LIV)



(LV)



(LVI)

Promin [sodium bis-(p-aminophenyl) sulphone N, N'-bis-(glucosesulphonate)] gave more encouraging results in guinea pigs[128, 129] but clinical studies were disappointing, because it causes excessive destruction of blood which results in the development of anaemia[130, 131]. Fagert and his co-workers[132] reported that promin may be used with advantages for the treatment of leprosy. The compound appears to be capable of inhibiting the progress of leprosy in a considerable percentage of cases, though no case of leprosy has been arrested under its influence.

Diasone [disodium formaldehydesulphoxylate bis-(p-aminophenyl) sulphone] was the first water-soluble preparation obtained with high therapeutic activity[133]. Its effectiveness against streptococci and pneumococci was first shown by Rosenthal[134]. As subcutaneous injection in mice, it has a therapeutic index against streptococci approximately five times as good as sulphanilamide, given orally. However, few animals permanently survived pneumococcal infection as a result of the therapy[133]. In a clinical trial[135] with diasone, sulphanilamide, sulphapyridine, sulphathiazole, and sulphathiazoline, diasone

produced the most beneficial results. Diasone is also far less toxic than bis-(p-aminophenyl) sulphone when tested orally and intravenously on mice, rats and rabbits[136].

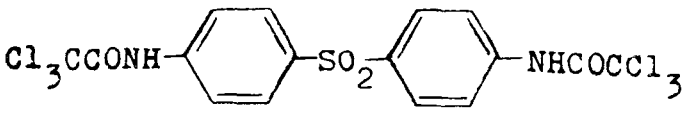
Sulphetrone [sodium tetrasulphonate of bis-(p-3-phenylpropylaminophenyl) sulphone], first prepared by Henry and Gray[137] proved to be comparable in activity to promin in the guinea pig[138] and remarkably free from chronic toxicity[139]. Applied to man it may have a use in certain forms of exudative tuberculosis of the lungs, but its final status is unknown[140-142]. It is synergic in action with streptomycin[143] and the combined therapy shows promise in miliary tuberculosis and tubercular meningitis[144]. Sulphetrone also appears to be a useful chemotherapeutic agent in the treatment of leprosy[145].

In promizole (p-aminophenyl 5-amino-2-thiazolyl sulphone) one of the phenyl groups in bis-(p-aminophenyl) sulphone has been replaced by a thiazolyl group with the amino group situated at the corresponding 5-position[146]. Feldman, Hinshaw and Mann[147] showed that this compound possessed tuberculo-therapeutic activity for a human strain of the tubercle in the guinea pig. A low degree of human toxicity was also noted for this compound[148]. But, like bis-(p-aminophenyl) sulphone, promin and diasone, promizole also does not meet all of the critical requirements for the perfect tuberculo-chemotherapeutic agent[149].

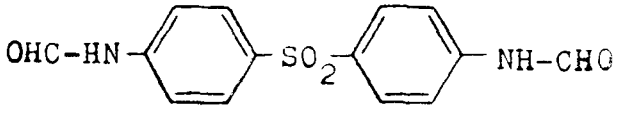
Apart from the above mentioned sulphones a host of other derivatives of bis-(p-aminophenyl) sulphone have been prepared and tested for their activity against tuberculosis. Most of the derivatives so prepared involved replacement of the hydrogen atom in one or both the amino groups by a suitable group. Some of the nuclear-substituted derivatives have also been prepared. It will be beyond the scope of this introduction to provide a complete review of the sulphones tested. But it will be of interest to know the effect of substitution in the amino groups and also of nuclear substitution on the activity of the compound. The relation between the chemical structure of sulphones and their bacteriostatic activity was studied by Youmans and Doub[150]. Fifty-nine sulphones were tested *in vitro* for their bacteriostatic activity for the virulent human type tubercle bacillus $H_{37}Rv$. The results indicated reduced bacteriostatic activity when one amino group is replaced by other substituents in various positions. Substitution of one or both the amino groups with a stable acyl group markedly reduced the activity. Symmetrical dialkylation destroyed activity completely in the single example tested. Nuclear substitution in one ring appeared to lower the activity. The heterocyclic analogs were less active *in vitro* than bis-(p-aminophenyl) sulphone but these generalisations are only restricted because of the limited nature of the study.

Buttle and his co-workers[151] prepared a number of Schiff's bases and acyl derivatives of bis-(p-aminophenyl) sulphone, as well as derivatives of 4-aminodiphenyl sulphone and certain sulphonamides. Of these compounds the glucoside and the diacetyl derivatives of bis-(p-aminophenyl) sulphone and 4-benzylideneaminodiphenyl sulphone were said to have certain advantages for clinical use. When tested in rabbits, the formyl, acetyl, propionyl and butyryl derivatives of bis-(p-aminophenyl) sulphone had bactericidal power not much different from the parent compound because of their hydrolysis in the body, to the parent compound[152]. The diacetyl derivative seems to possess lower toxicity. Bauer and Rosenthal[153] showed that it had a therapeutic index six times higher than sulphanilamide against streptococcal infections in mice, whereas the high toxicity of bis-(p-aminophenyl) sulphone makes its therapeutic index only twice that of sulphanilamide. The compound, $(H_2NC_6H_4SO_2NHC_6H_4)_2SO_2$, formed from bis-(p-aminophenyl) sulphone and sulphanilamide was found to have a high streptococcocidal power and low toxicity in the mouse[153]. It was also found that alkyl p-aminophenyl sulphones of the type $H_2NC_6H_4SO_2R$ increase successively in activity when R=CH_3, C_2H_5 and C_3H_7, then become less active with further lengthening of the chain[153]. The isopropyl and isobutyl compounds were less active than the normal derivatives.

