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SYNTHESIS OF β-AMINO, αβ-UNSATURATED AND BIS-(AMINOARYL) SULPHONES

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THESIS SUBMITTED FOR THE DEGREE OF
DOCTOR OF PHILOSOPHY

ANNAMALAI UNIVERSITY

☆

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March 1954

C O N T E N T S

PART I

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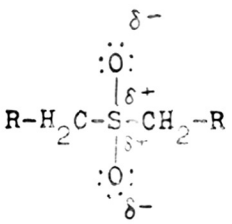
PART I

MANNICH AND KNOEVENAGEL REACTIONS INVOLVING THE ACTIVATING INFLUENCE OF SULPHONYL GROUP

INTRODUCTION

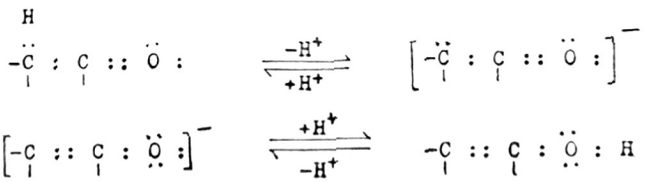
A consideration of the structure of ketones and sulphones will show that both these groups bear similarity in their structure. The electron distribution is such that the hydrogen atom attached to the α-carbon atom is activated, that is, the bond between this hydrogen and the carbon atom is loosened. In a sulphonyl group there is a fractional negative charge on the oxygen and a corresponding positive charge on the sulphur; in other words, sulphur becomes the positive end of the dipole as expressed in (1). Consequently the sulphur exerts an electromeric withdrawal of electrons from the adjacent carbon atom



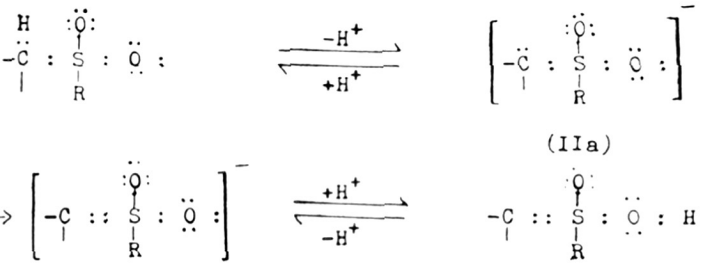
(I)

and thus facilitates the removal of a proton from that carbon atom.

In a keto group the oxygen has not only a strong electron attraction but also provides a suitable seat for the charge of the anion.



Similar structures can be given for a sulphone and it can be said that in addition to the inductive effect of the sulphonyl group



(IIb)

there is a mesomeric effect arising from resonance between the structures (IIa) and (IIb).

One of the above formulas (IIa) of the anions has an unshared electron pair on the carbon atom and the other (IIb) requires that sulphur expand its valency shell to accommodate ten electrons. There has been no general agreement regarding the expansion of the valency shell of the sulphur atom in the sulphonyl group. A number of investigators concluded on the basis of chemical evidence that the expansion of the valency shell of sulphur is quite probable[1-5]. The assumption of an expanded valency shell is rejected on the grounds that it violates the classical octet rule. But it is entirely possible that under certain conditions the sulphur atom can exceed a covalency of four[6-8]. In support of this view there is the indisputable case of sulphur hexafluoride where sulphur has a covalency of six. Those[9-12] who object to this view of expanded valency shell of sulphur attribute the activating influence of the sulphonyl group solely to the inductive effect. There is much physical evidence in support of the expanded valency of sulphur in sulphones. X-ray[13] and electron diffraction studies[14], dipole moment measurements[15] and thermochemical data[15] indicated that the sulphur-oxygen link in sulphones possesses considerable double bond character. In addition to these, ultraviolet absorption spectra of aryl sulphones[16-19] and benzenesulphonamides[20] and dipole moments of aryl sulphones[21] and sulphonamides[22] gave further evidence for the conjugative interaction of the sulphonyl group with an attached benzene ring. Determination of Hammett's substitution constant for methylsulphonyl group[23] and comparison of the sulphonyl group with the cyano group[24] also indicated the possible expansion of the valency shell of sulphur atom in the sulphonyl group.

The activating influence of the sulphonyl group has been discussed at length in the excellent book of Suter[25]. In simple sulphones the α-hydrogen atoms are not sufficiently activated to form sodium salts. But β-disulphones[9, 26] react with aqueous alkali to form sodium salts. Shriner and his co-workers[9] compared the activities of phenyl benzyl sulphone, dibenzyl sulphone and bis-(phenylsulphonyl)-methane. Sodium liberated hydrogen from all these sulphones in benzene solution. The sulphones in ethanolic solution gave no colour change with ferric chloride. Bis-(phenylsulphonyl)-methane readily dissolved in sodium and potassium hydroxide solutions. But phenyl benzyl sulphone was only partially soluble in alkali and dibenzyl sulphone was completely insoluble. Bis-(phenylsulphonyl)-methane was easily alkylated using methyl iodide and sodium ethoxide. Both the mono- and di-substituted products were got. Phenyl benzyl sulphone and dibenzyl sulphone failed to undergo alkylation. The pronounced activity of the disulphone is due to the presence of two sulphonyl groups one on either side of the methylene group. Penyl benzyl sulphone is less reactive because there is only one sulphonyl group. The dibenzyl sulphone is the least

reactive of the three, because the activating influence of the sulphonyl group is distributed btween two methylene groups.

In addition to bis- (phenylsulphonyl)-methane a number of other disulphones were methylated. Table 1 lists the sulphones that were methylated.

TABLE 1

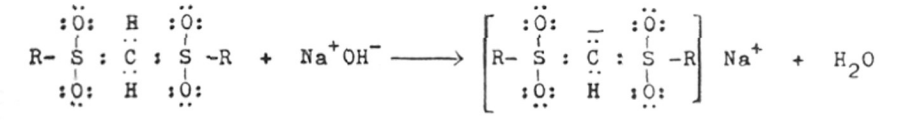
No	
1.	Bis-(ethylsulphonyl)- methane[27]
2.	Bis-(n-butylsulphonyl)-methane[26]
3.	Benzylsulphonylphenylsulphonylmethane[28]
4.	Bis-(benzylsulphonyl)-methane[29]
5.	α,α-Bis-(ethylsulphonyl)-ethane[27, 30]
6.	Bis-(ethylsulphonyl)-phenylmethane[27]
7.	α-Ethylsulphonyl- α-phenylsulphonylethane[28]

The last mentioned compound in the table[28] and α,α-bis-(ethylsulphonyl)-ethane[27, 30] were ethylated with ethyl iodide. p-Ethoxycarbonylphenylsulphonyl-p-tolylsulphonylmethane (III) was benzylated[31].

$$\underset{\text{(III)}}{p\text{-}H_5C_2OOCC_6H_4SO_2CH_2SO_2C_6H_4CH_3\text{-}p} + C_6H_5CH_2I + NaOC_2H_5 \longrightarrow$$

$$p\text{-}H_5C_2OOCC_6H_4SO_2\underset{\displaystyle CH_2C_6H_5}{\underset{|}{C}}HSO_2C_6H_4CH_3\text{-}p + NaI + C_2H_5OH$$

The high activity of the β-disulphones has been the cause for considerable discussion. Shriner and his co-workers[9] and *Arndt and Martius*[10] *concluded that when a β-disulphone was* converted to its sodium salt the methylene carbon atom carried the negative charge as expressed below:



These authors ruled out the possibility of the enol form because sulphur has to accommodate ten electrons in the valency shell which, according to them, is highly improbable. But definite chemical evidence has been put forward to show that this is not the case. If enolisation is not possible it should be possible to prepare an optically active β-disulphone. Since racemisation proceeds through enolisation, such a compound cannot racemise so easily as when enolisation is possible. But so far, attempts to resolve such a β-disulphone have met with failure.

Kipping[31] failed to resolve by the usual methods the acid (IV) or similar disulphones. It was possible to resolve the sulphide-sulphone (V), but oxidation of either form gave only the inactive disulphone.

$$p\text{-}CH_3C_6H_4SO_2CH(CH_2C_6H_5)SO_2C_6H_4COOH\text{-}p$$

(IV)

$$p\text{-}CH_3C_6H_4SCH(CH_3)SO_2C_6H_4COOH\text{-}p$$

(V)

$$p\text{-}CH_3C_6H_4SO_2C(CH_3)(SC_6H_5)SO_2C_6H_4COOH\text{-}p$$

(VI)

If both the hydrogen atoms of the methylene group between the two sulphonyl groups are substituted, then the enolisation of the compound will be impossible. It should be possible to resolve such a compound. It has been proved to be so in the case of compound (VI)[32].

This is a strong case in favour of enolisation of disulphones with expansion of the valency shell of sulphur to accommodate ten electrons. Their immediate racemisation and solubility in alkali can be explained satisfactorily only in this way. The anion of the β-disulphone can therefore be given the following structures in their resonance state:

The trisulphones of the general formula $(R\text{-}SO_2)_3CH$ are much more acidic than the disulphones, as it is to be expected. They liberate carbon dioxide from carbonate in the cold and are not precipitated from aqueous solutions of their salts by acetic acid. Attempts to resolve trisulphones of the type

$$RSO_2CH(SO_2R')SO_2R''$$

proved unsuccessful[33]. These results follow naturally from what has been said of the disulphones.

The ability of a sulphonyl group to activate the adjacent methyl or methylene groups was also studied by some investigators. Kohler and Potter reported[1] that methyl p-tolyl sulphone

condensed with benzaldehyde in presence of alkali to give a low yield of α-phenyl-β-p-tolylsulphonylethylene (VII) along with other products.

$$p\text{-}CH_3C_6H_4SO_2CH_3 + C_6H_5CHO \longrightarrow p\text{-}CH_3C_6H_4SO_2CH{=}CHC_6H_5 \quad (VII)$$

The experimental details of the reaction were not reported by the authors and the nature of the other products formed was also not mentioned. The mercuric chloride test for enolic substances was not answered by p-toyl benzyl sulphone, whereas bis-(phenylsulphonyl)-methane gave a positive test[3]. p-Tolyl benzyl sulphone failed to condense with benzaldehyde or isoamyl nitrite and was not oxidised by selenium dioxide. But this compound underwent Michael condensation with benzalacetophenone to give two stereoisomeric products[3]. In this reaction the sulphone reacted like the corresponding ketone, desoxybenzoin[34]. The

$$p\text{-}CH_3C_6H_4SO_2CH_2C_6H_5 + C_6H_5CH{=}CHCOC_6H_5 \longrightarrow$$

$$p\text{-}CH_3C_6H_4SO_2CH(C_6H_5)CH(C_6H_5)CH_2COC_6H_5$$

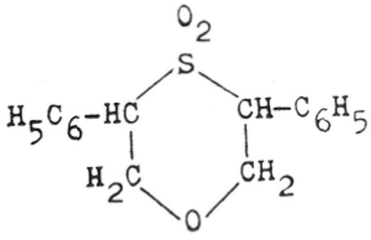
analogy between the reactions of ketones and sulphones in the Michael condensation has been extended still further. Both dibenzoylmethane[35] and bis-(phenylsulphonyl)-methane do not condense with benzalacetophenone. Similarly both p-tolyl benzyl sulphone and desoxybenzoin fail to react with methyl cinnamate. But methyl p-tolyl sulphone fails to react with benzalacetophenone whereas acetophenone condenses[36].

Another interesting reaction observed was that of benzyl sulphone with formaldehyde in presence of 10% sodium hydroxide solution[37]. An inert compound of unknown structure was isolated in this reaction. The product did not react with

$$(C_6H_5CH_2)_2SO_2 + 2\ HCHO \longrightarrow C_{16}H_{16}SO_3 + H_2O$$

an acyl halide. It was stable towards boiling hydrochloric acid-acetic acid mixture and potassium permanganate. It was

not affected by boling with nitric acid or fusion with alkali. Structure (VIIa) was suggested for this compound. Similar



(VIIa)

compounds were also obtained with benzyl p-tolyl sulphone and benzyl phenyl sulphone[38].

The condensation of some β-disulphones with formaldehyde in presence of a secondary amine as piperidine or diethylamine, is also interesting[39]. The reaction is expressed by the following equation:

$$2\ (RSO_2)_2CH_2 + CH_2O \longrightarrow (RSO_2)_2CHCH_2CH(SO_2R)_2$$

The following β-disulphones were condensed with formaldehyde:

Bis-(ethylsulphonyl)-methane

Bis-(n-propylsulphonyl)-methane

Bis-(isopropylsulphonyl)-methane

Trimethylenedisulphonylmethane

The introduction of a nitro group into the benzyl part of benzyl p-tolyl sulphone enhances the activity of the methylene hydrogen atoms[40]. With sodium ethoxide in ethanolic solution o- and p-nitrobenzyl p-tolyl sulphones gave coloured salts. Although these salts failed to react with an alkyl halide, they were readily brominated as shown below:

$$p\text{-}CH_3C_6H_4SO_2CH(Na)C_6H_4NO_2\text{-}o,\ or\ \text{-}p + Br_2$$
$$\longrightarrow p\text{-}CH_3C_6H_4SO_2CH(Br)C_6H_4NO_2\text{-}o,\ or\ \text{-}p$$

The iodo compound of p-nitrobenzyl p-tolyl sulphone was also prepared similarly. The m-nitro compound failed to react under these conditions. The acidity of 2, 4-dinitrobenzyl p-tolyl sulphone was even more pronounced than the other benzyl sulphones. Its potassium salt was isolated as a purple coloured cystalline

salt. It was also easily brominated. In addition, alkylation with methyl iodide readily occurred to give α-2, 4-dinitrophenyl-α-p-tolylsulphonylethane (VIII). Further, the reaction of this

$$2,4\text{-}(O_2N)_2C_6H_3CH(K)SO_2C_6H_4CH_3\text{-}p + CH_3I \longrightarrow 2,4\text{-}(O_2N)_2C_6H_3CH(CH_3)SO_2C_6H_4CH_3\text{-}p$$

(VIII)

compound with iodine gave α,β-di-(2, 4-dinitrophenyl-p-tolylsulphonyl)-ethane (IX).

$$2\left[2,4\text{-}(O_2N)_2C_6H_3CH(K)SO_2C_6H_4CH_3\text{-}p\right] + I_2 \longrightarrow \begin{matrix} 2,4\text{-}(O_2N)_2C_6H_3CHSO_2C_6H_4CH_3\text{-}p \\ | \\ 2,4\text{-}(O_2N)_2C_6H_3CHSO_2C_6H_4CH_3\text{-}p \end{matrix}$$

(IX)

Attempts to condense all these nitrobenzyl sulphones with benzaldehyde met with failure[40]. The claim[41] that methylation of benzyl p-nitrophenyl sulphone gave a dimethyl derivative, has been questioned by later workers[40, 42].

The reaction of sulphones with Grignard reagents is an additional example to show that hydrogen atoms in the α-position to the sulphonyl group are activated. The resulting halomagnesium derivatives closely resemble the corresponding keto compounds in their reactions. Methyl p-tolyl sulphone reacts with ethylmagnesium bromide forming a halomagnesium derivative of the sulphone and ethane. The halomagnesium derivative was benzoylated to give dibenzoylmethyl p-tolyl sulphone[1]. The

$$p\text{-}CH_3C_6H_4SO_2CH_3 + C_2H_5MgBr \longrightarrow p\text{-}CH_3C_6H_4SO_2CH_2MgBr + C_2H_6$$

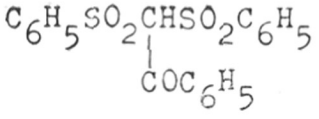
derivative on hydrolysis gave back methyl p-tolyl sulphone[43]. Reaction with bromine gave p-tolylsulphonylbromomethane[43]. *Phenylsulphonylmethylmagnesium bromide was found to react* with benzaldehyde to give β-hydroxy-β-phenylethyl phenyl sulphone (X) in 90% yield[44]. Similarly, p-tolylsulphonylmethyl-

$$C_6H_5SO_2CH_3 \xrightarrow[C_6H_5CHO]{C_2H_5MgBr} C_6H_5SO_2CH_2CH(OH)C_6H_5 \quad (X)$$

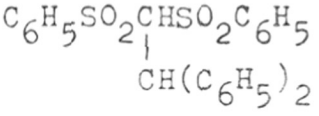
magnesium bromide[45] reacts with acetaldehyde and diisopropyl ketone to give the corresponding hydroxy compounds. Both

α-p-tolylsulphonylethylmagnesium bromide and α-p-tolylsulphonylisopropylmagnesium bromide add normally to benzaldehyde and acetone giving good yields of the products. Diethyl sulphone forms both a mono- and bis-Grignard derivative which add to benzaldehyde and acetone respectively, but the yields are relatively low. Methyl phenyl sulphone reacts with n-butyllithium and carbon dioxide to give phenylsulphonylacetic acid[46]. Ethyl phenyl sulphone, diphenyl sulphone and dibenzothiophene-5-dioxide also react in the same way. In these cases acidic substances were isolated but not in a pure condition to be able to identify them.

The halogen derivatives of β-disulphones behave like β-diketones in their reaction with Grignard reagents[47]. Bis-(phenylsulphonyl)-dibromomethane reacts with one equivalent of ethylmagnesium bromide to give a magnesium derivative of the monobromo compound. With two equivalents of ethylmagnesium bromide, the product isolated was a dimagnesium derivative. Both the mono- and di-magnesium derivatives react with benzoyl chloride and diphenylmethyl bromide giving compounds (XI) and (XII) respectively. Both the magnesium halide groups could not be replaced; only one could be replaced.