Several unsymmetrical diacyl derivatives of bis-(p-aminophenyl) sulphone were prepared by Shonle and Van Arendonk[154] and their relative activities toward streptococcus and pneumococcus were determined. The therapeutic effectiveness of a number of monoacyl derivatives were also determined[155]. Bis-trichloroacetyl derivative (dichlorone) LVII) and bis-formamido derivative (formilone) (LVIII) were observed to have high tuberculostatic action[156].

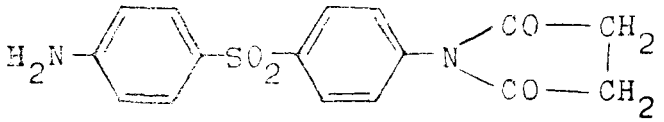


(LVII)

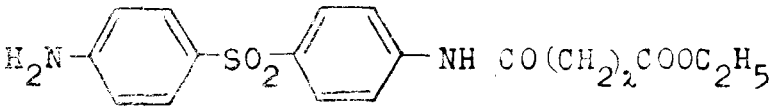


(LVIII)

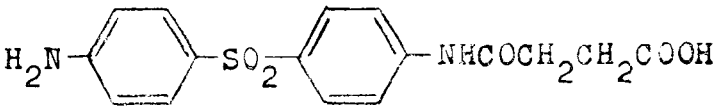
Of the several succinic acid derivatives tested[157] against experimental tuberculosis in guinea pigs, 4-amino-4′succinimidodiphenyl sulphone (LIX) was about as effective as promin but inferior to 4-amino-4′-n-propylaminodiphenyl sulphone. Compound (LX) was also equally effective. These compounds along



(LIX)



(LX)



(LXI)

with 4-amino-4′-*β*-carboxypropionylaminodiphenyl sulphone (LXI) and its amide were active when tested in experimental pneumococcus infection in mice.

Of the N-alkyl-substituted derivatives of bis-(p-aminophenyl) sulphone, mono-n-propyl and monoallyl derivatives were shown to have a measurable therapeutic effect on experimental tuberculosis[158]. 4, 4′-Bis-(methylaminophenyl) sulphone was effective *in vivo*, but not *in vitro*, possibly due to decomposition into the parent compound in the animal body[159].

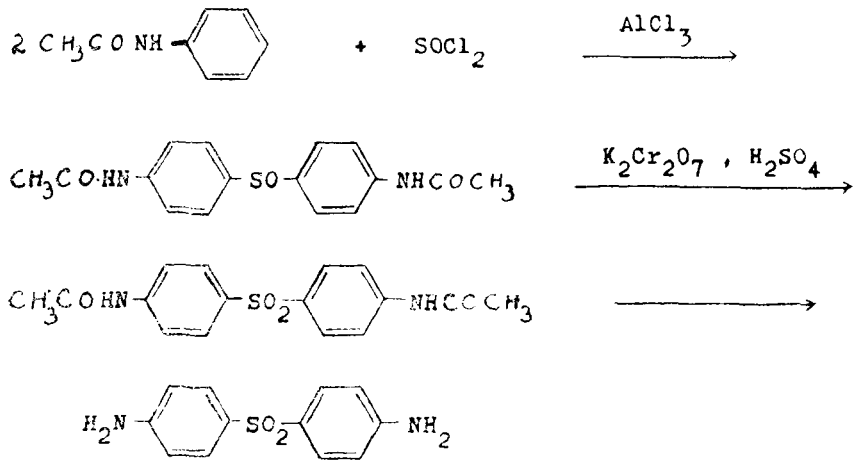
Several aromatic aldehydes have been condensed with bis-(p-aminophenyl) sulphone and some of the resulting anils showed activity. Sulphetrone was derived by the addition of sodium bisulphite to the dianil from cinnamaldehyde[137]. Of the other Schiff's bases, bis-(p-phenylpropylideneaminophenyl) sulphone[160] and N-p-dimethylaminobenzylidene derivative[161] were found to be of some value.

A few of the sugar derivatives were also prepared and tested. In addition to promin, N, N′-dilactoside (Erba sulphone), digalactoside (tibatin) and didextrose derivatives were used in the treatment of infantile tuberculosis[162].

The condensation product of bis-(p-aminophenyl) sulphone with L-ascorbic acid was shown to have high *in vivo* activity against tuberculosis when tested on animals and humans[163].

Comparatively only a limited number of nuclear-substituted derivatives of bis-(p-aminophenyl) sulphone have been tested for chemotherapeutic activity. Of the six possible isomers of bis-(aminophenyl) sulphone, only p, p'-isomer showed activity [164]. Bis-(p-aminoaryl) sulphones with substituents in the 2-position, namely, amino, chloro, sulphamyl, carbamyl and methyl groups were prepared by Baker and his co-workers[164]. Berg[165] synthesised some derivatives with halogen and hydroxy groups at the o-position to the sulphonyl group. The halogen derivatives were tested orally *in vivo* against Staph. aureus and Strep. pyogenes in mice. A decrease in toxicity in the order Cl< Br< I, together with corresponding decrease in activity was observed. Youmans and Doub[158] and Youmans, Feldman and Doub[159] reported that 2-chloro- and 2-hydroxy-bis-(p-aminophenyl) sulphones were less active than the parent compound for the virulent Mycobacterium tuberculosis, human type *in vitro* and that 2-chloro derivative was inactive *in vivo*. Chemotherapeutic studies were made on a number of new derivatives of bis-(p-aminophenyl) sulphone and some related unsymmetrical heterocyclic sulphones by Freedlander and French[161].