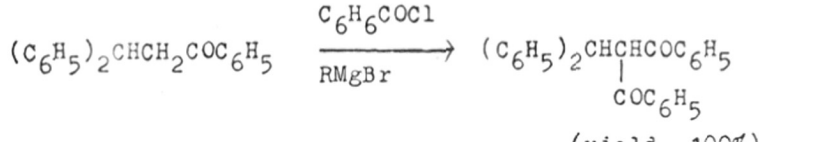


(XI)

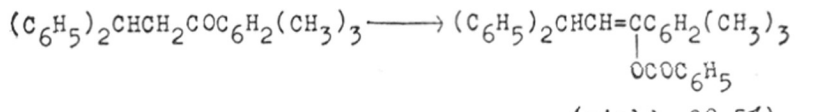


(XII)

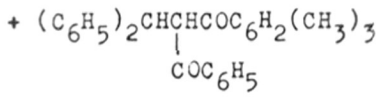
Kohler and his co-workers noted[48] a conspicuous difference in the reactions of magnesium derivatives of phenyl and mesitylenic ketones with benzyl chloride. The phenyl ketones were



(yield, 100%)



(yield, 98.5%)



(yield, 1.5%)

converted to diketones while the mesitylenic ketones were mostly converted to benzoates. This difference in behaviour of phenyl

and mesitylenic ketones can also be observed in diketones of similar type[40]. Hence it may be concluded that mesitylenic ketones have a tendency to enolise and form acyl and alkyl

$$(C_6H_5CO)_2CHMgX + C_6H_5COCl \longrightarrow (C_6H_5CO)_3CH \text{ (yield, 80.5\%)}$$

$$\left[(CH_3)_3C_6H_2CO\right]_2CHMgX + C_6H_5COCl \longrightarrow$$

$$(CH_3)_3C_6H_2C(OCOC_6H_5)=CHCOC_6H_2(CH_3)_3 \quad \text{(yield, 96\%)}$$

derivatives of the enolic modification. Arndt and Martius[10] claim that sulphonyl groups cannot promote enolisation of a carbonyl group in the β-position because they cannot serve as partners in conjugation. But contrary to this view, p-tolylsulphonylacetomesitylene reacts with alkylmagnesium halide and benzoyl chloride in a way similar to the compound[49],

$$\left[(CH_3)_3C_6H_2CO\right]_2CH_2.$$

The benzoate was formed in larger yields (64%) than the diketone (yield, 16%). Similar to the behaviour of dibenzoylmethane, benzoyl-p-tolylsulphonylmethane gave exclusively the diketone in 81% yield.

$$\left[p\text{-}CH_3C_6H_4SO_2\text{-}CH\text{-}(CH_3)_3C_6H_2CO\right]MgX \xrightarrow{C_6H_5COCl} p\text{-}CH_3C_6H_4SO_2CH=C(OCOC_6H_5)C_6H_2(CH_3)_3$$

$$+ p\text{-}CH_3C_6H_4SO_2CH(COC_6H_5)COC_6H_2(CH_3)_3$$

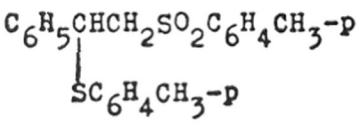
$$\left[p\text{-}CH_3C_6H_4SO_2\text{-}CH\text{-}C_6H_5CO\right]MgX \longrightarrow p\text{-}CH_3C_6H_4SO_2CH(COC_6H_5)_2$$

The behaviour of bis-(phenylsulphonyl)-methane was also analogous to the corresponding diketone. The C-benzoyl compound was the only product.

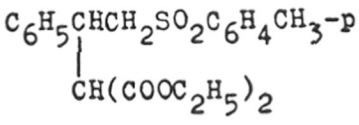
$$(C_6H_5SO_2)_2CHMgX \longrightarrow (C_6H_5SO_2)_2CHCOC_6H_5$$

The addition reactions of some unsaturated sulphones are also similar to those of the corresponding ketones. Kohler and

Potter[1] prepared α-phenyl-β-p-tolylsulphonylethylene in two stereoisomeric forms by the oxidation of the corresponding sulphides. Both forms behave like the α, β-unsaturated ketones in addition reactions. They combine with hydrogen, reduce potassium permangante, are oxidised by ozone, and form a stable dibromide with bromine. Conspicuously, they also add on readily p-thiocresol and malonic esters which are considered as typical reagents for 1, 4-addition to the conjugated system, C=C-C=O. The products (XIII) and (XIV) of these additions are similar to the compounds obtained from α, β-unsaturated ketones.

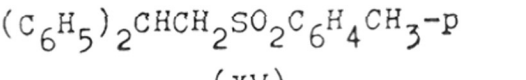


(XIII)



(XIV)

The similarity between ketones and sulphones is manifest in the addition of phenylmagnesium bromide to the unsaturated sulphone and the reactions of the resulting magnesium derivative. A yellow product was formed as the first stage of the addition, just as with an unsaturated ketone. It was changed to a colourless final product, which upon hydrolysis, gave a saturated sulphone (XV). The reaction of the magnesium derivative



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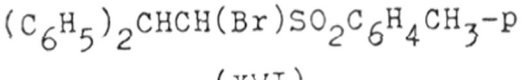
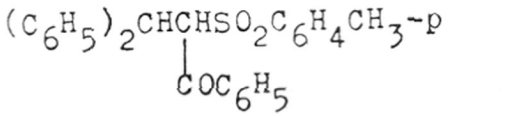
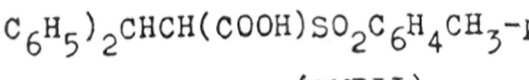


(XVI)



(XVII)



(XVIII)

with bromine gave an α-bromo sulphone (XVI), with benzoyl chloride a keto sulphone (XVII) and with carbon dioxide a carboxylic acid (XVIII).

The α, β-unsaturated keto sulphones also behave like unsaturated diketones. Kohler and Larsen[2] prepared α-benzoyl-β-phenylsulphonylethylene (XIX) and studied its reactions. The compound showed close analogy to α, β-dibenzoylethylene (XX).

$C_6H_5COCH=CHSO_2C_6H_5$ (XIX)

$C_6H_5COCH=CHCOC_6H_5$ (XX)

The two geometrical isomers of the keto sulphones were got. Their behaviour under the influence of light, heat and isomerising chemical agents was exactly similar to that of the corresponding pair of diketones. They were easily oxidised; they combine with hydrogen, bromine, hydrogen bromide, water and phenylmagnesium bromide. The products obtainable by the different reactions are:

$C_6H_5COCH_2CH_2SO_2C_6H_5$

$C_6H_5COCHBrCHBrSO_2C_6H_5$

$C_6H_5COCH_2CHBrSO_2C_6H_5$

$C_6H_5COCH_2CHOHSO_2C_6H_5$

$C_6H_5C(XMgO)=CHCH(C_6H_5)SO_2C_6H_5$

The primary 1, 4-addition product with phenylmagnesium bromide was not isolated, as it was cleaved during the reaction and the cleavage products immediately reacted further. The final products isolated were diphenylpropiophenone and diphenyl sulphoxide. The two addition products (XXI) and (XXII) were also obtained in small yields. The compound (XXI) was

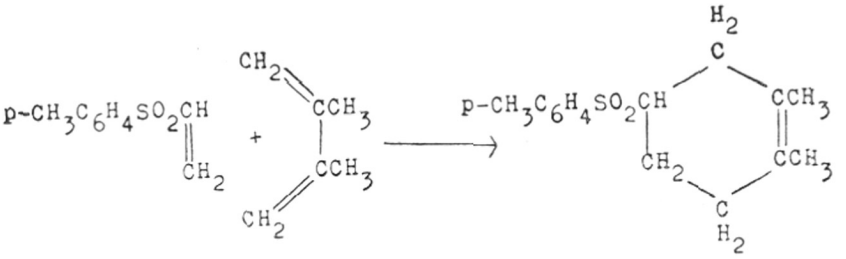
$(C_6H_5)_2C(OH)CH=CHSO_2C_6H_5$ (XXI)

$(C_6H_5)_2C=CHCH(OH)SO_2C_6H_5$ (XXII)

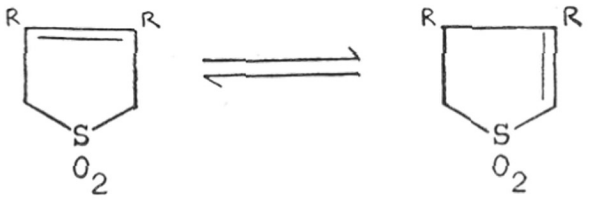
formed by 1, 2-addition of phenylmagnesium bromide to the carbonyl group. The allylic rearrangement of this compound gave (XXII).

Unsaturated compounds with a negative group at the α-position undergo Diels-Alder diene synthesis. It is note-

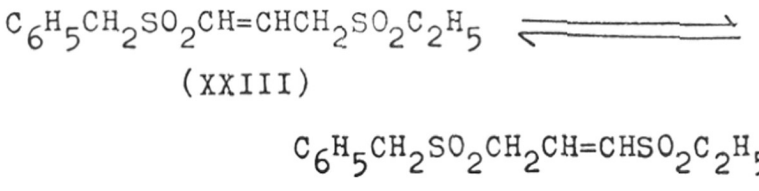
worthy that α, β-unsaturated sulphones also undergo this reaction[50].



Another effect observed due to the loosening of the bond between the carbon and hydrogen atoms by the sulphonyl group is the tautomerism in the three carbon system with a sulphonyl group. Cyclic butadiene sulphone and its derivatives were interconverted by the action of ultraviolet light or cold alkali[51-55]. The



attainment of equilibrium between the disulphones (XXIII) and (XXIV) was very rapid[4]. By the action of triamylamine or benzylpiperidine, allyl benzyl sulphone rearranges to propenyl benzyl sulphone[56].



(XXIII)

(XXIV)

The activating influence of the sulphonyl group is well brought out by the reactions of compounds with the general formula R-SO_2-CH_2X, where X is a carboxy, ethoxycarbonyl, carbamyl, cyano or acyl group. The activity of these compounds is comparable to that of the type R-CO-CH_2X. The sulphonyl group together with another negative group makes the hydrogen atoms attached to the α-carbon atom very labile.

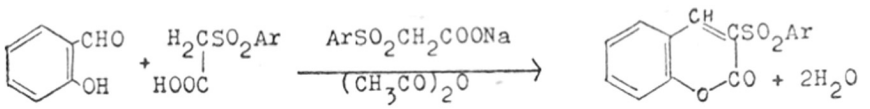
The activating influence of the sulphonyl group in alkyl- and arylsulphonylacetic acids and esters has been shown in many

ways. Determination of the ionisation constants of a number of alkylsulphonylacetic and propionic acids shows that these acids are much stronger than the corresponding sulphide acids[57]. The values for the sulphonyl acids were twenty times as large as those for the sulphide acids.

The carboxylic acids with a sulphonyl group at the α-position loose carbon dioxide readily on heating and form simple sulphones. On heating to 200° methylsulphonylacetic acid[58] and α-ethylsulphonylpropionic acid[59] yield methyl sulphone and ethyl sulphone respectively. Similarly sulphonyl-bis-acetic acid and sulphonyl-α,α-bis-propionic acid gave the corresponding sulphones.[60] α-Phenylsulphonylbutyric acid[61] or its sodium salt[62] gave phenyl propyl sulphone. When heated to 170° with potassium hydroxide solution α-phenylsulphonylisobutyric acid gave phenyl isopropyl sulphone[62]. A number of o-nitroaryl alkyl and aralkyl sulphones were prepared by heating the alkali metal salts of α-(o-nitrophenylsulphonyl)-alkane-α-carboxylic acids in slightly basic solutions[63]. α-Phenylsulphonylphenylacetic acid[64] gave phenyl benzyl sulphone at 142°. When a halogen is attached to the α-carbon of the sulphonylcarboxylic acid the decarboxylation becomes much easier[65-70]. When one halogen atom is present the free acid is decomposed by boling water. The salts of these acids were too unstable to prepare. No sulphonyldihaloacetic acid has ever been prepared because the carboxy group was lost spontaneously at room temperature.

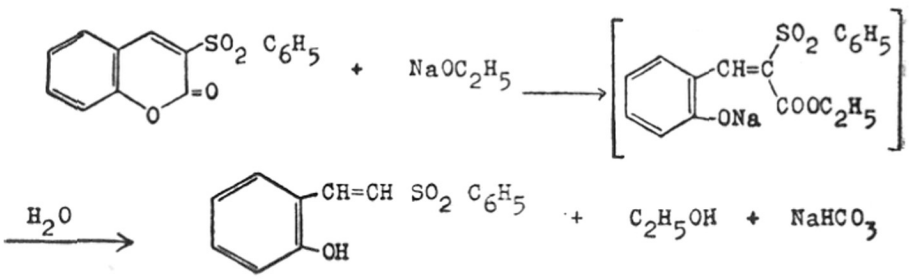
The α-aryl-or alkylsulphonylacetic esters form sodium salts with sodium ethoxide in alcoholic solution. Michael and Comey[71] first prepared the sodium salt of ethyl phenylsulphonylacetate which crystallised out from cold ethanol. The esters could be alkylated through their sodium salts and alkyl halides; both mono- and dialkyl derivatives were got[71, 72]. The sulphonylacetic acids could not be alkylated because of the loss of carbon dioxide on heating with alkali.

Tröger and his co-workers[73, 74] condensed phenylsulphonylacetic acid and the p-methyl and p-chloro derivatives with o-hydroxy aldehydes under the conditions of the Perkin reaction. The products of the reaction are 3-arylsulphonylcoumarins. By



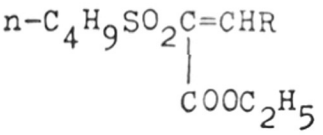
the action of sodium ethoxide in ethanol at 100° the coumarins were converted into α, β-unsaturated sulphones.

The condensation of 2, 4-dihydroxybenzaldehyde with sulphonylacetic acids gave 7-acetoxycoumarin derivatives which

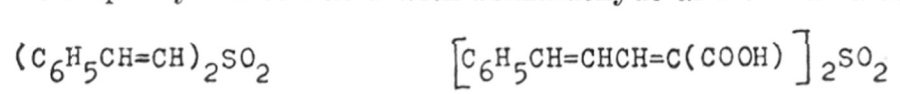


were converted to unsaturated sulphones by the action of 5% sodium hydroxide solution. Similar coumarin derivatives were obtained by condensing 2, 4, 5-, 2, 4, 6-, and 3, 4, 5-trihydroxybenzaldehydes, and 2-hydroxy-, 2, 6-dihydroxy-, and 2, 7-dihydroxy-1-naphthaldehydes with phenyl-, p-chlorophenyl-, and p-tolylsulphonylacetic acids.

The reaction of arylsulphonylacetic acids with aldehydes other than o-hydroxy aldehydes was not reported by Tröger and his co-workers. But recently Chodroff and Whitmore[75] subjected p-tolylsulphonylacetic acid to the Knoevenagel reaction and isolated unsaturated sulphones of the type $p\text{-}CH_3C_6H_4SO_2CH{=}CHR$. They, however, condensed only benzaldehyde and cinnamaldehyde. Tröger and Lux[76] failed to condense aldehydes other than salicylaldehyde with arylsulphonylacetic acid esters. But ethyl n-butylsulphonylacetate[75] was condensed with both aliphatic and aromatic aldehydes by heating the reactants in presence of piperidine acetate or ammonium acetate from thirty minutes to two hours; the compounds obtained were of the type.



The aldehydes used in this reaction were benzaldehyde, o-chlorobenzaldehyde, cinnamaldehyde, n-butyraldehyde, isobutyraldehyde, furfural and chloral. Recently Backer[77] was able to condense sulphonyldiacetic acid with benzaldehyde and cinnamalde-



(XXV) (XXVI)

hyde using piperidine acetate as the catalyst, and isolated distyryl sulphone (XXV) and sulphonyl-bis-cinnamylidene-acetic acid (XXVI).

The condensation of diethyl sulphonyldiacetate in presence of piperidine acetate with benzaldehyde, cinnamaldehyde and furfural gave[77] respectively the compounds (XXVII), (XXVIII) and (XXIX).

$$\left[C_6H_5CH{=}C(COOC_2H_5)\right]_2SO_2$$

(XXVII)

$$\left[C_6H_5CH{=}CHCH{=}C(COOC_2H_5)\right]_2SO_2$$

(XXVIII)

$$\left[(C_4H_3O)CH{=}C(COOC_2H_5)\right]_2SO_2$$

(XXIX)

Chodroff and Whitmore[75] attempted the Mannich reaction with a series of phenylsulphonyl-alkyl-acetic acids, formaldehyde and diethylamine. They could isolate only unsaturated sulphones of the type $C_6H_5SO_2CR{=}CH_2$ (where R is ethyl, n-butyl, isopropyl or benzyl); no Mannich base could be got. α-Methyl-α-p-tolylsulphonylethylene was also prepared in this way from diethylamine, formaldehyde and α-p-tolylsulphonylpropionic acid.

Arylsulphonylacetonitriles show the most pronounced activity of the α-hydrogen atoms among the compounds of the type RSO_2CH_2X. They undergo a number of reactions involving the activity of the hydrogen atoms. They dissolve in dilute alkalies forming sodium salts; alkylation with an alkyl halide and sodium ethoxide in ethanol leads to dialkyl derivatives readily[78]. In fact, the activity of these compounds is so pronounced that through alkylation no monoalkyl derivative could be isolated. Except in the benzylation of β-naphthylsulphonylacetonitrile when a monoalkyl derivative is formed the products are exclusively dialkyl derivatives.

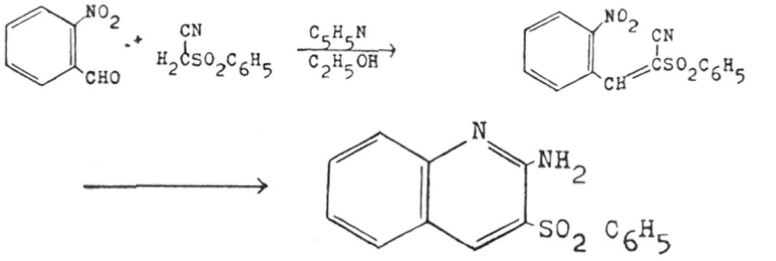
Sulphonylacetonitriles condense readily with aromatic aldehydes in presence of a trace of alkali[79-81], to give compounds of the type $RSO_2C(CN){=}CHAr$. The compounds that were prepared are given in Table 2.

TABLE 2.

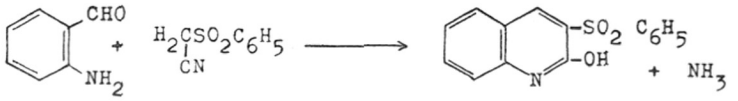
Condensation Products of Aromatic Aldehydes and Sulphonylacetonitriles, $RSO_2C(CN)=CHAr$

No	R	Ar	M.p., °C
1	C_6H_5	C_6H_5	135
2	C_6H_5	o-HOC_6H_4	160
3	C_6H_5	p-HOC_6H_4	214
4	C_6H_5	p-$H_3COC_6H_4$	113
5	C_6H_5	p-$O_2NC_6H_4$	159
6	C_6H_5	p-$(CH_3)_2NC_6H_4$	194
7	C_6H_5	p-$(CH_3)_2CHC_6H_4$	78
8	C_6H_5	$C_6H_5CH=CH$	146
9	p-$H_3CC_6H_4$	C_6H_5	114
10	p-$H_3CC_6H_4$	o-HOC_6H_4	152
11	p-$H_3CC_6H_4$	p-HOC_6H_4	133–135
12	p-$H_3CC_6H_4$	p-$H_3COC_6H_4$	110
13	p-$H_3CC_6H_4$	p-$O_2NC_6H_4$	198
14	p-$H_3CC_6H_4$	p-$(CH_3)_2NC_6H_4$	217
15	p-ClC_6H_4	p-HOC_6H_4	154–156
16	p-ClC_6H_4	p-$(CH_3)_2NC_6H_4$	245–246
17	p-BrC_6H_4	C_6H_5	119
18	p-BrC_6H_4	o-HOC_6H_4	143
19	p-BrC_6H_4	p-HOC_6H_4	166
20	p-BrC_6H_4	p-$H_3COC_6H_4$	146
21	p-BrC_6H_4	p-$O_2NC_6H_4$	210
22	p-BrC_6H_4	p-$(CH_3)_2NC_6H_4$	240–241
23	p-BrC_6H_4	$C_6H_5CH=CH$	176
24	p-IC_6H_4	p-$(CH_3)_2NC_6H_4$	222
25	2, 4, 5-$(CH_3)_3C_6H_2$	p-HOC_6H_4	181
26	2, 4, 5-$(CH_3)_3C_6H_2$	p-$(CH_3)_2NC_6H_4$	192
27	β-$C_{10}H_7$	C_6H_5	122
28	β-$C_{10}H_7$	o-HOC_6H_4	173
29	β-$C_{10}H_7$	p-HOC_6H_4	157
30	β-$C_{10}H_7$	p-$CH_3OC_6H_4$	117
31	β-$C_{10}H_7$	p-$O_2NC_6H_4$	187
32	β-$C_{10}H_7$	p-$(CH_3)_2NC_6H_4$	197
33	β-$C_{10}H_7$	p-$(CH_3)_2CHC_6H_4$	146
34	β-$C_{10}H_7$	$C_6H_5CH=CH$	157
35	CH_3	p-$(CH_3)_2NC_6H_4$	—

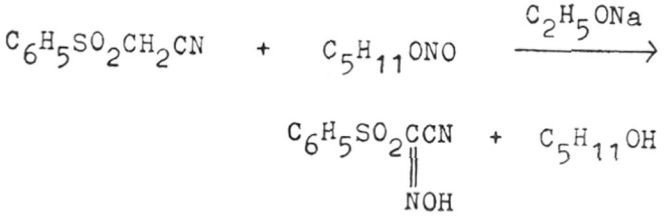
The compound got by the condensation of o-nitrobenzaldehyde with phenylsulphonylacetonitrile was reduced to a quinoline derivative[82]. The same compound was formed directly by using o-aminobenzaldehyde. If the reaction with o-aminoben-



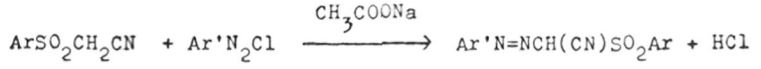
zaldehyde was carried out in a sealed tube at 170°, the amino group was lost giving a substituted carbostyril.



The sulphonylacetonitriles undergo condensation with amyl nitrite in presence of sodium ethoxide[79]. All attempts to hydrolyse the oximes to the ketones were unsuccessful.



Tröger and Wunderlich[83] condensed arylsulphonylaceto- and propionitriles with diazonium salts in presence of sodium acetate in alcoholic solution. Whether the products exist as



the azo compounds or the hydrazones is not known. The sulphones derived from sulphonylpropionitriles were necessarily the azo compounds.

The sulphonylacetonitriles were easily chlorinated by the action of bleaching powder on the nitriles dissolved in acetic acid[84]. The dichloronitriles were the products. Similarly bromine in acetic acid gave the dibromo compounds[84]. But iodine in potassium iodide solution failed to react with the nitriles. No

monohalo derivative of the sulphonylacetonitrile has been prepared. Attempts to oxidise the methylene group to the keto group by potassium permangante were unsuccessful[84].

The arylsulphonylacetamides are much less acidic than either the sulphonylacetonitriles or the sulphonylacetic acid esters, as they were insoluble in alkali. Although Tröger and Lux[76] failed to replace the active hydrogen atoms in the amides with alkyl groups, this has been achieved by later workers[85, 86], using an alkyl halide and sodium ethoxide in ethanol. The alkylsulphonylacetamides, on alkylation, gave three products, the amide group also being affected[87].

$$n\text{-}C_4H_9SO_2CH_2CONH_2 \xrightarrow[C_2H_5ONa]{(C_2H_5)_2SO_4} n\text{-}C_4H_9SO_2CH(C_2H_5)CONH_2$$

$$+\ n\text{-}C_4H_9SO_2CH_2CONHC_2H_5 + n\text{-}C_4H_9SO_2CH(C_2H_5)CONHC_2H_5$$

Bromination of the sulphonylacetamides takes place by the action of bromine in moist carbon tetrachloride, to yield monobromo derivatives[88]. Tröger and Lux[76] reported the failure of sulphonylacetamides to condense with aldehydes. Analogous to the nitriles, sulphonylacetamides react with amyl nitrite in presence of sodium ethoxide with the formation of oximes[76]. But this reaction failed to occur with sulphonylacetic acid esters; simple hydrolysis only occurred.

β-Keto sulphones of the type R-SO_2-CH_2-CO-R' are easily soluble in dilute cold alkali. They give the usual reactions of the keto group, forming oximes, semicarbazones, imides, and phenylhydrazones readily but do not add hydrogen cyanide[89]. Halogenation of phenylsulphonylacetone gave successively mono-, di- and trisubstitution products in which only the methyl group reacted[89, 90]. However, substitution in the methylene group occurred with ω-phenylsulphonylacetophenone.

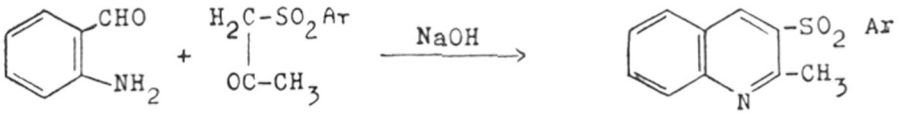
The reactivity of the methylene groups in β-keto sulphones is also manifest in the reaction of these compounds with esters

$$C_6H_5SO_2CH_2COCH_3 + p\text{-}CH_3C_6H_4SO_2SCH_3 \longrightarrow$$

$$C_6H_5SO_2\underset{\displaystyle SCH_3}{\underset{|}{C}}HCOCH_3 + p\text{-}CH_3C_6H_4SO_2H$$

of aromatic thiolsulphonic acids[32, 33, 91-93]. An alkyl- or arylthio group is introduced.

The condensation of β-keto sulphones with o-aminobenzal-dehyde or 3-methoxy-2-aminobenzaldehyde gives substituted quinolines with a sulphonyl group at the 3-position[94-99].



The reaction of o-aminobenzaldehyde with arylsulphonylaceto-phenones requires a temperature of 200°.

The reaction of β-keto sulphones with aldehydes other than o-aminobenzaldehyde, has not been reported. The action of amyl nitrite and diazonium salts on β-keto sulphones does not seem to have been studied.

From the foregoing review it can be seen that a number of reactions involving the activating influence of sulphonyl group on the hydrogen atom attached to the α-carbon atom have been studied. It is evident that sulphones resemble ketones closely in a number of reactions. But there exists a difference in the extent of activation and perhaps, in the mode of activation. In general sulphones are less reactive than ketones. This is obvious from the reactions of benzyl p-tolyl sulphone which fails to answer the mercuric chloride test for enolic substances, which does not condense with benzaldehyde or iso-amyl nitrite and which is not oxidised by selenium dioxide[3]. Also, the Michael addition with methyl p-tolyl sulphone fails. Alkylation of simple sulphones could not be carried out with an alkyl halide and sodium ethoxide.

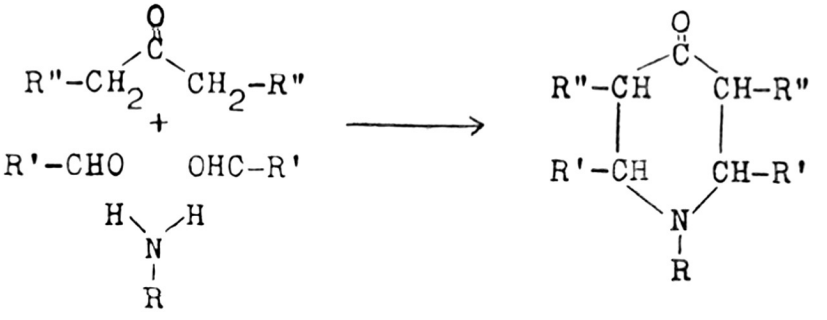
All these dissimilarities and similarities in the reactions of ketones and sulphones indicate that further study with sulphones, involving groups activated by sulphonyl group, will be helpful to elucidate the mechanism of the reactions undergone by sulphones. Though several condensations with compounds containing methyl or methylene groups activated by an adjacent sulphonyl group have been studied, the Mannich reaction with such compounds was not well investigated. Even the few attempts made[75] were not successful. It appeared desirable to make further attempts in this direction. Recently, sulphones especially, amino sulphones have become increasingly important as drugs. For example, the use of bis-(p-aminophenyl) sulphone and some of its derivatives for the treatment of leprosy can be mentioned. If the Mannich reaction using sulphones in place of ketones could be effected, a variety of amino sulphones will be available and it will be of interest to test the pharmacological activity of such amino sulphones. Hence, apart from the theoretical considerations, the practical importance of the amino sulphones also led the author to undertake a study of the Mannich reaction with sulphones.

DISCUSSION

The Mannich reaction is the condensation of a compound containing a reactive hydrogen atom with an aldehyde and ammonia or a primary or a secondary amine. In a general way the condensation can be represented by the following equation:

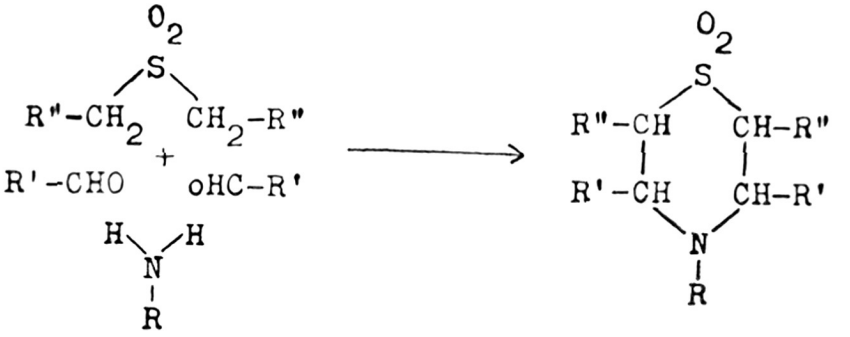
$$RCOCH_3 + R'CHO + R''_2NH,HCl \longrightarrow RCOCH_2\underset{\displaystyle R'}{\underset{|}{C}}HNR''_2,HCl + H_2O$$

Sometimes the reaction gives rise to other products also. For example, the condensation of diethyl ketone, 35% formaldehyde, and methylamine yielded five different products[100]. Noller and Baliah[101] developed a satisfactory procedure to condense aliphatic ketones with aromatic aldehydes and certain amines to get exclusively 4-piperidones (XXX). The success of the procedure

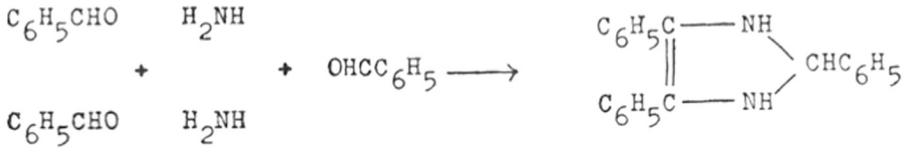


(XXX)

as developed by Noller and Baliah lay in the use of the amine as its acetate instead of as its hydrochloride which was employed by earlier workers. The yield of the products was generally good. In view of the structural similarity that exists between ketones and sulphones it appeared that sulphones might be condensed with aldehydes and amines to yield derivatives of tetrahydro-1,4-thiazine according to the following equation:



Attempts were made in the present investigation to condense simple sulphones of the type $RCH_2SO_2CH_2R$ with benzaldehyde and ammonia. Four sulphones, dimethyl sulphone, diethyl sulphone, di-n-propyl sulphone and di-n-butyl sulphone were prepared and used. They failed to undergo the reaction under a variety of conditions. The reaction only gave a small amount of a nitrogenous compound containing no sulphur. The compound was isolated as its hydrochloride. It was identified to be amarin (XXXI). Apparently, benzaldehyde and ammonia reacted in the following manner:



(XXXI)

The various experimental conditions tried to condense sulphones and the observations made are summarised below:

(1) The duration of heating the reactants in glacial acetic acid was varied from ten minutes to six hours. In all cases only amarin was obtained.

(2) Instead of glacial acetic acid, acetic anhydride was used as the solvent. Surprisingly, in this case, not amarin but another nitrogenous substance, containing no sulphur was formed. The properties of this compound were identical with those reported by Pinner[102] for his compound of molecular formula $C_{42}H_{37}N_3O_2$, the structure of which is unknown.

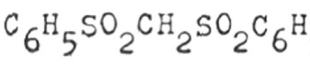
(3) A mixture of dimethyl sulphone, paraformaldehyde, diethylamine hydrochloride and absolute ethanol was refluxed for forty hours. No condensation seemed to occur.

(4) A solution of diethyl sulphone, benzaldehyde and ammonium acetate in absolute ethanol was heated under reflux for six hours. Only amarin was formed in small amounts.

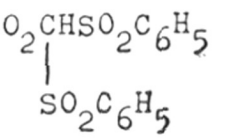
(5) A mixture of diethyl sulphone, benzaldehyde and ammonium acetate in glacial acetic acid was left aside at room temperature for about a month. No condensation took place. The use of absolute ethanol in place of acetic acid had also no effect.

The failure of these sulphones to undergo the Mannich reaction indicates that the hydrogen atoms, alpha to the sulphonyl group, are not sufficiently active. It also indicates that the activating influence of a sulphonyl group on the α-hydrogen atoms is less than that of a keto group.

Having failed to effect the condensation with simple monosulphones, it appeared worthwhile to examine the behaviour of methylene groups activated by two sulphonyl groups or methine groups activated by three sulphonyl groups. Accordingly, bis-(phenylsulphonyl)-methane (XXXII) and tris-(phenylsulphonyl)-methane (XXXIII) were prepared and their reaction with benzaldehyde and ammonium acetate was studied.

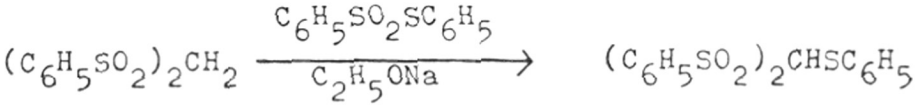


(XXXII)

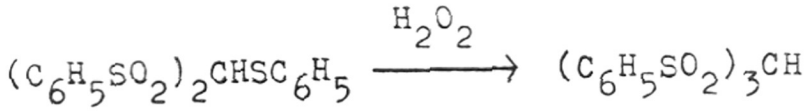


(XXXIII)

Bis-(phenylsulphonyl)-methane was prepared by the method of Shriner and his co-workers[9]. The condensation of sodium thiophenate with methylene iodide gave bis-(phenylthio)-methane in excellent yield. Oxidation of this compound with hydrogen peroxide (30%) in a mixture of glacial acetic acid and acetic anhydride gave the β-disulphone. For the preparation of tris-(phenylsulphonyl)-methane, bis-(phenylsulphonyl)-methane was refluxed with phenyl benzenethiolsulphonate in presence of sodium ethoxide. The resulting sulphide-disulphone (XXXIV) was oxidised with hydrogen peroxide in glacial acetic acid solution.



(XXXIV)



Under the conditions tried both bis-(phenylsulphonyl)-methane and tris-(phenylsulphonyl)-methane failed to undergo the Mannich reaction. It is interesting to note that these two sulphones which contain hydrogen atoms sufficiently labile to permit them to dissolve in alkalies, also fail to undergo the reaction.

Since the hydrogen atoms activated by two or three sulphonyl groups at the α-position failed to condense in the Mannich

reaction, it was decided to study the behaviour of hydrogen atoms activated by an adjacent sulphonyl group and another activating group such as, C_6H_5, COOH, COOR, COR or CN. The following types of compounds were prepared and tested:

$ArSO_2CH_2C_6H_5$

$ArSO_2CH_2COOH$

$ArSO_2CH(CH_3)COOH$

$ArSO_2CH_2COOC_2H_5$ (Ar = Phenyl or p-tolyl)

$ArSO_2CH_2COC_6H_5$

$ArSO_2CH_2CN$

The method followed for the preparation of benzyl phenyl sulphone was that of Shriner and his co-workers[9]. It involves a reaction between benzyl chloride and sodium benzenesulphinate.

$$C_6H_5CH_2Cl + C_6H_5SO_2Na \longrightarrow C_6H_5CH_2SO_2C_6H_5 + NaCl$$

Although a yield of 52% was reported in the literature for the compound the author was able to get a yield of 76%. Refluxing a mixture of benzyl phenyl sulphone, benzaldehyde, ammonium acetate and glacial acetic acid did not cause the desired condensation. Only a small amount of amarin could be isolated from the reaction mixture.

As representatives of compounds of the type $ArSO_2CH_2COOH$, p-tolylsulphonylacetic acid and phenylsulphonylacetic acid were prepared. The method of Gabriel[103], with slight modifications, was adopted for their preparation. It consists of refluxing a mixture of sodium chloroacetate and sodium arenesulphinate in water over a steam bath. During the preparation of these acids, small quantities of the corresponding methyl sul-

$$ArSO_2Na + ClCH_2COONa \longrightarrow ArSO_2CH_2COONa + NaCl$$

phones were also formed due to the decarboxylation of the sulphonylacetic acids. The formation of the methyl sulphones was not reported by Gabriel.

p-Tolylsulphonylacetic acid or phenylsulphonylacetic acid readily condensed with benzaldehyde and ammonia. It was found that several aromatic aldehydes could be used in place of benzaldehyde and that several aliphatic primary amines could be used in place of ammonia. During the reaction, the sulphonylacetic acid underwent decarboxylation. The condensation

yielded both a Mannich base (XXXV) and an α,β-unsaturated sulphone (XXXVI). The products of the reaction indicate that

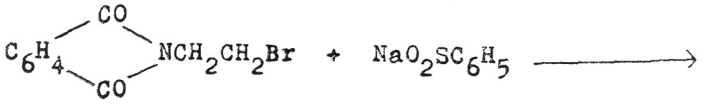
$$ArSO_2CH_2COOH + Ar'CHO + RNH_2 \xrightarrow[-H_2O]{-CO_2}$$

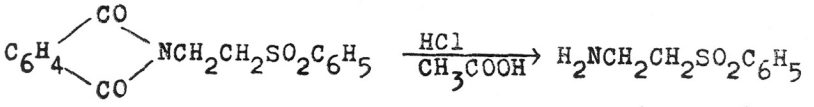
$$ArSO_2CH_2CH(Ar')NHR \quad + \quad ArSO_2CH{=}CHAr'$$

(XXXV) (XXXVI)

both the Mannich reaction and the Knoevenagel reaction have occurred simultaneously. The mechanism of their formation will, however, be considered at a later stage in this discussion.