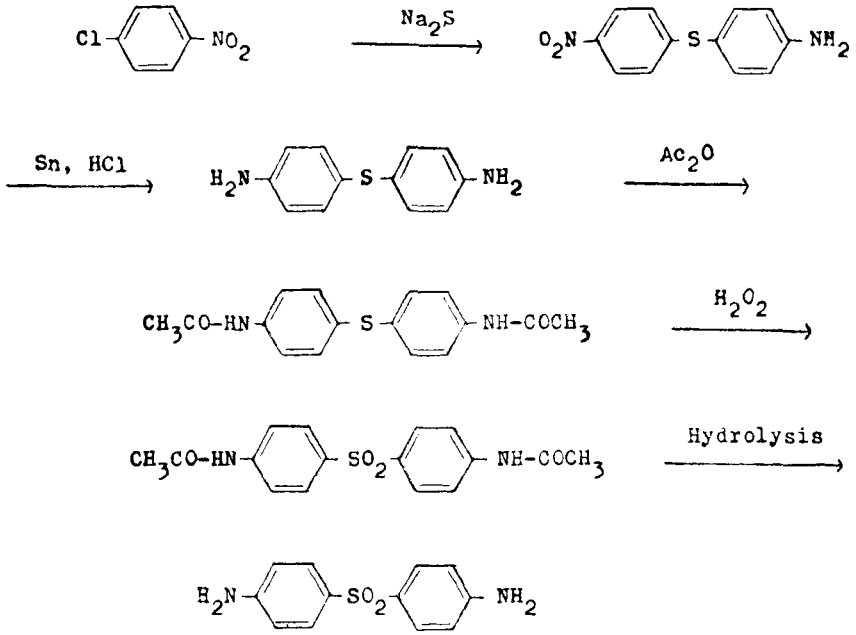
It seemed desirable to prepare more nuclear-substituted bis-(aminoaryl) sulphones and study their therapeutic potentialities. Sugasawa and Sakurai[166] prepared bis-(p-aminophenyl) sulphone by condensing acetanilide with thionyl chloride in presence of anhydrous aluminium chloride, oxidising the resulting bis(p-acetamidophenyl) sulphoxide to the sulphone and then removing the acetyl groups by hydrolysis. A similar reaction does not seem to have been studied with the three isomeric acettoluidides. Hence the present investigation was taken up to



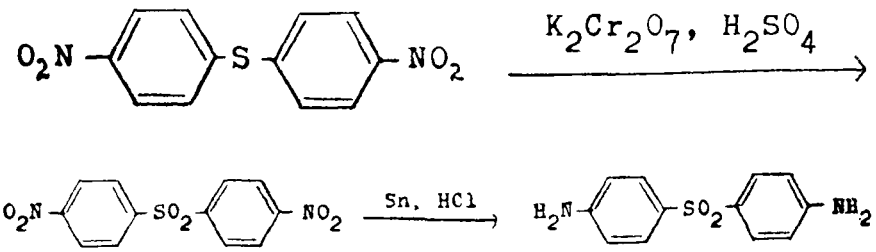
examine the possibilty of preparing new bis-(aminoaryl) sulphones by this method. If the reaction of acet-toluidides with thionyl chloride takes the expected course, it should be possible to get several bis-(aminoaryl) sulphones whose antituberculous and antileprous activities would be worth examining.

DISCUSSION

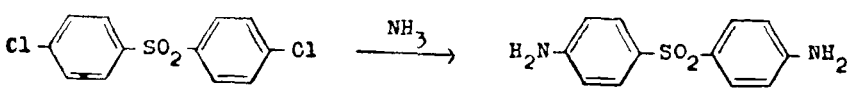
There are several methods of preparing bis-(p-aminophenyl) sulphone. In one method[167,168], bis-(p-acetamidophenyl) sulphide, obtained according to the scheme given below, is oxidised to bis-(p-acetamidophenyl) sulphone and the latter is then deacetylated.



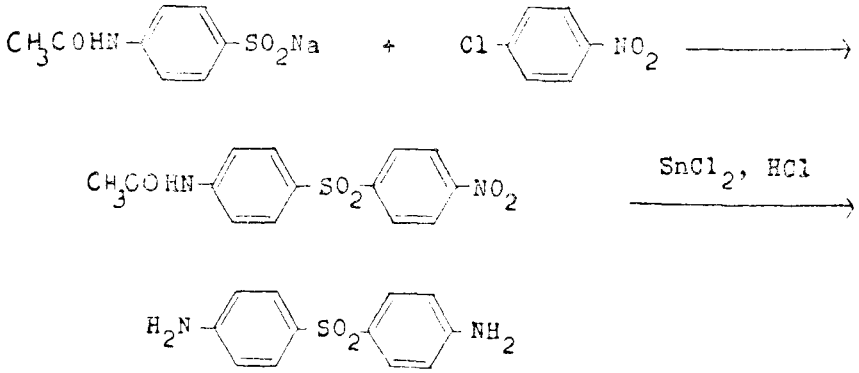
In another method[124] bis-(p-nitrophenyl) sulphide, obtained from p-chloronitrobenzene and sodium sulphide, is oxidised to the sulphone and then reduced.



Bis-(chlorophenyl) sulphones react with ammonia, primary or secondary aliphatic amines under high pressures and elevated temperatures[169].



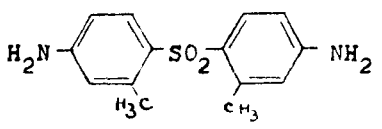
Reaction of sodium p-acetamidobenzenesulphinate with p-chloronitrobenzene and reduction of the resulting nitro sulphone also give the diamino sulphone[170,171].