Only a few compounds of the type (XXXV) and (XXXVI) are known so far. β-Aminoethyl phenyl sulphone (XXXVII) was synthesised by the Gabriel method[104] as expressed by the following scheme:





(XXXVII)

The action of ammonia on β-chloroethyl aryl sulphones resulted in the formation of secondary amines[105]. In view of the difficulty encountered in the preparation of β-aminoethyl aryl sulphones, the present method using arylsulphonylacetic acids provides a simple and direct route for the preparation of a number of substituted-β-aminoethyl aryl sulphones.

The number of hitherto known α,β-unsaturated sulphones is very small. α-Phenyl-β-p-tolylsulphonylethylene (XXXVIII) was obtained first by Kohler and Potter[1] and later by Chodroff and Whitmore[75]. Kohler and Potter prepared its cis and trans forms, starting with phenylacetylene. Their method of preparation is given by the scheme shown below:

$$C_6H_5C{\equiv}CH + p\text{-}CH_3C_6H_4SH \longrightarrow C_6H_5CH{=}CHSC_6H_4CH_3\text{-}p$$

$$\xrightarrow{\text{Oxidation}} \quad C_6H_5CH{=}CHSO_2C_6H_4CH_3\text{-}p$$

(XXXVIII)

As already mentioned in the introduction, Chodroff and Whitmore condensed p-tolylsulphonylacetic acid with benzaldehyde, as well as cinnamaldehyde and obtained α-phenyl-β-p-tolylsulphonylethylene and α-styryl-β-p-tolylsulphonylethylene respectively. They reported the failure of the reaction with other aldehydes. α-Phenyl-β-phenylsulphonylethylene (XXXIX) was prepared by Field[44] by dehydration of the alcohol (XL).

$$C_6H_5SO_2CH_2CH(OH)C_6H_5 \xrightarrow{-H_2O} C_6H_5SO_2CH{=}CHC_6H_5$$

(XL) (XXXIX)

Similar compounds[73,74] were prepared by Tröger and his coworkers from 3-arylsulphonylcoumarins, through the action of alkali. The fact that arylsulphonylacetic acids can be made to undergo either the Mannich reaction or the Knoevenagel reaction is important in that a variety of β-amino sulphones and α, β unsaturated sulphones can be very readily obtained by this method.

These condensations with arylsulphonylacetic acids deserve to be considered in some detail. The reaction was generally carried out by refluxing a mixture of equimolecular quantities of the arylsulphonylacetic acid, an aromatic aldehyde and ammonium acetate or an amine in glacial acetic acid. The use of equimolecular quantities were strictly adhered to, throughout. The duration of refluxing was five to fifteen minutes. The reaction occurred with brisk evolution of carbon dioxide and the colour of the solution changed to yellow or brown. The completion of the reaction was indicated by the stoppage of the evolution of carbon dioxide. The reaction proceeds rather fast at the beginning but gradually slackens. After it was complete, the mixture was allowed to cool and ether was added. Most of the reaction mixture went into solution in ether leaving a small viscous layer which was mostly ammonium acetate. The ether layer was separated and dry hydrogen chloride was passed into it. Too much of the hydrogen chloride was avoided, as it tended to colour the product. In a few cases even a slight excess of hydrogen chloride coloured the product yellow or brown; to avoid the formation of coloured products in such cases the hydrochloride was precipitated by the addition of enough quantity of ether saturated with hydrogen chloride. The hydrochloride of the amino sulphone usually separated immediately. In certain cases, only a clear solution was obtained at first but, after standing for a short time, the solution began to yield fine crystals of the hydrochloride. After allowing sufficient time for the complete separation of the hydrochloride, it was collected at

the pump and washed with ether and acetone. The hydrochloride, thus obtained, was usually colourless and of high purity. The α,β-unsaturated sulphone was obtained from the filtrate which was got after removal of the hydrochloride. Evaporation of the ether from the filtrate gave the unsaturated sulphone; sometimes only an oil was obtained due to contamination with unreacted aldehyde and acetic acid. In such cases, shaking the oily residue with a few cc. of methanol afforded fine crystals of the unsaturated sulphone. The purity of these sulphones was generally high. The unsaturated sulphone formed from m-nitrobenzaldehyde and p-tolylsulphonylacetic acid was only very sparingly soluble in ether. Consequently, after the addition of ether to the reaction mixture, the solution deposited crystals of the unsaturated sulphone. After removal of this compound by filtration, the filtrate was saturated with hydrogen chloride to get the Mannich base as hydrochloride.

Both p-tolylsulphonylacetic acid and phenylsulphonylacetic acid condensed with many aldehydes and amines furnishing substituted β-aminoethyl aryl sulphones and substituted-vinyl aryl sulphones. The products obtained from p-tolylsulphonylacetic acid and their yields are given in Table 3. The compounds obtained from phenylsulphonylacetic acid are listed in Table 4.

TABLE 3.

β-Amino Sulphone Hydrochlorides, p-$CH_3C_6H_4SO_2CH_2$-CH(Ar)NHR,HCl *and* α,β-*Unsaturated Sulphones,* p-$CH_3C_6H_4$-$SO_2CH{=}CHAr$ *Prepared from p-Tolylsulphonylacetic Acid.*

No	Ar	R	Yield of β-Amino sulphone hydrochloride, %	Yield of α,β-unsaturated sulphone, %
1	C_6H_5	H	23	25
2	3,4-(CH_2O_2) : C_6H_3	H	22	15
3	2-$H_3COC_6H_4$	H	19	23
4	4-$H_3COC_6H_4$	H	19	12
5	4-ClC_6H_4	H	19	31
6	2-$O_2NC_6H_4$	H	18	5
7	3-$O_2NC_6H_4$	H	25	20
8	4-$H_3CC_6H_4$	H	25	22
9	2-Thienyl	H	15	20

TABLE 3—(*Contd.*)

No	Ar	R	Yield of β-Amino sulphone hydrochloride, %	Yield of α,β-unsaturated sulphone, %
10	C_6H_5	CH_3	8	35
11	$3\text{-}O_2NC_6H_4$	CH_3	30	48
12	C_6H_5	C_2H_5	21	54
13	$3\text{-}O_2NC_6H_4$	C_2H_5	23	41
14	C_6H_5	Allyl	13	43
15	$3\text{-}O_2NC_6H_4$	Allyl	33	62
16	C_6H_5	$n\text{-}C_4H_9$	9	60
17	$3\text{-}O_2NC_6H_4$	$n\text{-}C_4H_9$	14	70
18	C_6H_5	$n\text{-}C_8H_{17}$	11	61
19	$3\text{-}O_2NC_6H_4$	$n\text{-}C_8H_{17}$	19	53
20	C_6H_5	$C_6H_5CH_2$	36	64
21	$3,4\text{-}(CH_2O_2) : C_6H_3$	$C_6H_5CH_2$	27	30
22	$3\text{-}O_2NC_6H_4$	$C_6H_5CH_2$	10	56

TABLE 4.

β-Amino Sulphone Hydrochlorides, $C_6H_5SO_2CH_2CH(Ar)NHR,HCl$ *and* α, β-*Unsaturated Sulphones*, $C_6H_5SO_2CH{=}CHAr$
Prepared from Phenylsulphonylacetic Acid.

No.	Ar	R	Yield of β-Amino Sulphone Hydrochloride, %	Yield of α, β-Unsaturated Sulphone, %
1	C_6H_5	H	27	21
2	$3,4\text{-}(CH_2O_2)\text{: }C_6H_3$	H	30	19
3	$2\text{-}H_3CO\text{-}C_6H_4$	H	20	28
4	$4\text{-}ClC_6H_4$	H	24	28
5	$2\text{-}O_2NC_6H_4$	H	7	10
6	$3\text{-}O_2NC_6H_4$	H	21	14
7	$4\text{-}H_3CC_6H_4$ [a]	H	–	17
8	2-Thienyl [b]	H	14	–
9	C_6H_5	$C_6H_5CH_2$	10	27

a Only α, β-unsaturated sulphone could be obtained.

b Only β-amino sulphone could be isolated.

Except in the two cases noted at the foot-note of Table 4, in all other cases both the Mannich base and the α,β-unsaturated sulphone were got. The Mannich base was always isolated as the hydrochloride. These hydrochlorides crystallised well either from ethanol or a mixture of ethanol and ether. Attempts were made to liberate the bases by dissolving the hydrochlorides in ethanol and making the solution alkaline with aqueous ammonia. But most of the bases were obtained as oils. In view of their instability they could not be purified by distillation. Crystalline bases were, however, obtained when the aldehyde component of the reactants was either m-nitrobenzaldehyde or p-chlorobenzaldehyde. The yield of the hydrochloride in most cases, as could be seen from Tables 3 and 4, was about 20%. The yield of the unsaturated compound varied from 5% in the case of p-tolylsulphonylacetic acid, o-nitrobenzaldehyde and ammonia, to 31% with the same acid, p-chlorobenzaldehyde and ammonia. A change of amine did not cause any appreciable alteration in the yield of the β-amino sulphone. But there was a marked increase in the yield of the unsaturated sulphone when amines were used in place of ammonia, the yield varying from 27 to 70%. It is rather significant that the yield of the unsaturated sulphone increased with the increase in the molecular weight of the amine. This can be seen from the results obtained in the reaction of p-tolylsulphonylacetic acid with benzaldehyde and different amines. The yield of α-phenyl-β-p-tolylsulphonylethylene obtained with each amine is given in Table 5.

TABLE 5.

Amine	Yield of α-Phenyl-β-p-tolyl-sulphonylethylene, %
Ammonia	25
Methylamine	35
Ethylamine	54
n-Butylamine	60
n-Octylamine	61
Benzylamine	64

Benzylamine seems to be the most reactive for β-amino sulphone formation and also the most effective to cause the formation of α,β-unsaturated sulphone. In its reaction with p-tolylsulphonylacetic acid and benzaldehyde the over-all yield of the α,β-unsaturated sulphone and the β-N-benzylamino sul-

phone was 100%. From the facts stated it follows that the best method of synthesising α,β-unsaturated sulphones is to use an amine such as benzylamine or an aliphatic primary amine of high molecular weight in the condensation.

Among the aldehydes that could be condensed successfully in the reaction, benzaldehyde, m-nitrobenzaldehyde and p-chlorobenzaldehyde were found to be relatively very reactive. Hence benzaldehyde and m-nitrobenzaldehyde were selected as representative aldehydes for several condensations studied. For example, both these aldehydes were condensed with different amines and p-tolylsulphonylacetic acid with a view to find how the yield of β-alkylamino sulphone varies with the amine used. The results obtained are recorded in Table 6. They indicate that no generalisations can be made regarding the effect of structural variations of the amines and aldehydes on the yield of the Mannich base. Generally better yields were obtained with m-nitrobenzaldehyde.

TABLE 6.

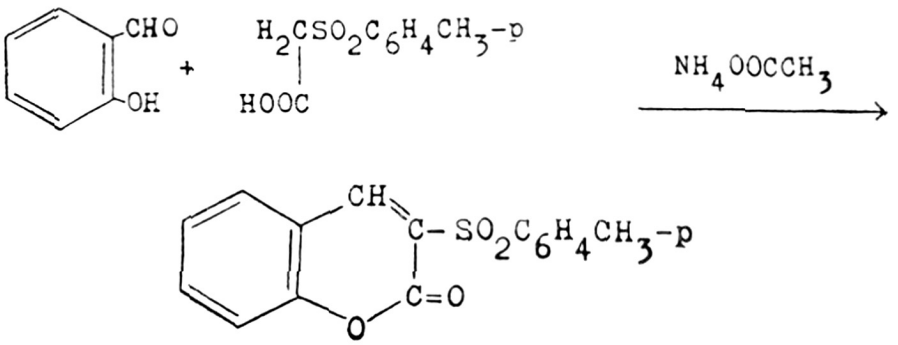
Effect of Ar and R on the Formation of

p-$CH_3C_6H_4SO_2CH_2CH(Ar)NHR$

R	Yield, %	
	Ar = C_6H_5	Ar = 3-$O_2NC_6H_4$
H	23	25
CH_3	8	30
C_2H_5	21	23
Allyl	13	33
n-C_4H_9	9	14
n-C_8H_{17}	11	19
$C_6H_5CH_2$	36	10

Comparing the reactivity of the three isomeric nitrobenzaldehydes, o-nitrobenzaldehyde comes next to m-nitrobenzaldehyde. No condensation seems to take place with p-nitrobenzaldehyde. All attempts to condense it with ammonia and p-tolylsulphonylacetic acid were unsuccessful. The reaction of salicylaldehyde with ammonia and p-tolylsulphonylacetic acid is interesting to note in that neither the β-amino sulphone nor the expected α,β-unsaturated sulphone could be obtained. The product of

the reaction was 3-p-tolylsulphonylcoumarin. The course of the reaction is expressed by the following equation:



(XLI)

Compound (XLI) and similar coumarins were obtained by Tröger and his co-workers[73, 74] from p-tolylsulphonylacetic acid and salicylaldehyde under the conditions of the Perkin reaction.

The reactions of arylsulphonylacetic acids described so far, seem to be limited to aromatic aldehydes. Some heterocyclic aldehydes like thiophene-2-aldehyde also condense. No product could, however, be obtained with furfural. Cinnamaldehyde failed to react. It is remarkable that not even a single aliphatic aldehyde underwent either the Mannich-type condensation or the Knoevenagel-type condensation with arylsulphonylacetic acids. The aliphatic aldehydes tried were formaldehyde, acetaldehyde, n-butyraldehyde, isobutyraldehyde and chloral. Formaldehyde was used in the form of 40% solution and also as paraformaldehyde. Acetaldehyde was used in the form of paraldehyde and acetaldehyde-ammonia. When acetaldehyde-ammonia was used, ammonium acetate was dispensed with, since the aldehyde-ammonia itself supplied the necessary ammonia required for the reaction. Except in the case of chloral, in all other cases only decarboxylation of the sulphonylacetic acid occurred with the formation of methyl arylsulphone. It is to be noted that decarboxylation of the sulphonylacetic acid to give the methyl sulphone occurred at a temperature (about 120° in the present experiment) which is much lower than that at which α-sulphonylacetic acids were reported to loose carbon dioxide[58-64].

The reaction of chloral with p-tolylsulphonylacetic acid is interesting. Because of the presence of three chlorine atoms chloral should be expected to be more reactive than other aliphatic aldehydes. It underwent aldol condensation, resulting in

the formation of 3, 3, 3-trichloro-2-hydroxypropyl p-tolyl sulphone (XLII).

$$p\text{-}CH_3C_6H_4SO_2CH_2COOH + Cl_3CCHO \longrightarrow p\text{-}CH_3C_6H_4SO_2CH_2CH(OH)CCl_3 + CO_2$$

(XLII)

Regarding the amines that could be condensed with arylsulphonylacetic acids and aldehydes to get β-amino sulphones, only aliphatic primary amines appeared to condense. Attempts to condense piperidine or diethylamine with p-tolylsulphonylacetic acid and benzaldehyde were not successful. However, when piperidine was used, the α, β-unsaturated sulphone, α phenyl-β-p-tolylsulphonylethylene, was obtained in 20% yield. With diethylamine most of the sulphonylacetic acid underwent decarboxylation to give methyl p-tolyl sulphone. Aromatic amines do not seem to react. All attempts to condense aniline were unsuccessful.

It has already been mentioned that glacial acetic acid was used as a solvent for the condensations described. It seemed worthwhile to investigate the suitability of other solvents and the relative merits of glacial acetic acid, if any. In the first instance, glacial acetic acid was replaced by the basic solvent, pyridine. The reaction of p-tolylsulphonylacetic acid with benzaldehyde and ammonium acetate in pyridine was carried out by refluxing the reactants for twenty minutes. There was no perceptible change in the yield of the Mannich base. But the unsaturated sulphone was obtained in a higher yield. Whereas, α-phenyl-β-p-tolyl sulphonylethylene was got in 25% yield in acetic acid, it was obtained in 40% yield when pyridine was used as a solvent. The higher yield of the unsaturated sulphone indicates that pyridine is a better solvent than acetic acid when α,β-unsaturated sulphone is the desired product. But when benzylamine acetate was condensed with benzaldehyde and p-tolylsulphonylacetic acid using pyridine as a solvent, the results of the experiment proved otherwise. Whereas in glacial acetic acid the Mannich base was obtained in 36% yield and the unsaturated sulphone was obtained in 64% yield, the corresponding yields in pyridine were 3 and 34% respectively. Using benzylamine as such and not as benzylamine acetate, in pyridine the yield of the products were still poorer; in this case the Mannich base was obtained in 1.5% yield and the unsaturated sulphone in 15% yield. These experiments suggest that the acetate ion exerts a favourable influence on the formation of the Mannich base.

When triethylamine was used as a solvent, the reaction of p-tolylsulphonylacetic acid, benzaldehyde and ammonium acetate

gave the Mannich base in about 10% yield, but no unsaturated sulphone could be isolated. When ethanol was used as a solvent the reaction failed completely with ammonium acetate, benzaldehyde and p-tolylsulphonylacetic acid. The condensation was also tried without the use of acetate ion in neutral solvents like ethanol and benzene. Although ammonia failed to react in ethanol, benzylamine did give small yields of both the Mannich base and the unsaturated sulphone in ethanol as well as benzene. It should now be clear that glacial acetic acid is the best solvent for the Mannich reaction of arylsulphonylacetic acids.

By varying the duration of refluxing in the reaction of p-tolylsulphonylacetic acid, benzaldehyde and ammonia in acetic acid solution, noteworthy results were obtained. A longer period of refluxing always gave a higher yield of the unsaturated sulphone and the yield of the Mannich base was drastically reduced. In fact, refluxing the reactants for a period of forty minutes gave no Mannich base at all; the unsaturated sulphone was obtained in higher yield. These results indicate that the increase in the yield of the unsaturated sulphone resulted at the expense of the Mannich base. The obvious conclusion is that it is the Mannich base which formed first. On prolonged heating it looses ammonia giving rise to the unsaturated sulphone. Such a view is substantiated by the observation that the heating of α -phenyl-β -p-tolylsulphonylethylamine alone in glacial acetic acid under reflux gave the unsaturated sulphone, α-phenyl- β-p-tolylsulphonylethylene.

$$p\text{-}CH_3C_6H_4SO_2CH_2\underset{\displaystyle C_6H_5}{\underset{|}{C}}HNH_2 \longrightarrow p\text{-}CH_3C_6H_4SO_2CH{=}CHC_6H_5 + NH_3$$

The Mannich reaction with α -p-tolylsulphonylpropionic acid (XLIII) and β -p-tolylsulphonylpropionic acid (XLIV) was also attempted. The former compound was chosen to note the influence of the additional methyl group on the course of the reaction. The latter was chosen to examine the reactivity of the methylene group (a) in (XLIV) in view of its being separated

$p\text{-}CH_3C_6H_4SO_2CH(CH_3)COOH$ (XLIII)

$p\text{-}CH_3C_6H_4SO_2CH_2CH_2COOH$ (XLIV)

(a)

from the sulphonyl group by another methylene group. If (XLIV) does not undergo the condensation reactions which are characteristic of p-tolylsulphonylacetic acid, it would be established beyond doubt that the reactivity of the methylene group in p-tolylsulphonylacetic acid is partly due to its proximity with the sulphonyl group.