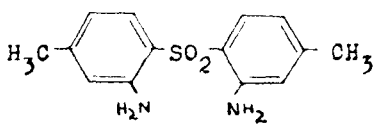
p-Acetamidobenzenesulphonyl chloride reacts with acetanilide in presence of aluminium chloride to give bis-(p-acetamidophenyl) sulphone[172].

The method of Sugasawa and Sakurai[166] has already been referred to (page 67). In the present investigation the possibility of preparing symmetrical aminoaryl sulphones from o-, m- and p-toluidines by the method of Sugasawa and Sakurai has been studied. The reaction of acet-o-toluidide with thionyl chloride in presence of aluminium chloride yielded a pasty mass from which no crystalline product could be obtained. But, both m- and p-toluidides gave crystlline sulphoxides in good yields. A higher yields was obtained with acet-m-toluidide. The sulphoxides could be oxidised to the corresponding sulphones using potassium permangante or hydrogen peroxide. The acetamido sulphones, on acid hydrolysis, yielded amino sulphones. The structures of the aminoaryl sulphones, obtained from acet-m-toluidide and acet-p-toluidide, were established as follows.

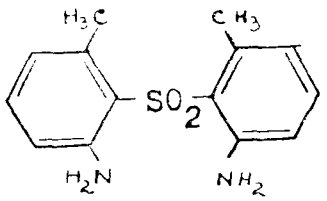
The analytical data of the acetamido sulphoxide, acetamido sulphone and amino sulphone obtained from acet-m-toluidide showed that two molecules of the toluidide had reacted with one molecule of thionyl chloride. Taking the directive influence of methyl and acetamido groups into consideration, the amino sulphone can have one of the following three structures:



(LXII)

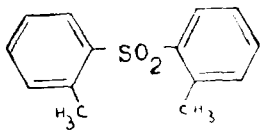


(LXIII)

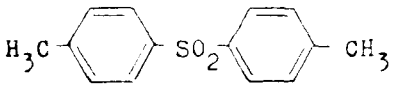


(LXIV)

When acet-m-toluidide reacts with thionyl chloride the formation of the sulphoxide link at the carbon atoms flanked by methyl and acetamido groups would be inhibited. Hence, structure (LXIV) does not deserve serious consideration. Structure (LXII) or (LXIII) may be regarded as more probable. On deamination, (LXII) should yield di-o-tolyl sulphone (LXV). If the compound has structure (LXIII), deamination should give di-p-tolyl sulphone (LXVI). The deamination of the sul-

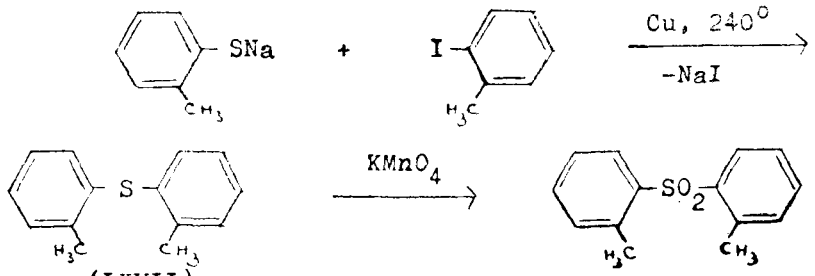


(LXV)



(LXVI)

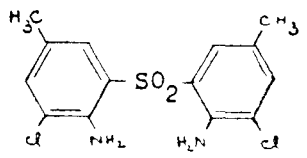
phone was effected with hypophosphorous acid, since ethanol did not give satisfactory results. The analytical data of the sulphone, thus obtained, corresponded with those calculated for a ditolyl sulphone. The compound melted at 103-104.5°. But this did not correspond with the reported melting point of either di-p-tolyl sulphone (158°) [173] or di-o-tolyl sulphone (134-135°)[174]. The di-o-tolyl sulphone reported by Purgotti[174] was obtained by the oxidation of a liquid boiling at 285° which he described as di-o-tolyl sulphide. He obtained this compound by the reaction of sodium sulphide with diazotised o-toluidine. But it was shown by Zeiser[175] and Mauthner[176] that di-o-tolyl sulphide was a solid melting at 64° and boiling at 174°/15 mm. Thus, Purgotti's sulphide and hence the sulphone are open to question. In order to establish the identity of di-o-tolyl sulphone beyond doubt, it was synthesised unequivocally in the present work. It was obtained by oxidising di-o-tolyl sulphide, prepared by the method of Mauthner.



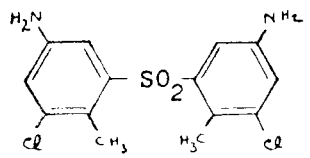
(LXVII)

The sulphide (LXVII), thus obtained, melted at 64-64.5° as reported by Zeiser[175] and Mauthner[176]. Oxidation with potassium permangante gave di-o-tolyl sulphone which melted at 104.5-105.5°. This establishes that the compound obtained by Purgotti was not di-o-tolyl sulphone. A mixed melting point of this compound with the sulphone obtained by deamination showed no depression. That the amino sulphone obtained from acet-m-toluidide has the structure (LXII) is thus proved beyond doubt.