α-p-Tolylsulphonylpropionic acid was prepared by Otto[105] by the hydrolysis of its ethyl ester which was in turn got by heating ethyl α-bromopropionate with sodium p-toluenesulphinate in ethanolic solution at 150° under pressure. In the present investigation the acid was prepared by direct synthesis from sodium α-bromopropionate and sodium p-toluenesulphinate by heating them in aqueous solution. The yield of the product was good. Its reaction with benzaldehyde and ammonium acetate, as well as with m-nitrobenzaldehyde and ammonium acetate was studied. Both the Mannich base and the unsaturated sulphone were obtained in these reactions. But α-p-tolylsulphonylpropionic acid was found to be much less reactive than the arylsulphonylacetic acids. One hour's refluxing of the reaction mixture was found to be necessary. The yields of the products were also much less. The low reactivity of α-p-tolylsulphonylpropionic acid is to be expected; methyl group is an electron-repelling group and the replacement of one of the reactive hydrogen atoms in p-tolylsulphonylacetic acid by a methyl group reduces the mobility of the other α-hydrogen atom.

β-p-Tolylsulphonylpropionic acid was prepared by Kohler and Reimer[107] by the addition of p-toluenesulphinic acid to fumaric or maleic acid in boiling water and also by the action of sodium p-toluenesulphinate in water with alkali-neutralised solution of β-iodopropionic acid. In the present investigation it was prepared by heating a mixture of sodium p-toluenesulphinate and sodium β-chloropropionate in ethanol-water mixture. The product was obtained in 26% yield.

The condensation of β-p-tolylsulphonylpropionic acid with benzaldehyde and ammonium acetate was not successful. This failure indicates that the separation of the sulphonyl and carboxy groups by two methylene groups renders the hydrogen atoms alpha to the carboxy group less reactive and that the sulphonyl group or the carboxy group alone cannot activate the α-hydrogen atoms to such a degree as to cause the Mannich and Knoevenagel reactions. Incidentally, the view that the sulphonyl group is an activating group like the nitro and the carbonyl groups is also substantiated.

Since arylsulphonylacetic acids undergo the Mannich reaction, their esters should be expected to exhibit the same reactivity. As has already been mentioned, Chodroff and Whitmore[75] heated ethyl n-butylsulphonylacetate with both aromatic and aliphatic aldehydes and ammonium acetate or piperidine acetate. They did not isolate any Mannich base; only α,β-unsaturated sulphones were obtained. In the present work ethyl phenylsulphonylacetate was prepared by the method of Ashley and Shriner[72] and the compound was subjected to the Mannich reaction. In the reaction of ethyl phenylsulphonylacetate with m-nitrobenzaldehyde and ammonium acetate only the α,β-un-

saturated sulphone (XLV) could be obtained. No Mannich base was obtained.

$$C_6H_5SO_2CH_2COOC_2H_5 + m\text{-}O_2NC_6H_4CHO \xrightarrow{CH_3COONH_4}$$

$$C_6H_5SO_2C(COOC_2H_5)=CHC_6H_4NO_2\text{-}m$$

(XLV)

The reaction was tried using glacial acetic acid as well as absolute ethanol as solvents. In both the cases only the unsaturated sulphone was obtained.

The methylene group in arylsulphonylacetonitriles, $ArSO_2CH_2CN$, should be expected to be very reactive, since the cyano group is a powerful electron-attracting group. Hence it was decided to study the behaviour of phenylsulphonylacetonitrile in the Mannich and the Knoevenagel reactions. The compound was prepared by refluxing a mixture of chloroacetonitrile and sodium benzenesulphinate in ethanol. This compound was prepared by Tröger and Hille[108] by heating the reactants in a sealed tube at an elevated temperature. The present method is simpler

$$C_6H_5SO_2Na + ClCH_2CN \longrightarrow C_6H_5SO_2CH_2CN + NaCl$$

and equally effective, though a longer time of heating the reactants is necessary.

The behaviour of phenylsulphonylacetonitrile was found to be analogous to that of ethyl phenylsulphonylacetate. The reaction of various aldehydes with the nitrile gave unsaturated sulphones; the amino sulphones could not be obtained.

$$C_6H_5SO_2CH_2CN + ArCHO \xrightarrow{CH_3COONH_4}$$

$$C_6H_5SO_2C(CN)=CHAr + H_2O$$

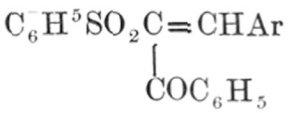
Tröger and his co-workers[79, 80] investigated the condensation of arylsulphonylacetonitriles with aromatic aldehydes and synthesised a number of unsaturated sulphones. They used a trace of alkali as the condensing agent. Exceptionally good yields of the unsaturated sulphone were got by the author in the reaction of phenylsulphonylacetonitrile with aromatic aldehydes in presence of ammonium acetate. The reaction occurs either in glacial acetic acid or in 95% ethanol. Ethanol was, however,

found to be a better solvent. As soon as the reactants were mixed in ethanol, the product began to separate out in the cold itself as a crystalline mass. The mixture was heated for a few minutes to complete the reaction.

Although phenylsulphonylacetonitrile condenses with aromatic aldehydes with such ease it failed to react with aliphatic aldehydes. The reaction was attempted with paraformaldehyde, isobutyraldehyde, n-butyraldehyde and chloral. In all these cases the sulphonylacetonitrile was recovered unchanged. Even long hours of refluxing did not prove helpful.

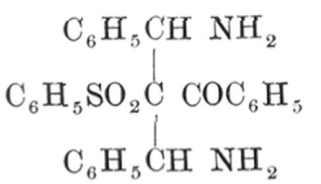
Eventhough a keto group alone can sufficiently activate an adjacent methylene group to cause the Mannich reaction, the behaviour of ω-phenylsulphonylacetophenone was studied to find out the influence of the sulphonyl group on the course of the reaction. ω-Phenylsulphonylacetophenone was prepared by the condensation of ω-bromoacetophenone with sodium benzenesulphinate in ethanolic solution. Tröger and Beck[109] obtained it from a mixture of ω-chloroacetophenone and sodium benzenesulphinate.

In the reaction of ω-phenylsulphonylacetophenone with aromatic aldehydes and ammonium acetate, interesting results were obtained. When glacial acetic acid was used as a solvent in the reaction, the unsaturated sulphone (XLVI) was the only product that could be isolated but, when absolute ethanol was

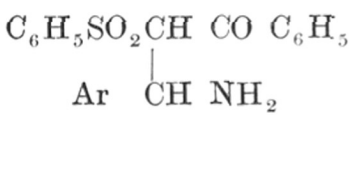


(XLVI)

used as a solvent, basic products were also formed with certain aldehydes, in addition to unsaturated sulphones. For example, benzaldehyde, p-chlorobenzaldehyde and m-nitrobenzaldehyde yielded basic products. The other aldehydes gave only the un-



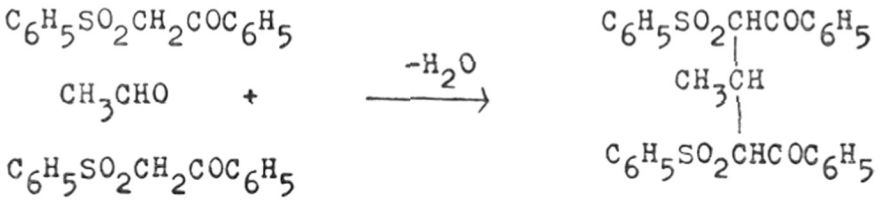
(XLVI a)



(XLVI b)

saturated compounds. The basic compound obtained from benzaldehyde was identified to be the diamine (XLVIa). p-Chlorobenzaldehyde and m-nitrobenzaldehyde yielded the normal Mannich bases (XLVIb).

ω-Phenylsulphonylacetophenone did not condense with ammonium acetate and aliphatic aldehydes, such as, formaldehyde, isobutyraldehyde and chloral. When acetaldehyde-ammonia was used in the reaction, it reacted in a way quite different from the other aldehydes. A neutral, saturated sulphone was the product. It did not contain nitrogen. Analytical data suggest that it may have structure (XLVII). Such a product can result by the condensation of two molecules of the β-keto sulphone with one molecule of acetaldehyde.



(XLVII)

The various observations made on the condensations of arylsulphonylacetic acids and their derivatives with aldehydes and amines are of great value in understanding the mechanism of the Mannich and Knoevenagel reactions. Any acceptable mechanism should be in accordance with the following facts:

(*a*) Both the β-amino sulphone and the α, β-unsaturated sulphone are formed only when the aldehyde used is an aromatic aldehyde and the amine used is either ammonia or an aliphatic primary amine.

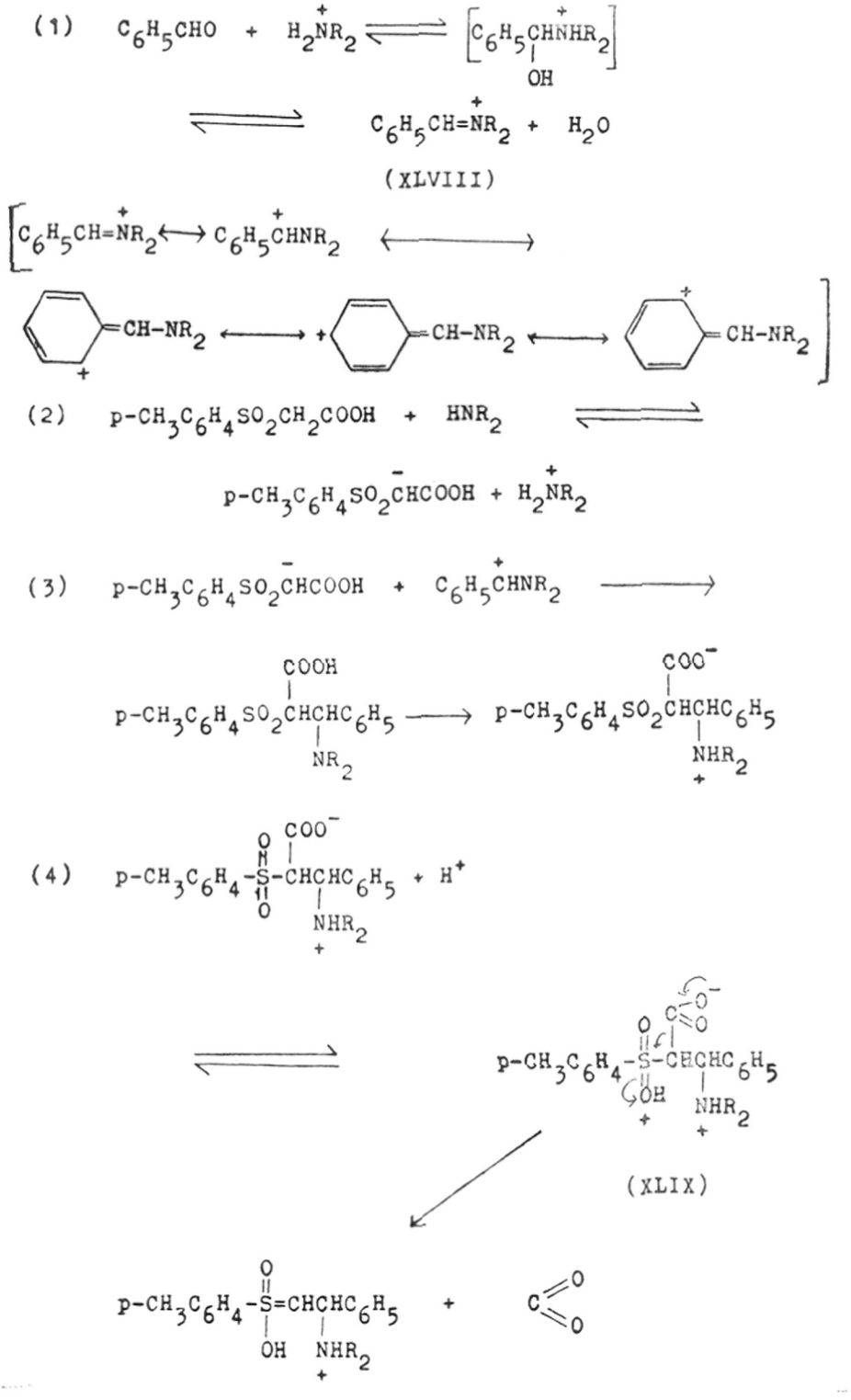
(*b*) No reaction occurs when an aliphatic aldehyde is used.

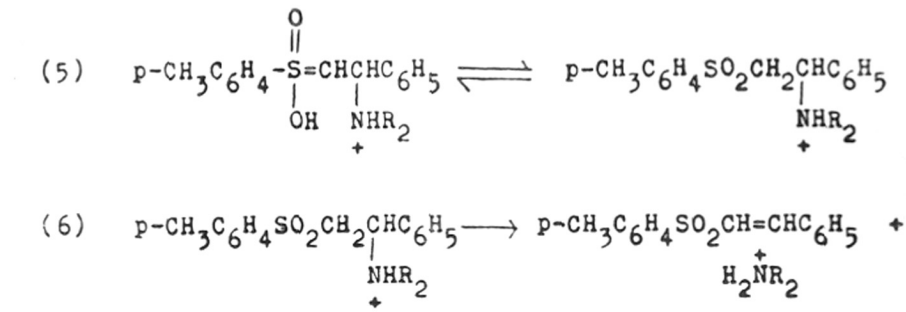
(*c*) The use of a secondary amine yields α,β-unsaturated sulphone but not the Mannich base.

(*d*) When a tertiary amine is used, no condensation occurs. (If the role of the base in the Knoevenagel reaction is only to accept the proton from the reactive methylene group and not to form intermediates with the reactants, a tertiary amine acetate should also be expected to cause the Knoevenagel condensation just like ammonium acetate or piperidine acetate.)

(*e*) The use of arylsulphonylacetic esters and arylsulphonylacetonitriles in place of arylsulphonylacetic acids results in the formation of α,β-unsaturated sulphones but not β-amino sulphones.

Taking the foregoing facts into consideration the following mechanism is suggested for the Mannich and Knoevenagel reactions occurring with p-tolylsulphonylacetic acid, benzaldehyde and an amine acetate.





In step (1) the formation of the iminium ion (XLVIII) is assumed. Though a tertiary amine cannot take part in the Mannich condensation, it should be able to bring about the Knoevenagel condensation. The fact that tertiary amines failed to cause the Knoevenagel condensation substantiates step (1). The recent kinetic studies of Crowell and Peck[110] also support the formation of a compound of the type (XLVIII) as an intermediate in the Knoevenagel condensation. The striking difference between aromatic and aliphatic aldehydes in their ability to undergo the Knoevenagel condensation also supports this step; the iminium ion formation, postulated in this step, is fecilitated by resonance stabilisation of the ion. Only two structures will be involved in resonance when an aliphatic aldehyde is used in the reaction. Steps (2) and (3) do not need any special comment. The decarboxylation of the β-sulphonyl acid, as shown in step (4), is in accordance with the mechanism given for the decarboxylation of β-ketonic acids by Pedersen[111] and of quinaldinic acid by Brown and Hammick[112]. In structure (XLIX) the sulphur-oxygen links are represented by double bonds. This is admissible according to the recent work [1-5, 13-24]. Step (6) needs no comment as the author has actually shown it to be so.

The fact that the use of a secondary amine yielded only the α,β-unsaturated sulphone and not the Mannich base needs to be explained. The Mannich base might have actually formed in the reaction but it might have decomposed due to its instability. In fact, Rodionow[113] isolated the Mannich base in the condensation of malonic acid with benzaldehyde and piperidine and he recorded that this compound looses the amine more readily than the Mannich bases derived from primary amines or ammonia.

It is thus seen that the Mannich reaction and the Knoevenagel reaction are closely related. The Mannich base is only an intermediate in the Knoevenagel reaction. Some Mannich bases readily loose the amine to form the Knoevenagel unsaturated compounds, while others are stabler. The loss of an amine molecule from the Mannich base seems to occur with extreme ease when the resulting ethylenic bond forms a conjugated system with a group like CN, COOR, COOH or NO_2. It is due to this reason that in most Knoevenagel condensations the unsaturated compound happens to be the only product.

EXPERIMENTAL

Preparation of Dialkyl Sulphides.—The procedure followed was essentially that of Klason[114]. One mole of the dry alcohol was cooled in the ice water and was esterified by the addition in small quantities, of 98.0 g. (1.0 mole) of 100% sulphuric acid. The mixture was left overnight and then neutralised with a saturated solution of sodium carbonate, using ice water for cooling. A solution of potassium sulphide was prepared by dissolving 56.0 g. (1.0 mole) of potassium hydroxide in 112 cc. of water, saturating half of this solution with hydrogen sulphide and then mixing with the other half. Meanwhile, the solution of sodium alkyl sulphate prepared previously was concentrated to a volume of about 100 cc, allowed to cool and mixed with the solution of potassium sulphide. The mixture was left overnight, heated under reflux for 1 hour and then distilled with steam. The dialkyl sulphide that collected was extracted with ether and the solution was dried over calcium chloride. After removal of ether the sulphide was distilled. The data concerning the sulphides prepared are given in the following Table:

Dialkyl Sulphides, RSR

No.	R	Yield. %	B. p., °C
1	C_2H_5	26	90-92
2	n-C_3H_7	28	141-142
3	n-C_4H_9	34	180-182

Preparation of Dialkyl Sulphones.—One volume of dialkyl sulphide was dissolved in 10 volumes of glacial acetic acid and to the cooled solution a 30% solution of hydrogen peroxide (50% excess of the theoretical quantity) was gradually added. The oxidation occurred with evolution of heat. The mixture was left in ice water for 1 hour and then it was heated on a water bath for 2 hours. The solution was evaporated on a water bath to remove the solvents. The sulphone was left as a residue which was recrystallised from a suitable solvent. Details regarding the sulphones prepared are given below:

Dialkyl Sulphones, RSO_2R

No.	R	Yield, %	Solvent for crystallisation	M. p., °C
1	CH_3	77	Ethanol	108–109
2	C_2H_5	89	Ethanol	72– 73
3	n-C_3H_7	82	—	oil
4	n-C_4H_9	98	Water	43–44

Bis-(phenylsulphonyl)-methane.—It was prepared by the method of Shriner and his co-workers[9]. In 40 cc. of absolute ethanol, 2.30 g. (0.1 mole) of sodium cut into small pieces, was dissolved. To this solution 11.0 g. (0.1 mole) of thiophenol was added in a slow stream, with continuous shaking. The mixture was brought to reflux on a water bath and 13.40 g. (0.05 mole) of methylene iodide was added drop by drop during the course of 45 minutes. After the addition was over, the mixture was refluxed for 2 more hours and poured into crushed ice with stirring. The solid that separated was collected and dried. The crude bis-(phenylthio)-methane, melting at 34-36°, weighed 11.30 g. (97%).