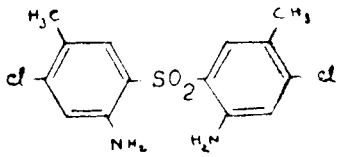
The sulphoxide obtained in the reaction of thionyl chloride with acet-p-toluidide was oxidised to the sulphone which, on hydrolysis, gave a diamino sulphone (A). All the three compounds, the sulphoxide, the diacetamido sulphone and the diamino sulphone contained chlorine. Their analytical data showed the presence of two chlorine atoms for each molecule. Hence chlorination must have also occurred during the Friedel-Crafts reaction. If the two chlorine atoms are symmetrically situated in the bis- (aminoaryl) sulphone, the compound should have one of the following six structures:



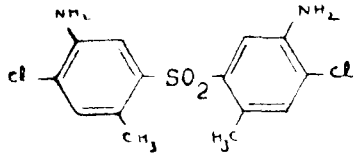
(LXVIII)



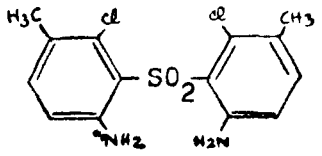
(LXIX)



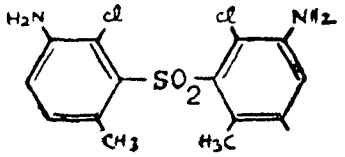
(LXX)



(LXXI)

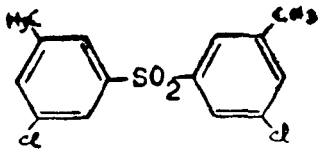


(LXXII)

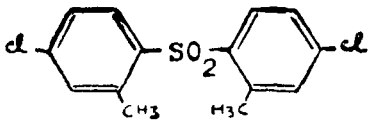


(LXXIII)

Considering the directive influence of the different groups and the steric factors involved, structure (LXVIII) or (LXXI) appeared to be probable. Deamination of the bis-(aminoaryl) sulphone gave a bis-(chlorotolyl) sulphone (B). The probable structure for this compound would then be either (LXXIV) or (LXXV).

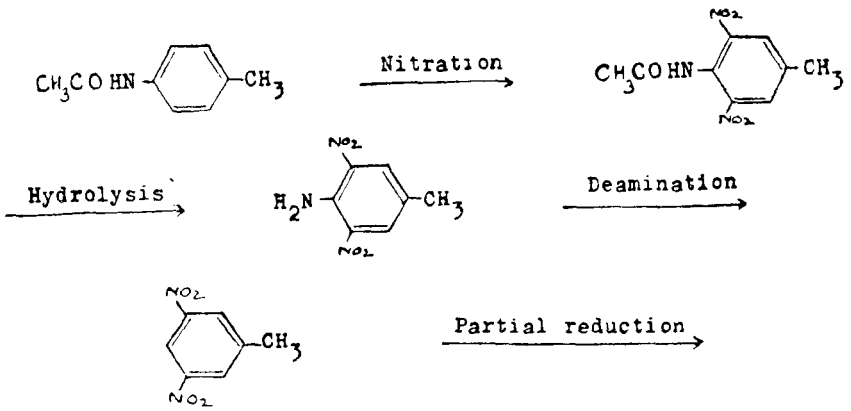


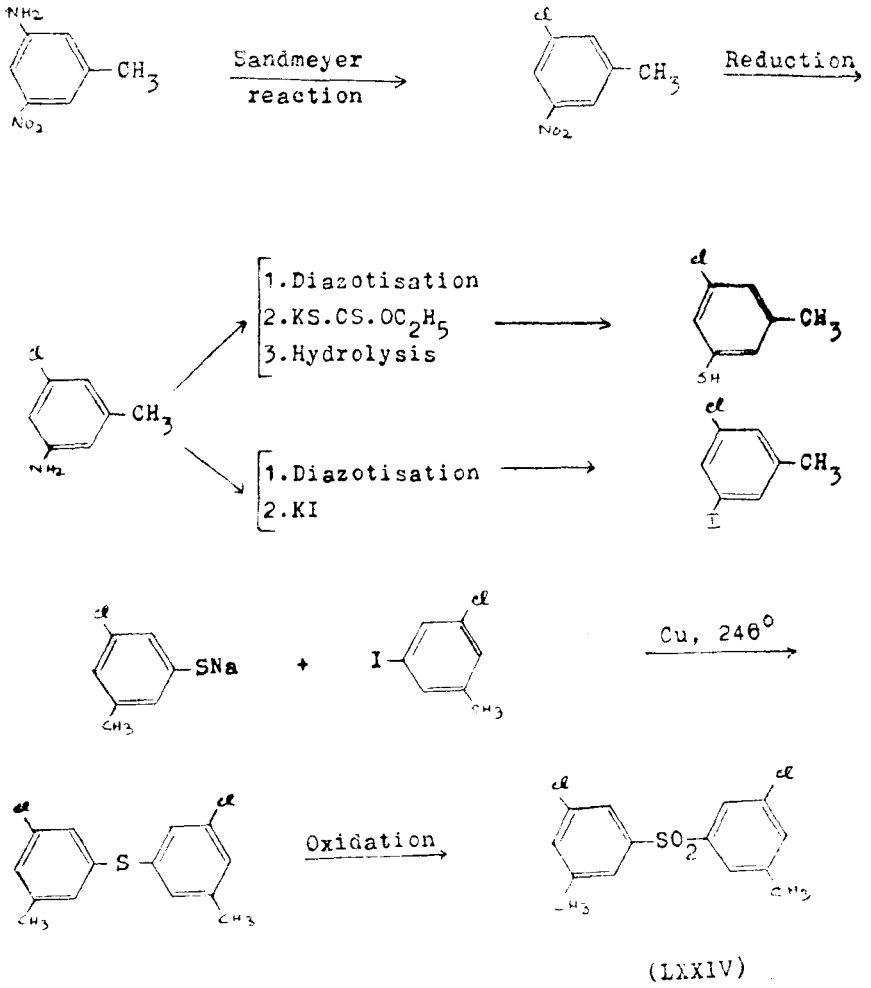
(LXXIV)