In a mixture of 150 cc. of glacial acetic acid and 40 cc. of acetic anhydride 10.0 g. (0.043 mole) of bis-(phenylthio)-methane was dissolved. The solution was cooled in ice water and 25 cc. of hydrogen peroxide (30%) was added gradually. The mixture was kept at 15° for 2 hours and then at room temperature for 36 hours. Dilution with 500 cc. of ice water gave bis-(phenylsulphonyl)-methane in an almost pure form. It was collected at the pump and washed with water. The product melted at 119-121° and weighed 11.20 g. (88%). Recrystallisation from ethanol gave shining needles melting at 120-121°.

Bis-(phenylsulphonyl)-phenylthiomethane.—In 40 cc. of absolute ethanol 0.40 g. (0.018 mole) of sodium was dissolved. To this solution was added 4.20 g. (0.014 mole) of bis-(phenylsulphonyl)-methane when the sodium salt of the disulphone separated out as a white solid. Next, 3.60 g. (0.014 mole) of phenyl benezenethiolsulphonate (prepared by oxidation of diphenyl disulphide in glacial acetic acid with hydrogen peroxide (3%) by the method of Hinsberg[115]) was added and the whole was heated under reflux for 6 hours on a water bath. The resulting mixture was poured into 150 cc. of water and made alkaline with a 10% solution of sodium hydroxide. After removing the alkali-insoluble matter by extraction with ether, the aqueous solution was acidified with dilute hydrochloric acid. The

crystals that separated were collected, washed first with water and then with ethanol. The product, after recrystallising twice from glacial acetic acid, weighed 3.80 g. (66%) and melted at 177.5-178.5° (Laves[116] records m.p. 176°).

Tris-(phenylsulphonyl)-methane.—Three grams (0.0074 mole) of bis-(phenylsulphonyl)-phenylthiomethane were dissolved in 50 c.c. of hot glacial acetic acid, treated with 2.5 c.c. of hydrogen peroxide (30%) and heated on a boiling water bath for 2 hours. On cooling, crystals of tris-(phenylsulphonyl)-methane separated. The crystals were removed by filtration and washed with water. The filtrate, on dilution with water, yielded more of the tri-sulphone. The total yield was 2.10 g. (64%). The compound, after recrystallisation from glacial acetic acid, melted at 215-217° (Laves gives[117] m.p. 215°).

Benzyl phenyl sulphone.—This was prepared by the method of Shriner and his co-workers[9]. A solution of 12.70 g. (0.1 mole) of benzyl chloride in 50 c.c. of absolute ethanol was mixed with 17.80 g. (0.1 mole) of sodium benzenesulphinate. The mixture was refluxed on a water bath for 8 hours and then poured into 150 c.c. of water with stirring. The product that separated was collected and dried at 100°. The crude product weighed 18.50 g. (76%) and melted at 146-147.5°. Recrystallisation from ethanol gave white needles melting at 147-148°.

p-Tolylsulphonylacetic Acid.—The procedure followed was essentially that of Gabriel[103]. The sodium p-toluenesulphinate used in the reaction was prepared by the reduction of p-toluenesulphonyl chloride with zinc dust and water. In 200 c.c. of water, 107 g. (0.5 mole) of recrystallised sodium p-toluenesulphinate dihydrate and 57 g. (0.6 mole) of chloroacetic acid were dissolved. The mixture was made just alkaline with a 50% solution of sodium hydroxide. The solution was heated over a boiling water bath for 2 hours, cooled and extracted twice with 75 c.c. portions of benzene. The combined benzene extracts, after drying with calcium chloride and distilling off the benzene, yielded 6.30 g. (7% based on the weight of sodium p-toluenesulphinate used) of methyl p-tolyl sulphone. The aqueous solution was acidified with dilute hydrochloric acid (congo red paper used), when crystals of p-tolylsulphonylacetic acid began to separate. The mixture was left overnight in the refrigerator to complete the separation of the compound. The product was collected at the pump, washed with water and dried. The yield was 72 g. (67% based on the weight of sodium p-toluenesulphinate). It melted at 116-117° after recrystallising from benzene.

Phenylsulphonylacetic Acid.—A solution of 100 g. (0.61 mole) of sodium benzenesulphinate and 63.5 g. (0.67 mole) of chloroacetic acid in 75 c.c. of water was made just alkaline with a 50% solution of sodium hydroxide. After refluxing over a boiling water bath for 2 hours, the contents of the flask were transferred into a china-dish and most of the water was evaporated off. The residue was extracted twice with 100 c.c. portions of benzene. From the combined benzene extracts 9.0 g (9%) of methyl phenyl sulphone was obtained after removal of the solvent by distillation. The residual sodium salts were made acidic with strong hydrochloric acid and the mixture was extracted with ether thrice, using 100 c.c. of the solvent each time. The combined ether extracts were dried over anhydrous magnesium sulphate. Removal of ether yielded an oil which gradually set to a solid, when kept in the refrigerator for 2 days. The yield was 65 g. (54% calculated on the weight of sodium benzenesulphinate). The compound melted at 111-112°.

α-Phenyl-β p-tolylsulphonylethylamine Hydrochloride.—A mixture of 21.40 g. (0.1 mole) of p-tolylsulphonylacetic acid, 10.60 g. (0.1 mole) of benzaldehyde, 7.70 g. (0.1 mole) of ammonium acetate and 20 c.c. of glacial acetic acid was heated under reflux on a hot plate. In a few minutes there was brisk evolution of carbon dioxide. The heating was continued with occasional swirling for 20 minutes; at the end of this period the evolution of carbon dioxide practically ceased. The clear yellow solution thus obtained, when allowed to cool, separated into two layers. A mixture of 100 c.c. of ether and 100 c.c. of benzene was added, shaken well and allowed to stand for 1 hour. A small quantity of a viscous layer containing mostly unreacted ammonium salts settled at the bottom. The clear ether layer was separated and treated with dry hydrogen chloride. Excess of hydrogen chloride was avoided as it tended to colour the product brown. Colourless, almost pure hydrochloride of α-phenyl-β-p-tolylsulphonylethylamine separated. The mixture, after dilution with 200 c.c. of ether, was left aside for 2 days during which time more of the hydrochloride separated in fine needles. The product was collected at the pump and the filtrate preserved (filtrate A). The residue was washed with ether and then with acetone. It weighed 7.0 g. (23%). The compound was recrystallised by dissolving in absolute ethanol, filtering the solution and adding ether to the filtrate until a turbidity appeared when colourless needles began to separate. The compound melted at 204-206°.

Anal. Calcd. for $C_{15}H_{18}O_2NClS$: C, 57.8; H, 5.8; Cl^-, 11.4. Found : C, 58.1; H, 5.6; Cl^-, 11.3.

α-Phenyl-β-p-tolylsulphonylethylene.—Filtrate A of the above preparation was allowed to evaporate over a water bath.

An oily residue, which was left, gradually deposited fine needles. The mixture was agitated with 15 c.c. of methanol and allowed to stand for 15 minutes to complete the separation of the crystals. The crystals were collected and washed with 10 c.c. of methanol. The colourless product melted at 119-121° and weighed 6.50 g. (25%). Recrystallisation from methanol yielded colourless shining needles, m.p. 120.5-121°.

Anal. Calcd. for $C_{15}H_{14}O_2S$: C, 69.8; H, 5.4. Found : C, 69.8; H, 5.4.

α-3, 4-*Methylenedioxyphenyl-β-p-tolylsulphonylethylamine Hydrochloride.*-A mixture of 4.28 g. (0.02 mole) of p-tolylsulphonylacetic acid, 3.0 g. (0.02 mole) of piperonal, 1.54 g. (0.02 mole) of ammonium acetate and 2 c.c. of glacial acetic acid was heated gently under reflux. There was brisk evolution of carbon dioxide. The heating was stopped after 5 minutes when the contents of the flask became turbid due to the separation of a second phase. After allowing to cool, 50 c.c. of ether was added to the mixture and was shaken well. The flask was left aside for 1 hour. The clear ethereal solution was mixed with 20 c.c. of ether saturated with dry hydrogen chloride. The separated hydrochloride was removed by filtration and washed successively with ether and acetone. The hydrochloride weighed 1.52 g. (22%). Recrystallisation from absolute ethanol-ether mixture gave colourless needles melting at 213-214° with decomposition.

Anal. Calcd. for $C_{16}H_{18}O_4NSCl$: C, 54.0; H, 5.0; Cl^-, 10.0. Found : C, 53.8; H, 5 1; Cl^-, 10.1.

α-3, 4-*Methylenedioxyphenyl-β-p-tolylsulphonylethylene.*— The filtrate got after separation of the above hydrochloride was transferred into a china-dish and the ether was allowed to evaporate. An oil was left which gradually set to a yellow solid. Crystallisation from methanol yielded 0.90 g. (15%) of colourless needles melting at 113-114.5°. One more recrystallisation from methanol gave the analytical sample, m.p. 114-114.5°.

Anal. Calcd. for $C_{16}H_{14}O_4S$: C, 63.6; H, 4.6. Found : C, 63.6; H, 4.5.

α-4-*Methoxyphenyl-β-p-tolylsulphonylethylamine Hydrochloride.*—For the preparation of this compound, heating the reaction mixture on a steam bath was found to be more advantageous than heating directly over a flame or a hot plate. In this way better yields were got.

A mixture of 4.28 g. (0.02 mole) of p-tolylsulphonylacetic acid, 2.72 g. (0.02 mole) of anisaldehyde, 1.54 g. (0.02 mole) of ammonium acetate and 2 c.c. of glacial acetic acid was refluxed on a steam bath for 1 hour. There was only a slow evolution

of carbon dioxide and the solution gradually became coloured deep yellow. The mixture was left aside for 4 days. At the end of this period, it was shaken with 40 c.c. of dry ether and left aside for 1 hour. The clear ethereal solution was separated and treated with sufficient quantity of ether saturated with dry hydrogen chloride. The precipitated hydrochloride was in a semi-solid state initially but changed into a crystalline mass during the course of 24 hours. It was separated by filtration and washed with ether. The yield was 1.30 g. (19%). Recrystallisation from absolute ethanol gave colourless needles, m.p. 231-232°.

Anal. Calcd. for $C_{16}H_{20}O_3NClS$: C, 56.2; H, 5.8; Cl^-, 10.4. Found : C, 56.0; H, 6.1; Cl^-, 10.6.

α-4-*Methoxyphenyl-β-p-tolylsulphonylethylene.*—The ether from the filtrate, got after removal of the hydrochloride in the above preparation, was evaporated off and the resulting oily residue was shaken with 20 c.c. of methanol, when slowly crystals separated out. The product, when recrystallised from methanol, yielded 0.80 g. (12%) of colourless shining needles. The compound softened at 88° and melted at 100°.

Anal. Calcd. for $C_{16}H_{16}O_3S$: C, 66.7; H, 5.6. Found : C, 66.4; H, 5.6.

α-2-*Methoxyphenyl-β-p-tolylsulphonylethylamine Hydrochloride.*—A solution of 428 g. (0.02 mole) of p-tolylsulphonylacetic acid, 2.72 g. (0.02 mole) of o-methoxybenzaldehyde and 1.54 g. (0.02 mole) of ammonium acetate in 4 c.c. of glacial acetic acid was heated over a hot plate for 5 minutes. The resulting red solution was extracted with 40 c.c. of ether. The ethereal solution was saturated with hydrogen chloride. Initially the solution remained clear but fine needles of the hydrochloride separated gradually. After setting aside for 2 days the compound was collected on a filter and washed with ether. The yield was 1.30 g. (19%). It was obtained as colourless shining needles from ethanol-ether, m.p. 220-222°.

Anal. Calcd. for $C_{16}H_{20}O_3NClS$: C, 56.2; H, 5.8; Cl^-, 10.4. Found : C, 56.1; H, 6.0; Cl^-, 10.6.

α-2-*Methoxyphenyl-β-p-tolylsulphonylethylene.*—The ether was allowed to evaporate off from the filtrate got in the above experiment. This left a yellow oil, to which 15 c.c. of methanol was added, agitated well and the mixture cooled in ice. The crystals thus obtained were collected at the pump and washed with 10 c.c. of 50% methanol. The yield was 1.31 g. (23%). Recrystallisation from methanol gave glistening needles; m.p. 81-82°.

Anal. Calcd. for $C_{16}H_{16}O_3S$: C, 66.7; H, 5.6. Found : C, 66.8; H, 5.6.

α-2-*Nitrophenyl-β-p-tolylsulphonylethylamine. Hydrochloride.*—Refluxing a mixture of 4.28 g. (0.02 mole) of p-tolylsulphonylacetic acid, 3.02 g. (0.02 mole) of o-nitrobenzaldehyde and 1.54 g. (0.02 mole) of ammonium acetate in 4 c.c. of glacial acetic acid for 10 minutes gave a deep red solution. After allowing to cool, the solution was extracted with 75 c.c. of ether and the ethereal solution was saturated with hydrogen chloride. Next day the precipitated hydrochloride was removed by filtration and washed with ether and then with acetone. The yield was 1.30 g. (18%). On recrystallising from ethanol, light yellow needles were obtained; m.p. 237-239° with decomposition.

Anal. Calcd. for $C_{15}H_{17}O_4N_2ClS$: C, 50.5; H, 4.8; Cl^-, 10.0. Found : C, 50.2; H, 5.1; Cl^-, 10.0.

α-2-*Nitrophenyl-β-p-tolylsulphonylethylene.*—Removal of ether by evaporation from the filtrate got above yielded a crystalline residue which, after washing with 10 c.c. of methanol and drying, weighed 0.30 g. (5%). The sulphone was obtained as pale yellow needles from methanol, m.p. 158.5-160°.

Anal. Calcd. for $C_{15}H_{13}O_4NS$: C, 59.4; H, 4.3. Found : C, 59.3; H, 4.5.

α-3-*Nitrophenyl-β-p-tolylsulphonylethylamine Hydrochloride.*—A solution of 2.14 g. (0.01 mole) of p-tolylsulphonylacetic acid, 1.51 g. (0.01 mole) of m-nitrobenzaldehyde and 0.77 g. (0.01 mole) of ammonium acetate in 2 c.c. of glacial acetic acid was refluxed for 10 minutes. The mixture, after cooling, was shaken with 30 c.c. of ether and left aside overnight. The unsaturated sulphone separated as fine needles. It was filtered and the hydrochloride was precipitated from the filtrate as usual by passing hydrogen chloride. After a day, the product was collected, washed with ether and acetone and dried. The yield was 0.90 g. (25%). Colourless needles, melting at 219-220°, were got from ethanol-acetone mixture.

Anal. Calcd. for $C_{15}H_{17}O_4N_2ClS$: Cl^-, 10.0. Found : Cl^-, 10.3.

α-3-*Nitrophenyl-β-p-tolylsulphonylethylamine.*—The above hydrochloride was dissolved in ethanol and the solution was made alkaline with aqueous ammonia. Dilution with water precipitated the base which was crystallised from methanol. Yellow needles, melting at 97-98°, were obtained.

Anal. Calcd. for $C_{15}H_{16}O_4N_2S$: C, 56.3; H, 5.0. Found : C, 56.3; H, 4.9.

α-3-*Nitrophenyl-β-p-tolylsulphonylethylene.* — The ethereal solution obtained after removal of the hydrochloride was

allowed to evaporate. It left a residue which was washed with methanol and combined with the bulk of the unsaturated sulphone that was got before precipitation of the hydrochloride. Recrystallisation from ethanol gave 0.62 g. (20%) of pale yellow needles melting at 146-147°.

Anal. Calcd. for $C_{15}H_{13}O_4NS$: C, 59.4; H, 4.3. Found : C, 59.3; H, 4.3.

α-4-Chlorophenyl-β-p-tolylsulphonylethylamine Hydrochloride.—To 5 c.c. of glacial acetic acid were added 4.28 g. (0.02 mole) of p-tolylsulphonylacetic acid, 2.80 g. (0.02 mole) of p-chlorobenzaldehyde and 1.54 g. (0.02 mole) of ammonium acetate and the mixture was heated under reflux for 15 minutes. After cooling, it was dissolved in 50 c.c. of ether, saturated with hydrogen chloride and left aside overnight. The precipitated hydrochloride was washed first with ether and then with a small quantity of water. The yield was 1.28 g. (19%). Recrystallisation from ethanol-ether gave colourless shining needles, m.p. 206-209°.

Anal. Calcd. for $C_{15}H_{17}O_2NCl_2S$: C, 51.9; H, 4.9; Cl^-, 10.2. Found : C, 52.1; H, 5.2; Cl^-, 10.2.

α-4-Chlorophenyl-β-p-tolylsulphonylethylene.—It was obtained as usual from the filtrate got after separation of the hydrochloride. The yield was 1.82 g. (31%). Recrystallisation from methanol gave shining needles, melting at 151-153°.

Anal. Calcd. for $C_{15}H_{13}O_2ClS$: C, 61.6; H, 4.4. Found : C, 61.6; H, 4.5.

α-p-Tolyl-β-p-tolylsulphonylethylamine Hydrochloride.—Using 4.28 g. (0.02 mole) of p-tolylsulphonylacetic acid, 2.40 g. (0.02 mole) of p-toluic aldehyde, 1.54 g. (0.02 mole) of ammonium acetate and 5 c.c. of glacial acetic acid, the condensation was effected as in the case of the 4-chloro derivative. The yield of the hydrochloride was 1.63 g. (25%). Recrystallisation from ethanol-ether gave colourless needles, m.p. 195-197.5°.

Anal. Calcd. for $C_{16}H_{20}O_2NClS$: C, 59.0; H, 6.1; Cl^-, 10.9. Found : C, 59.0; H, 6.3; Cl^-, 11.1.

α-p-Tolyl-β-p-tolylsulphonylethylene.—It was obtained in 22% yield (1.20 g.) during the preparation of the above compound. The usual procedure was adopted for its isolation. On recrystallising from methanol, colourless needles melting at 154-155° were obtained.

Anal. Calcd. for $C_{16}H_{16}O_2S$: C, 70.6; H, 5.9. Found : C, 70.4; H, 5.6.