(LXXV)

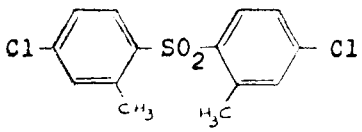
Bis-(3-chloro-5-methylphenyl) sulphone (LXXIV) was synthesised unequivocally according to the following scheme:



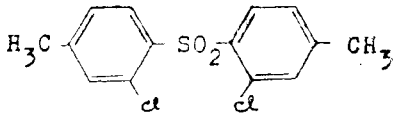


(LXXIV)

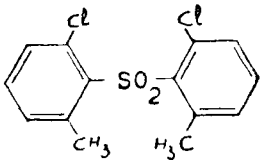
The sulphone (LXXIV), thus obtained, melted at 163.5-164.5° whereas, the bis-(chlorotolyl) sulphone (B) obtained by deamination melted at 134-135°. Since both these compounds were not indentical, bis-(4-chloro-2-methylphenyl) sulphone (LXXV) was sought to be obtained by the reaction of m-chlorotoluene with thionyl chloride in presence of aluminium chloride and oxidising the resulting sulphoxide. The Friedel-Crafts reaction of m-chlorotoluene and thionyl chloride gave a resinous product from which a sulphoxide could not be obtained in a crystalline form. But a sulphone was obtained in a pure form by the oxidation of the resinous product with potassium permangante. The sulphone, so obtained, melted at 131-132°. When admixed with sulphone (B) got by deamination, it melted at 132-134°. This proves that both the compounds are identical. The sulphone, obtained by the reaction of m-chlorotoluene with thionyl chloride and subsequent oxidation, can have one of the following three structures:



(LXXVI)



(LXXVII)



(LXXVIII)

Sulphonyl chlorides[173,177,178] and thionyl chloride[179], when used in the Friedel-Crafts reaction for condensation with aromatic compounds containing a halogen or a methyl group, are known to react only at the position para to the halogen atom or methyl group. Hence, the structure of the compound under consideration should be either (LXXVI) or (LXXVII). The sulphonyl group in (LXXVII) is para to methyl and, as such (LXXVII) could not be the structure for a sulphone obtained by the deamination of bis-(chloro-p-aminotolyl) sulphone (A) which has amino groups para to methyl groups. Hence the bis-(aminoaryl) sulphone obtained from acet-p-toluidide is bis-(5-amino-4-chloro-2-methylphenyl) sulphone (LXXI).

EXPERIMENTAL

Bis-(4-acetamido-2-methylphenyl) Sulphoxide.—To a solution of 14.9 g. (0.1 mole) of acet-m-toluidide in 150 cc. of carbon disulphide was added 26.6 g. (0.2 mole) of finely powdered aluminium chloride. The mixture was kept at 40-45° on a water bath, while a solution of 6.0 g. (0.05 mole) of thionyl chloride in 10 cc. of carbon disulphide was added dropwise with continuous stirring, during the course of 45 minutes. The reaction occurred with copious evolution of hydrogen chloride. After the addition was over, the stirring and refluxing was continued for 2 hours at the end of which period the temperature of the water bath was increased to 50° and the mixture was refluxed for 1 more hour. Finally, the reaction mixture was allowed to cool and the carbon disulphide layer was separated from the sulphoxide-aluminium chloride complex which had separated as a viscous insoluble liquid. The complex was decomposed by the addition of 300 cc. of ice water. The crystalline product that resulted was collected at the pump and washed with water. To remove the unreacted acet-m-toluidide the product was transferred into a beaker, agitated with 100 cc. of ether and then filtered washing first with ether and then with water. The yield was 14.0 g. (81%). The compound crystallised as colourless plates from acetone (50%) and melted at 142-148°. It was found to contain water of hydration. After drying at 110° in a drying pistol for 4 hours the anhydrous compound melted at 209-211°.

Anal. Calcd. for $C_{18}H_{20}O_3N_2S$: C, 62.8; H, 5.8. Found : C, 62.7; H, 6.05.

Bis-(4-acetamido-2-methylphenyl) Sulphone.- Nine grams (0.026 mole) of the above sulphoxide was dissolved in 90 cc. of glacial acetic acid and the solution was heated to boiling. To the boiling solution 5.4 g. of potassium permangante in 160 cc. of water was added little by little with stirring. After the addition was over the mixture was kept boiling for 1 hour and then allowed to cool. The precipitated manganese dioxide was dissolved by passing sulphur dioxide into the mixture. After dilution with water the sulphone that was obtained was collected at the filter and washed with water. The yield of the product melting at 238-240° (with darkening) was 7.0 g. (74%). Recrystallisation from glacial acetic acid gave fine needles melting at 243-244°.

Anal. Calcd. for $C_{18}H_{20}O_4N_2S$: C, 60.0; H, 5.6. Found : C, 59.8; H, 5.5.

Bis-(4-amino-2-methylphenyl) sulphone.— A mixture of 6.0 g. (0.017 mole) of the acetamido sulphone and 80 cc. of

hydrochloric acid (1:1) was heated under reflux until complete solution occurred (20 minutes). A little decolourising charcoal was added to the solution, again refluxed for 10 minutes and then filtered. The filtrate was made alkaline with aqueous ammonia. The amino sulphone that was thrown out was collected at the pump and washed with water. The yield was 4.2 g. (91%). Recrystallisation from ethanol gave pale yellow needles melting at 280° with decomposition.

Anal. Calcd. for $C_{14}H_{16}O_2N_2S$: C, 60.9; H, 5.8. Found : C, 60.6; H, 5.9.

Deamination of Bis-(4-amino-2-methylphenyl) Sulphone.— One gram of the amino sulphone was dissolved in a mixture of 3 cc. of hydrochloric acid and 3 cc. of water. Following the usual procedure the solution was tetrazotised with 0.52 g. of sodium nitrite dissolved in 2 cc. of water. To the tetrazotised solution kept at 0°, was gradually added with stirring 6 cc. of a 50% solution of hypophosphorous acid which was precooled to 0°. Evolution of nitrogen occurred during the addition. The mixture was stirred for 10 minutes and then left in the refrigerator overnight. The product that was obtained was extracted with 15 cc. of benzene. The benzene solution was washed twice with 5 cc. portions of a 5% solution of sodium hydroxide and then with water. Removal of the solvent from the solution yielded a red pasty mass which was extracted thrice with hot ethanol. The ethanolic extract (25 cc.) was boiled with decolourising charcoal and filtered. The filtrate was concentrated to one half. The resulting solution was gradually diluted with water until most of the coloured impurities were thrown out as a yellowish-red precipitate, which was filtered off. The filtrate was diluted to 50 cc. with water and left in the refrigerator for 24 hours. The crystals, which separated by then, were collected and recrystallised from dilute ethanol. The compound melted at 103-104.5°.

Anal. Calcd. for $C_{14}H_{14}O_2S$: C, 68.3; H, 5.7. Found : C, 68.0; H, 5.8.

Di-o-tolyl Sulphide.—To a solution of sodium ethoxide, obtained by dissolving 1.0 g. (0.0435 mole) of sodium in 15 cc. of absolute ethanol, 5.40 g. (0.0435 mole) of o-thiocresol was added. After removing the alcohol by distillation, the sodium salt of thiocresol was mixed with 0.2 g. of copper powder and 9.5 g. (0.0435 mole) of o-iodotoluene. The mixture was heated over an oil bath at 235-240° for 3 hours, cooled, treated with 20 cc. of ethanol and acidified with dilute sulphuric acid. After the addition of 2 g. of zinc dust, the mixture was steam distilled to remove unreacted o-thiocresol and o-iodotoluene. The residue

was extracted with ether, dried over calcium chloride and distilled. The liquid boiling at 170-175°/15 mm. was collected. The liquid slowly set to a solid (4.5 g., 48%) which was recrystallised from ethanol. Shining plates of di-o-tolyl sulphide melting at 64-64.5° were obtained.

Di-o-tolyl Sulphone.—In 100 cc. of glacial acetic acid 3.0 g. (0.014 mole) of di-o-tolyl sulphide was dissolved. With constant stirring, the sulphide was oxidised by the addition of a 5% solution of potassium permanganate until an excess of it has been added. Sulphur dioxide was passed through the mixture until the solution was clear. Dilution with water, filtering and washing the precipitate gave 3.2 g. (94%) of di-o-tolyl sulphone melting at 102-104°. After recrystallisation from methanol the compound melted at 104.5-105.5°.

Anal. Calcd. for $C_{14}H_{14}O_2S$: C, 68.3; H, 5.7. Found: C, 68.6; H, 5.6.

Bis-(5-acetamido-4-chloro-2-methylphenyl) Sulphoxide.—When acet-p-toluidide was condensed with thionyl chloride in presence of aluminium chloride, using the reactants in the same proportion as with acet-m-toluidide, the yield of the resulting sulphoxide was found to be very poor (5%). Better yield was, however, obtained when an excess of thionyl chloride was used in the reaction. The reaction was effected using a mixture of 74.5 g. (0.5 mole) of acet-p-toluidide, 59.5 g. (0. 5 mole) of thionyl chloride, 100 g. (0.75 mole) of aluminium chloride, and 500 cc. of carbon disulphide. The procedure followed was exactly similar to that in the preparation of bis-(4-acetamido-2-methylphenyl) sulphoxide. The yield was 45 g. (44%, calculated on the amount of acet-p-toluidide used). The crystals obtained, after recrystallisation from glacial acetic acid, melted at 208.5-210°.

Anal. Calcd. for $C_{18}H_{18}O_3N_2Cl_2S$: C, 52.3; H, 4.4. Found: C, 52.5; H, 4.4.

Bis-(5-acetamido-4-chloro -2- methylphenyl) Sulphone.—Ten grams (0.024 mole) of the above sulphoxide were dissolved in 150 cc. of hot glacial acetic acid and the solution was mixed with 6 cc. of hydrogen peroxide (30%). The mixture was left to stand overnight and then heated on a steam bath for 1 hour. The solution was finally poured into water and the precipitated sulphone was collected at the filter and washed with water. After two crystallisations from glacial acetic acid it was obtained in 60% yield (6.2 g.) It gave colourless needles melting at 278-280°.

Anal. Calcd. for $C_{18}H_{18}O_4N_2Cl_2S$: C, 50.4; H, 4.2. Found: C, 50.5; H, 4.3.

Bis-(5-amino-4-chloro-2-methylphenyl) Sulphone.—Six grams (0.014 mole) of the acetamido sulphone was hydrolysed with a mixture of 30 cc. of concentrated sulphuric acid and 60 cc. of water, refluxing for a period of 45 minutes. The yield of the amino sulphone was 4.6 g. (96%). Recrystallisation from ethanol gave pale yellow needles, melting at 181-182°.

Anal. Calcd. for $C_{14}H_{14}O_2N_2Cl_2S$: C, 48.7; H, 4.1. Found: C, 48.6; H, 4.0.