α-2-Thienyl-β-p-tolylsulphonylethylamine Hydrochloride.—A mixture of 2.14 g. (0.01 mole) of p-tolylsulphonylacetic acid, 1.12 g. (0.01 mole) of thiophene-2-aldehyde, and 0.77 g. (0.01 mole) of ammonium acetate in 3 c.c. of glacial acetic acid was refluxed gently for 15 minutes. The resulting greenish-yellow solution was extracted with 40 c.c. of ether and saturated with hydrogen chloride. No hydrochloride was obtained immediately. More ether (40 c.c.) was added to the solution and allowed to stand overnight. The crystals formed were removed and washed with ether and acetone. The yield was 0.48 g. (15%). Recrystallisation from a mixture of absolute ethanol and ether gave colourless shining plates, m.p. 196.5-198.5° with decomposition.

Anal. Calcd. for $C_{13}H_{16}O_2NClS_2$: C, 49.1; H, 5.0; Cl^-, 11.2. Found : C, 49.4; H, 5.3; Cl^-, 11.2.

α-2-Thienyl-β-p-tolylsulphonylethylene.—The ethereal filtrate from the above experiment was worked up as usual. It gave 0.52 g. (20%) of the unsaturated sulphone; shining needles from methanol, m.p. 132.5-133.5°.

Anal. Calcd. for $C_{13}H_{12}O_2S_2$: C, 59.1; H, 4.6. Found : C, 59.4; H, 4.7.

N-Alkyl-α-aryl-β-p-tolylsulphonylethylamine Hydrochlorides.—Several aliphatic primary amines were condensed with p-tolylsulphonylacetic acid and aromatic aldehydes in the usual way. In each case the Mannich base as well as the α,β-unsaturated sulphone was obtained. The analytical data and other details regarding the compounds obtained are recorded in Table 7 (next page). Since the unsaturated sulphones formed in these condensations are same as the ones obtained when ammonium acetate was used, the table gives only their yields. Other relevent information about them has already been given.

α-Aryl-β-phenylsulphonylethylamine Hydrochlorides.—Phenylsulphonylacetic acid was condensed with different aromatic aldehydes and ammonium acetate. It was also condensed with benzaldehyde and benzylamine. The procedure followed was exactly the same as that used for similar condensations with p-tolylsulphonylacetic acid. The relevant data concerning the compounds obtained are recorded in Table 8 (page 49).

α-Aryl-β-phenylsulphonylethylenes.—These compounds were obtained when phenylsulphonylacetic acid was condensed with aromatic aldehydes and ammonium acetate. The usual procedure was adopted for their isolation. Table 9 (page 50) records the data concerning them.

TABLE 7.

N–Alkyl–α–aryl–β–p–tolylsulphonylethylamine Hydrochlorides.
p–$CH_3C_6H_4SO_2CH_2CH$ (Ar) NHR, HCl

No	R	Ar	M.p., °C	Yield,* %	Formula	Carbon, %		Hydrogen, %		Chlorine, % (ionic)	
						Calcd.	Found	Calcd.	Found	Calcd.	Found
1	CH_3	C_6H_5	185–188	8 (35)	$C_{16}H_{20}O_2NClS$	59.0	58.8	6.1	5.7	10.9	10.8
2	CH_3	3–$O_2NC_6H_4$	203–205	30 (48)	$C_{16}H_{19}O_4N_2ClS$	–	–	–	–	9.6	9.4
3	C_2H_5	C_6H_5	199–200	21 (54)	$C_{17}H_{22}O_2NClS$	60.1	60.1	6.5	6.7	10.4	10.6
4	C_2H_5	3–$O_2NC_6H_4$	208–210	23 (41)	$C_{17}H_{21}O_4N_2ClS$	53.1	53.0	5.5	5.8	9.2	9.0
5	Allyl	C_6H_5	177–178.5	13 (43)	$C_{18}H_{22}O_2NClS$	61.5	61.5	6.3	6.3	10.1	10.4
6	Allyl	3–$O_2NC_6H_4$	210–213	33 (62)	$C_{18}H_{21}O_4N_2ClS$	54.5	54.5	5.3	4.9	8.9	9.1
7	n–C_4H_9	C_6H_5	185–188	9 (60)	$C_{19}H_{26}O_2NClS$	62.0	61.9	7.1	7.1	9.6	9.9
8	n–C_4H_9	3–$O_2NC_6H_4$	195–198	14 (70)	$C_{19}H_{25}O_4N_2ClS$	55.3	55.5	6.1	6.2	8.6	8.6
9	n–C_8H_{17}	C_6H_5	169–171	11 (61)	$C_{23}H_{34}O_2NClS$	65.2	65.0	8.0	8.3	8.4	8.4
10	n–C_8H_{17}	3–$O_2NC_6H_4$	197–199	19 (53)	$C_{23}H_{33}O_4N_2ClS$	58.9	58.7	7.0	6.6	7.6	7.6
11	$C_6H_5CH_2$	C_6H_5	194–195.5	36 (64)	$C_{22}H_{24}O_2NClS$	65.8	65.6	6.0	6.2	8.8	8.9
12	$C_6H_5CH_2$	3–$O_2NC_6H_4$	207–209.5	10 (56)	$C_{22}H_{23}O_4N_2ClS$	59.1	59.2	5.2	5.2	7.9	8.0
13	$C_6H_5CH_2$	3,4–(CH_2O_2):C_6H_3	205–206	27 (30)	$C_{23}H_{24}O_4NClS$	61.9	61.8	5.4	5.4	8.0	8.3

* The percentage yields within the brackets are those of the α, β–unsaturated sulphones. The base corresponding to No. 2 was obtained by the treatment of the hydrochloride with aqueous ammonia in ethanol; m.p. 108.5–109.5° (prisms from methanol). *Anal.* Calcd. for $C_{16}H_{18}O_4N_2S$: C, 57.5; H, 5.4. Found: C, 57.4; H, 5.4.

TABLE 8.

α-Aryl-β-phenylsulphonylethylamine Hydrochlorides.

$C_6H_5SO_2CH_2CH(Ar)NH_2,HCl$

No	Ar	M.p., °C	Yield, %	Formula	Cabon, %		Hyderogen, %		Chlorine, % (ionic)	
					Calcd.	Found	Calcd.	Found	Calcd.	Found
1	C_6H_5	190–193	27	$C_{14}H_{16}O_2NClS$	56.6	56.2	5.4	5.7	11.9	12.0
2	3,4-$(CH_2O_2):C_6H_3$	213–215(d)	30	$C_{15}H_{16}O_4NClS$	52.7	52.6	4.7	5.1	10.4	10.4
3	2-$H_3COC_6H_4$	211–213	20	$C_{15}H_{18}O_3NClS$	55.0	54.6	5.5	5.6	10.8	10.8
4	4-ClC_6H_4	213–215	24	$C_{14}H_{15}O_2NCl_2S$	50.6	50.6	4.5	4.3	10.7	10.7
5	2-$O_2NC_6H_4$	225–228(d)	7	$C_{14}H_{15}O_4N_2ClS$	49.1	49.4	4.4	4.5	10.4	10.4
6	3-$O_2NC_6H_4$	217–219	21	$C_{14}H_{15}O_4N_2ClS$	49.1	48.8	4.4	4.6	10.4	10.2
7	2-Thienyl	210–212(d)	14	$C_{12}H_{14}O_2NClS_2$	47.5	47.6	4.6	4.9	11.7	12.0

(d) With decomposition. All the compounds were recrystallised from ethanol-ether.

TABLE 9.

α-Aryl-β-phenylsulphonylethylenes, $C_6H_5SO_2CH{=}CHAr$.

No	Ar	M.p., °C	Yield, %	Formula	Carbon, %		Hydrogen, %	
					Calcd.	Found	Calcd.	Found
1	C_6H_5	74–74.5	21	$C_{14}H_{12}O_2S$[a]	68.9	68.7	4.9	4.6
2	$3,4\text{-}(CH_2O_2) : C_6H_3$	107–108	19	$C_{15}H_{12}O_4S$[b]	62.5	62.5	4.2	4.5
3	$2\text{-}H_3COC_6H_4$	93–94	28	$C_{15}H_{14}O_3S$[c]	65.7	65.6	5.1	4.9
4	$4\text{-}ClC_6H_4$	129.5–130	28	$C_{14}H_{11}O_2ClS$[c]	60.3	60.3	4.0	4.2
5	$2\text{-}O_2NC_6H_4$	130–132	10	$C_{14}H_{11}O_4NS$[d]	58.1	58.4	3.8	3.8
6	$3\text{-}O_2NC_6H_4$	145–146	14	$C_{14}H_{11}O_4NS$[c]	58.1	57.8	3.8	4.1
7	$4\text{-}H_3CC_6H_4$	135.5–136.5	17	$C_{15}H_{14}O_2S$[c]	69.8	70.1	5.4	5.6

Recrystallised from [a] dimethylcarbinol, [b] methanol, [c] ethanol and [d] acetone.

α-Phenyl-β-phenylsulphonyl-N-benzylethylamine Hydrochloride.—A solution of 1.07 g. (0.01 mole) of benzylamine in 2 c.c. of glacial acetic acid was mixed with 2.0 g. (0.01 mole) of phenylsulphonylacetic acid and 1.06 g. (0.01 mole) of benzaldehyde and refluxed for 10 minutes. Extracting the product with 40 c.c. of ether and saturating the ethereal extract with hydrogen chloride gave 0.40 g. (10%) of the hydrochloride. (The filtrate yielded 0.65 g. (27%) of α-phenyl-β-phenylsulphonylethylene). After recrystallising from ethanol-ether, the hydrochloride melted at 179-181°.

Anal. Calcd. for $C_{21}H_{22}O_2NClS$: C, 65.0; H, 5.7; Cl^-, 9.2. Found : C, 64.9; H, 5.5; Cl^-, 9.4.

3,3,3-*Trichloro-2-hydroxypropyl p-Tolyl Sulphone.*—A mixture of 4.28 g. (0.02 mole) of p-tolylsulphonylacetic acid, 2.86 g. (0.02 mole) of anhydrous chloral, 1.54 g. (0.02 mole) of ammonium acetate and 4 c.c. of glacial acetic acid was heated under reflux for 30 minutes. The resulting brown solution was dissolved in 60 c.c. of ether and saturated with hydrogen chloride. The ammonium chloride that separated was filtered off. Evaporation of the ether from the filtrate gave a liquid which gradually yielded crystals of the sulphone. Recrystallisation of it from benzene gave colourless rhombic crystals, weighing 0.72 g. (11%); m.p. 127-129°.

Anal. Calcd. for $C_{10}H_{11}O_3Cl_3S$: C, 37.8; H, 3.5. Found : C, 37.9; H, 3.3.

The Effect of Solvent on the Yield of β-Amino Sulphone and α, β -Unsaturated Sulphone.—

(*a*) Use of Pyridine as Solvent.

A mixture of 2.14 g. (0.01 mole) of p-tolylsulphonylacetic acid, 1.06 g. (0.01 mole) of bentaldehyde, 0.77 g. (0.01 mole) of ammonium acetate, and 5 c.c. of pyridine was refluxed gently for 20 minutes. Within 10 minutes of heating the clear solution changed into a turbid, viscous mass. The mixture was poured into crushed ice with stirring when a semi-solid was obtained. It was extracted with 30 c.c. of ether and the ethereal solution was washed several times with water and dried over anhydrous magnesium sulphate. The solution was saturated with hydrogen chloride and allowed to stand overnight. The colourless needles that separated were collected at the pump and washed with ether. The yield of α-phenyl-β-p-tolylsulphonylethylamine hydrochloride was 0.60 g. (19%); m.p. 204-206°.

The ethereal filtrate gave 1.14 g. (40%) of α-phenyl-β-p-tolylsulphonylethylene; m.p. 119-120°. (Compare the yield reported on page 43).

(*b*) Use of Ethanol as Solvent.

In 2.5 c.c. of absolute ethanol were dissolved 1.0 g. (0.0047 mole) of p-tolylsulphonylacetic acid, 0.50 g. (0.0047 mole) of benzaldehyde and 0.50 g. (0.0047 mole) of benzylamine and the solution was refluxed for 10 minutes. After cooling, it was mixed with 30 c.c. of ether and saturated with hydrogen chloride. A mixture of benzylamine hydrochloride and α-phenyl-β-p-tolylsulphonyl-N-benzylethylamine hydrochloride was thrown out. Washing with water removed the benzylamine hydrochloride, leaving the other compound. The yield of the product was 0.12 g. (6%); m.p. 193-195°.

The yield of α-phenyl-β-p-tolylsulphonylethylene was 0.19 g. (16%).

(*c*) Use of Benzene as Solvent.

A mixture of 1.0 g. (0.0047 mole) of p-tolylsulphonylacetic acid, 0.50 g. (0.0047 mole) of benzaldehyde and 0.50 g. (0.0047 mole) of benzylamine in 3 c.c. of benzene was refluxed gently. The p-tolylsulphonylacetic acid went into solution gradually. After 20 minutes, the mixture was diluted with 30 c.c. more of benzene and saturated with hydrogen chloride. The solid was removed by filtration and washed with ether and water. The yield of α-phenyl-β-p-tolylsulphonyl-N-benzylethylamine hydrochloride was 0.10 g. (5%).

Evaporation of the filtrate gave 0.19 g. (16%) of α-phenyl-β-p-tolylsulphonylethylene.

The Condensation of p-Tolylsulphonylacetic Acid with Benzaldehyde in Presence of Piperidine Acetate.—A mixture of 2.14 g. (0.01 mole) of p-tolylsulphonylacetic acid and 1.06 g. (0.01 mole) of benzaldehyde was taken with a solution of 1 c.c. of piperidine in 5 c.c. of glacial acetic acid. After refluxing for 15 minutes, the red solution obtained was dissolved in 50 c.c. of ether and saturated with hydrogen chloride. The precipitate formed was found to be exclusively piperidine hydrochloride and hence it was filtered off. The filtrate, on evaporation of the solvent, gave a liquid. On shaking it with a small quantity of methanol, colourless needles of α-phenyl-β-p-tolylsulphonylethylene, weighing 0.52 g. (20%), were obtained.

α-p-Tolylsulphonylpropionic Acid.—A solution of 15.2 g. (0.1 mole) of α-bromopropionic acid and 21.4 g. (0.1 mole) of sodium p-toluenesulphinate in 40 c.c. of water was neutralised with a 50% solution of sodium hydroxide and heated on a water bath for 11 hours. The solution, after cooling, was extracted with 50 c.c. of ether to remove alkali-insoluble compounds. Acidifying the aqueous solution gave a yellow oil. It was extracted

with ether and dried over anhydrous magnesium sulphate. On evaporating off the ether, the sulphonyl acid was obtained as a yellow liquid. The yield was 16.70 g. (73%). Attempts to get it in a crystalline condition were not successful. Otto[106] records the m.p. of the compound, prepared by the hydrolysis of the ethyl ester, as 37°.

β-p-Tolylsulphonylpropionic Acid.—In 40 c.c. of ethanol was taken a mixture of 10.0 g. (0.047 mole) of sodium p-toluenesulphinate dihydrate and 5.0 g. (0.047 mole) of β-chloropropionic acid. The mixture was neutralised with a 50% solution of sodium hydroxide and refluxed on a water bath for 6 hours. Most of the ethanol was then removed by distillation and the remaining solution was diluted with 100 c.c. of water. On acidification with strong hydrochloric acid a brown oil separated. This was extracted with ether and the ethereal solution was washed with water. The oil that was left after the removal of ether by evaporation, was boiled with 100 c.c. of water using a little animal charcoal and filtered. From the filtrate, on cooling, a colourless oil separated which soon set to a solid. One more recrystallisation from water gave 2.80 g. (26%) of β-p-tolylsulphonylpropionic acid as shining colourless plates, m.p. 111-112°. Kohler and Reimer[107] give the m.p. 110-113°.

β-Methyl-α-phenyl-β-p-tolylsulphonylethylamine Hydrochloride.—To a solution of 2.28 g. (0.01 mole) of α-p-tolylsulphonylpropionic acid and 1.06 g. (0.01 mole) of benzaldehyde in 2 cc. of glacial acetic acid, 0.77 g. (0.01 mole) of ammonium acetate was added and the mixture was heated under reflux for 1 hour. The rate of evolution of carbon dioxide was rather slow when compared to that in the condensation of p-tolylsulphonylacetic acid. After cooling, the product was extracted with 50 cc. of ether. After saturation with hydrogen chloride, the ethereal solution gradually yielded the hydrochloride. It was filtered and washed with ether and then with acetone. The yield was 0.22 g. (7%). Recrystallisation from ethanol-ether gave colourless needles, melting at 235-240° with decomposition.

Anal. Calcd. for $C_{16}H_{20}O_2NClS$: C, 59.0; H, 6.1; Cl^-, 10.9. Found : C, 58.9; H, 6.4; Cl^-, 10.9.

β-Methyl-α-phenyl-β-p-tolylsulphonylethylene.—Evaporation of the ethereal filtrate from the above experiment yielded a residue which was agitated with 5 cc. of ethanol and filtered. The yield was 0.32 g. (12%). After recrystallising from ethanol, the compound melted at 118.5-119.5°.

Anal. Calcd. for $C_{16}H_{16}O_2S$: C, 70.6; H, 5.9. Found : C, 70.5; H, 5.9.

β-Methyl-α-3-nitrophenyl-β-p-tolylsulphonylethylamine Hydrochloride.—Using a mixture of 2.28 g. (0.01 mole) of

α-p-tolylsulphonylpropionic acid, 1.51 g. (0.01 mole) of m-nitrobenzaldehyde, 0.77 g. (0.01 mole) of ammonium acetate and 2 cc. of glacial acetic acid and following the same procedure as described above for the α-phenyl compound, 0.59 g. (16%) of the hydrochloride was obtained. Colourless needles, melting at 245-254° with decomposition, were obtained from ethanol.

Anal. Calcd. for $C_{16}H_{19}O_4N_2ClS$: C, 51 8; H, 5.1; Cl^-, 9.6. Found : C, 52.0; H, 5.3; Cl^-, 9.5.

β-Methyl-α-3-nitrophenyl- β-p-tolylsulphonylethylene.—The oil obtained from the ethereal filtrate of the above experiment was mixed with 10 cc. of ethanol. The precipitate which was thrown out was washed with ethanol; the yield was 0.31 g. (10%). It was obtained as pale yellow plates from methanol, m.p. 132-133°.

Anal. Calcd. for $C_{16}H_{15}O_4NS$: C, 60.6; H, 4.7. Found : C, 60.4; H, 4.8.

Ethyl Phenylsulphonylacetate.—This was prepared by the method of Ashley and Shriner[72]. To 300 cc. of absolute ethanol 82 g. (0.5 mole) of sodium benzenesulphinate was added. Refluxing the mixture over water bath, 76.7 g. (0.625 mole) of ethyl chloroacetate was added during a period of 1 hour with continuous stirring. The mixture was refluxed for 8 hours, allowed to stand overnight and then refluxed for 2 more hours. After removing about 250 cc. of ethanol by distillation, 200 cc. of water was added and the oil that separated was extracted with ether. The ethereal extract (500 cc.) was washed with water and dried over anhydrous magnesium sulphate. The ether was then distilled off and the liquid boiling at 175-205° /5 mm. was collected. The oil set to a solid melting at 40-43°. The yield was 55.0 g. (49%, based on the amount of sodium benzenesulphinate used).