Deamination of Bis-(5-amino-4-chloro-2-methylphenyl) Sulphone.—The procedure followed was exactly the same as for the deamination of bis-(4-amino-2-methylphenyl) sulphone. The crystals got after recrystallisation from ethanol melted at 134-135°.

Anal. Calcd. for $C_{14}H_{12}O_2Cl_2S$: C, 53.3; H, 3.8. Found: C, 53.4; H, 3.6.

Bis-(4-chloro-2-methylphenyl) Sulphone.—A mixture of 5.0 g. (0.04 mole) of m-chlorotoluene and 10.0 g. (0.08 mole) of well powdered aluminium chloride in 50 cc. of carbon disulphide was heated to reflux on a water bath. To the mixture 4.8 g. (0.04 mole) of thionyl chloride was added in small quantities. After refluxing for 1 hour, the evolution of hydrogen chloride practically stopped. From the reaction mixture carbon disulphide was removed by distillation and the residue was mixed with crushed ice. The resulting resinous product could not be converted to a crystalline from. It was dissolved in 100 cc. of glacial acetic acid and the solution was heated to boiling. To the boiling solution an excess of a 5% solution of potassium permanganate was added in small quantities with constant stirring. After dissolving away the manganese dioxide formed by passing sulphur dioxide, the sulphone was precipitated with water. The compound, after three recrystallisations from ethanol, weighed 2.3 g. (37%); m.p. 131-132°.

Its mixed melting point with the sulphone obtained by deamination was 132-134°.

Anal. Calcd. for $C_{14}H_{12}O_2Cl_2S$: C, 53.3; H, 3.8. Found: C, 53.3; H, 3.6.

2,6-*Dinitro-acet-p-toluidide.*—It was obtained by the nitration of acet-p-toluidide, adopting the procedure of Staedel[180]. The compound melted at 189-191°, after crystallisation from ethanol.

3,5-*Dinitrotoluene.*—Following the procedure of Cohen and McCandlish[181], 2,6-dinitro-acet-p-toluidide was hydrolysed to the

amine which was then deaminated by diazotising and heating with absolute ethanol. The compound formed light yellow needles from ethanol; m.p. 92-93°.

3-*Amino*-5-*nitrotoluene*.—It was obtained by Staedel's[180] method by reducing 3,5-dinitrotoluene with ammonium hydrosulphide.

3-*Amino*-5-*chlorotoluene*.—By the Sandmeyer reaction, 3-amino-5-nitrotoluene was converted to 3-chloro-5-nitrotoluene. Reduction of the nitro compound by the method of Hönig[182] gave 3-amino-5-chlorotoluene as an oil. The hydrochloride of the amine melted at 253-256° with decomposition.

3-*Chloro*-5-*iodotoluene*.—The procedure followed for the preparation of this compound was essentially that of McAlister and Kenner[183].

3-*Chloro*-5-*mercaptotoluene*.—Nine grams (0.063 mole) of 3-amino-5-chlorotoluene was diazotised by the customary procedure, using 40 cc. of hydrochloric acid (50%) and 6 g. of sodium nitrite. The diazonium salt solution was added dropwise with continuous stirring to a solution of potassium ethyl xanthate (12.0 g. in 15 cc. of water), kept at 40-45°. After the addition was over, the mixture was heated at the same temperature for 1 more hour and the resulting red oil was extracted with ether and dried over calcium chloride. After removing the ether, the oil was dissolved in 60 cc. of ethanol and brought to refluxing on a water bath. Twenty grams of potassium hydroxide pellets were added in small quantities through the condenser and refluxed for 8 hours. At the end, about 50 cc. of ethanol was removed by distillation and the residue was dissolved in minimum amount of water. The mixture was acidified with sulphuric acid (1:1), mixed with 5 g. of zinc dust and steam-distilled. The thiophenol distilled over, after extraction with ether and drying over anhydrous magnesium sulphate, weighed 5.7 g. (57%). On distillation, it boiled at 94-95°/8 mm.; $n^{27}D$ 1.5875.

Anal. Calcd. for C_7H_7ClS: C, 53.0; H, 4.4. Found: C, 52.8; H, 4.6.

Benzoyl derivative.—The compound, obtained by the usual method, melted at 77.5-78.5° (from methanol).

Anal. Calcd. for $C_{14}H_{11}OClS$: C, 64.0; H, 4.2. Found: C, 64.4; H, 4.5.

Bis-(3-*chloro*-5-*methylphenyl*) *Sulphide*.—In 15 cc. of absolute ethanol 0.6 g. (0.026 mole) of sodium was dissolved and the solution was mixed with 3.76 g. (0.024 mole) of 3-chloro-5-

mercaptotoluene. After removing the ethanol by distillation, the residue was mixed with 6.0 g. (0.024 mole) of 3-chloro-5-iodotoluene and 0.2 g. of copper powder, heated on an oil bath at 240-245° for 3.5 hours and cooled. Twenty cc. of ethanol and 1 g. of zinc dust were added to the mixture, acidified with dilute sulphuric acid and distilled with steam. The residue, after extraction with ether and drying over calcium chloride, yielded 4.0 g. (59%) of the sulphide, m.p. 34-35° (from ethanol).

Anal. Calcd. for $C_{14}H_{12}Cl_2S$: C, 59.4; H, 4.2. Found: C, 59.4; H, 4.1.

Bis-(3-chloro-5-methylphenyl) Sulphone.—The above sulphide was oxidised in glacial acetic acid with potassium permanganate (5%). The yield was 97%. Recrystallisation from ethanol gave shining plates, m.p. 163.5-164.5°.

Anal. Calcd. for $C_{14}H_{12}O_2Cl_2S$: C, 53.3; H, 3.8. Found: C, 53.4; H, 3.9.