β-Ethoxycarbonyl- α-3-nitrophenyl- β-phenylsulphonylethylene.—To a solution of 2.28 g. (0.01 mole) of ethyl phenylsulphonylacetate and 1.51 g. (0.01 mole) of m-nitrobenaldehyde in 5 cc. of absolute ethanol, was added 0.77 g. (0.01 mole) of ammonium acetate. The mixture, after heating under reflux for 15 minutes, was allowed to cool. The oil that separated set to a solid. After 3 hours, the product was removed by filtration and washed with 5 cc. of ethanol twice. The yield was 2.13 g. (59%). It was recrystallised from glacial acetic acid, yellow tables, m.p. 154-155°.

Anal. Calcd. for $C_{17}H_{15}O_6NS$: C, 56.5; H, 4.2. Found: C, 56.2; H, 4.3.

Phenylsulphonylacetonitrile.—A mixture of 12.0 g. (0.159 mole) of chloroacetonitrile and 30.0 g. (0.183 mole) of sodium

benzenesulphinate in 50 cc. of absolute ethanol was refluxed over a water bath for 16 hours and poured into 250 cc. of cold water. The sulphonylacetonitrile that separated was filtered and washed with water. The yield was 15.5 g. (54%, based on the weight of chloroacetonitrile). Recrystallisation from ethanol gave colourless, glistening plates melting at 112-114°.

Preparation of α-Aryl-β-cyano-β-phenylsulphonylethylenes.—The condensation of phenylsulphonylacetonitrile with aromatic aldehydes proceeds with remarkable ease in presence of ammonium acetate. The reaction takes place even in the cold. In general, a mixture of the aldehyde, the nitrile, and ammonium acetate (0.005 mole each) in 10 cc. of ethanol was refluxed for 5 minutes and allowed to cool. The α,β-unsaturated sulphone that separated out was collected and recrystallised from a suitable solvent. Table 10 (next page) records details regarding the compounds prepared.

ω-Phenylsulphonylacetophenone.—Hundred grams (0.5 mole) of ω-bromoacetophenone and 82 g. (0.5 mole) of sodium benzenesulphinate were mixed with 250 cc. of absolute ethanol and heated under reflux on a water bath for 8 hours. The mixture was then poured into 500 cc. of ice water. A brown solid separated. It was collected at the pump and washed with light petroleum (b.p. 100-110°) until the product became colourless. The yield was 60 g. (46%). Recrystallisation from ethanol gave colourless needles melting at 95-96°.

Rection of ω-Phenylsulphonylacetophenone with Benzaldehyde and Ammonia.—With 75 c.c. of absolute ethanol were mixed 13.0 g. (0.05 mole) of ω-phenylsulphonylacetophenone and 3.85 g. (0.05 mole) of ammonium acetate. The mixture was heated over a hot plate until a clear solution was obtained. It was mixed with 5.30 g. (0.05 mole) of benzaldehyde and boiled for 2 minutes. On cooling a crystalline mass separated slowly. After a day 50 c.c. of water was added and the product was separated by filtration. It was washed first with water and then with 10 c.c. of ethanol. The colourless material, thus obtained, was agitated with 150 c.c. of light petroleum (b.p. 80°) and filtered. The product, *β-benzoyl-α, γ-diphenyl-β-phenylsulphonyltrimethylenediamine*, which was insoluble in cold petroleum weighed 5.0 g. (43% based on benzaldehyde). It crystallised from petroleum as colourless needles, m.p. 149-52°.

Anal. Calcd. for $C_{28}H_{26}O_3N_2S$: C, 71.5; H, 5.5. Found: C, 71.1; H, 5.33.

The fraction which dissolved in petroleum was treated with a dilute solution of sodium hydroxide to dissolve away any unreacted ω-phenylsulphonylacetophenone. The alkali-insoluble

TABLE 10.

α-Aryl-β-cyano-β-phenylsulphonylethylenes,

$ArCH=C(CN)SO_2C_6H_5$.

No	Ar	M.p., °C	Yield, %	Formula	Carbon, %		Hydrogen, %	
					Calcd.	Found	Calcd.	Found
1	C_6H_5	137–138[a]	100	$C_{15}H_{11}O_2NS$	—	—	—	—
2	3, 4-(CH_2O_2) : C_6H_3	170–171	96	$C_{16}H_{11}O_4NS$[b]	61.4	61.6	3.5	3.7
3	2-H_3CO-C_6H_4	106–107.5	73	$C_{16}H_{13}O_3NS$[c]	64.2	64.2	4.4	4.5
4	4-ClC_6H_4	155–156	95	$C_{15}H_{10}O_2NClS$[d]	59.1	59.4	3.3	3.6
5	3-$O_2NC_6H_4$	149–150.5	93	$C_{15}H_{10}O_4N_2S$[e]	57.3	57.2	3.2	3.5

[a] Tröger and Prochnow[79] record m.p. 135°. [b] Yellow plates from acetone. [c] Light yellow needles from methanol. [a,d] Colourless needles from ethanol. [e] Colurless needles from ethanol-acetone.

product, *β- benzoyl- α -phenyl- β -phenylsulphonylethylene*, weighed 5.20 g. (30%). It was obtained as colourless plates from ethanol; m.p. 137-138°.

Anal. Calcd. for $C_{21}H_{16}O_3S$: C, 72.4; H, 4.6. Found : C, 72.3; H, 4.8.

The Condensation of ω-Phenylsulphonylacetophenone with Benzaldehyde in Acetic Acid.—A mixture of 2.60 g. (0.01 mole) of ω-phenylsulphonylacetophenone, 1.06 g. (0.01 mole) of benzaldehyde, and 0.77 g. (0.01 mole) of ammonium acetate in 3 c.c. of glacial acetic acid was refluxed for 10 minutes. The solution was cooled, dissolved in 50 c.c. of ether and hydrogen chloride was passed. The precipitated ammonium chloride was filtered off and from the filtrate, the solvents were removed by evaporation. The yellow residue became colourless on washing with 5 c.c. of methanol. The product was taken in a beaker, stirred up with 20 c.c. of a dilute solution of sodium hydroxide, filtered and washed with water until free from alkali. The yield of β-benzoyl-α -phenyl-β-phenylsulphonylethylene was 1.61 g. (46%), m.p. 137-138° (recrystallised from ethanol).

β-Benzoyl-α -3-nitrophenyl- β-phenylsulphonylethylamine.—A mixture of 2.60 g. (0.01 mole) of ω-phenylsulphonylacetophenone and 0.77 g. (0.01 mole) of ammonium acetate was dissolved in 25 c.c. of boiling absolute ethanol. To the hot solution, 1.51 g. (0.01 mole) of m-nitrobenzaldehyde was added and the solution was allowed to cool when an oil separated out. The mixture was diluted with 75 c.c. of ethanol and heated until a clear solution was obtained. The crystals, that separated out on cooling, were collected after 3 days and washed with ethanol. The amine weighing 2.13 g. (52%) was crystallised from chloroform. It melted at 146-147°.

Anal. Calcd. for $C_{21}H_{18}O_5N_2S$: C, 61.5; H, 4.4. Found : C, 61.7; H, 4.2.

β-Benzoyl-α-3-nitrophenyl-β- phenylsulphonylethylene.—To 5 c.c. of glacial acetic acid were added 2.60 g. (0.01 mole) of ω-phenylsulphonylacetophenone, 1.51 g. (0.01 mole) of m-nitrobenzaldehyde, and 0.77 g. (0.01 mole) of ammonium acetate and the mixture was refluxed for 10 minutes. The resultant solution was allowed to stand for 24 hours, at the end of which period, crystals began to separate. Fifty c.c. of ether was added to the mixture and after standing for further 24 hours, the separation of the crystals was complete. The yield of the product after washing with ether was 1.90 g. (48%). It separated from acetone as pale yellow plates with m.p. 169-171°.

Anal. Calcd. for $C_{21}H_{15}O_5NS$: C, 64.1; H, 3.8. Found : C, 64.4; H, 4.0.

β-Benzoyl-α-4-chlorophenyl-β phenylsulphonylethylene and *β -Benzoyl- α -4-chlorophenyl- β -phenylsulphonylethylamine.*—A mixture of 1.40 g. (0.01 mole) of p-chlorobenzaldehyde, 2.60 g. (0.01 mole) of ammonium acetate, and 25 c.c. of absolute ethanol was heated to boiling over a hot plate and allowed to cool. Immediately a crystalline product separated. It was filtered and washed with 10 c.c. of ethanol. The compound melted at 135-150° and weighed 3.50 g. Part of it dissolved in hot ethanol. The amine, insoluble in hot ethanol, weighed 2.5 g. (63%). It crystallised in fine colourless needles from petroleum, m.p. 167-168.5°.

Anal. Calcd. for $C_{21}H_{18}O_3NClS$: C, 63.1; H, 4.5. Found: C, 63.0; H, 4.6.

The portion, soluble in hot ethanol, was found to be the unsaturated sulphone, colourless needles (from ethanol), m.p. 161.5-163°.

Anal. Calcd. for $C_{21}H_{15}O_3ClS$: C, 65.9; H, 3.9. Found: C, 65.6; H, 4.2.

β-Benzoyl-α-3, 4-methylenedioxyphenyl-β-phenylsulphonylethylene.—A mixture of 2.60 g. (0.01 mole) of ω -phenylsulphonylacetophenone, 1.50 g. (0.01 mole) of piperonal, and 0.77 g. (0.01 mole) of ammonium acetate in 10 c.c. of absolute ethanol was heated under reflux for 10 minutes. The resulting yellow solution was diluted with 10 c.c. of ethanol and cooled. Crystallisation of the product was induced by scratching the sides of the reaction flask with a glass rod. The mixture was left aside for 24 hours and then filtered. The solid was washed with a little ethanol. The filtrate, with the washings, was diluted with 50 c.c. of water. The crystals, that separated, were collected and combined with the portion already got. The whole material was stirred with 25 c.c. of a 5% solution of sodium hydroxide to dissolve away the unreacted keto sulphone, filtered and washed with water. The yield was 0.65 g. (17%). Recrystallisation from a mixture of 1, 4-dioxane and ethanol gave fine yellow needles melting at 178-179°.

Anal. Calcd. for $C_{22}H_{16}O_5S$: C, 67.4; H, 4.1. Found: C, 67.6; H, 4.1.

β-Benzoyl-α-4-methoxyphenyl-β-phenylsulphonylethylene.—Using a mixture of 2.60 g. (0.01 mole) of ω-phenylsulphonylacetophenone, 1.36 g. (0.01 mole) of anisaldehyde, 0.77 g. (0.01 mole) of ammonium acetate, and 10 c.c. of absolute ethanol the condensation was carried out following the same procedure as described for the α-3, 4-methylenedioxyphenyl compound. The

yield of the product was 1.07 g. (28%). Light yellow rhombic crystals, melting at 161-163°, were obtained from ethanol.

Anal. Calcd. for $C_{22}H_{18}O_4S$: C, 69.8; H, 4.8. Found: C, 70.2; H, 5.0.

β-Benzoyl-α-2-methoxyphenyl-β-phenylsulphonylethylene.- After dissolving a mixture of 2.60 g. (0.01 mole) of ω-penylsulphonylacetophenone, 1.36 g. (0.01 mole) of o-methoxybenzaldehyde, and 0.77 g. (0.01 mole) of ammonium acetate in 50 c.c. of hot absolute ethanol, the solution was kept boiling for 2 minutes and left aside. After 2 days the crystals deposited were collected and washed with ethanol. Any unreacted ω-phenylsulphonylacetophenone was removed by washing with alkali. The product weighed 2.92 g. (77%). It crystallised as pale yellow tablets from aqueous 1, 4-dioxane; m.p. 130-131°.

Anal. Calcd. for $C_{22}H_{18}O_4S$: C, 69.8; H, 4.8. Found: C, 69.8; H, 5.0.

β-Benzoyl-β-phenylsulphonyl-α-p-tolylethylene.—A mixture of 2.60 g. (0.01 mole) of ω-phenylsulphonylacetophenone, 1.20 g. (0.01 mole) of p-toluic aldehyde, and 0.77 g. (0.01 mole) of ammonium acetate in 25 c.c. of absolute ethanol was heated until a clear solution was obtained. Next day, the crystals formed were filtered and washed successively with alkali and water. The yield was 2.45 g. (68%). Colourless needles melting at 174-175.5° were obtained from ethanol.

Anal. Calcd. for $C_{22}H_{18}O_3S$: C, 72.9; H, 5.0. Found: C, 2.8; H, 5.2.

α,α-Bis-(benzoylphenylsulphonylmethyl)-ethane.—To 20 c.c. of absolute ethanol 2.60 g. (0.01 mole) of ω-phenylsulphonylacetophenone and 0.31 g. (0.005 mole) of acetaldehyde-ammonia were added and heated under reflux for 30 minutes. When allowed to stand, crystals began to appear after 2 days. After two more days the product was filtered and washed with a 5% solution of sodium hydroxide and then with water and ethanol. The product weighed 1.0 g. (37%). After recrystallisation from 1,4-dioxane, it softened at 192° and melted at 202-203°.

Anal. Calcd. for $C_{30}H_{26}O_6S_2$: C, 65.9; H, 4.8. Found: C, 65.6; H, 4.8.

PART II

SYNTHESIS OF SOME BIS-(AMINOARYL) SULPHONES

INTRODUCTION

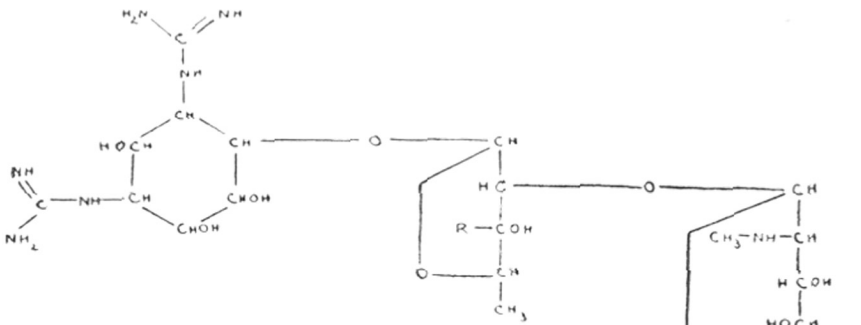
Tuberculosis stands high on the list of man-killing diseases. The disease is characterised by the formation in the tissues of nodular bodies or tubercles (hence, tuberculosis) and is manifested symptomatically in the pulmonary form by fever, cough and progressive loss of weight. The causative agent is 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.

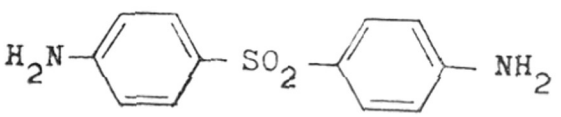
The first of the modern synthetic tuberculostats to be discovered are the sulphones. The parent compound of this group is bis-(p-aminophenyl) sulphone (LII). The compound was first synthesised by Fromm and Wittmann[124]. The chemotherapeutic activity of the sulphone was first evaluated by Buttle and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



(L) : R = CHO

(LI) : R = CH_2OH

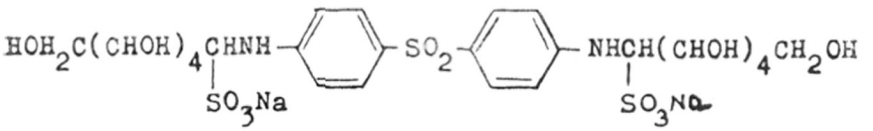
co-workers[125] and later Rist[126] demonstrated its high antibacterial activity. Buttle and his co-workers observed that it is hundred times as active as sulphanilamide. Though the com-



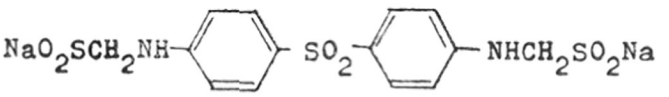
(LII)

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.

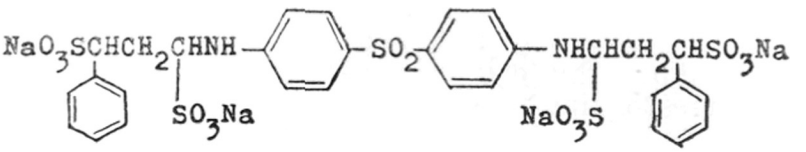
Compounds such as promin (LIII), diasone (LIV), sulphetrone (LV) and promizole (LVI) are some of the more promising ones. In these cases, though the solubilities are increased and the toxicities are decreased, the activities are also somewhat decreased.



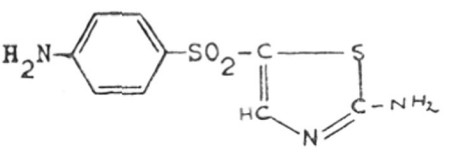
(LIII)



(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[135]. 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].

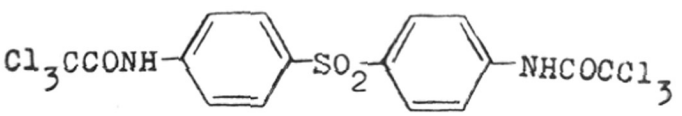
Sulphetrone [sodium tetrasulphonate of bis-(p-3-phenylpropylaminophenyl) sulphone], first prepared by Henry and Gray[137] proved to be comparable in activity to promin in the guinea pig[138] and remarkably free from chronic toxicity[139]. Applied to man it may have a use in certain forms of exudative 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].

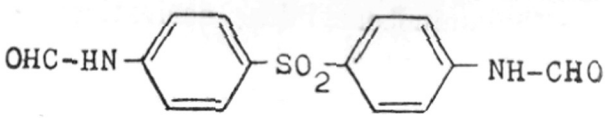
Apart from the above mentioned sulphones a host of other derivatives of bis-(p-aminophenyl) sulphone have been prepared and tested for their activity against tuberculosis. Most of the derivatives so prepared involved replacement of the hydrogen atom in one or both the amino groups by a suitable group. 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[133] 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].

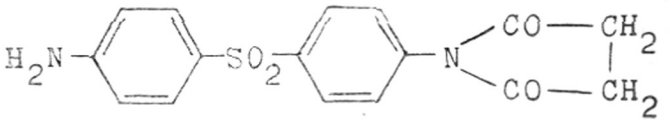


(LVII)

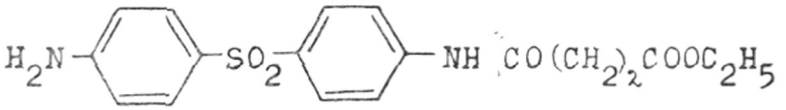


(LVIII)

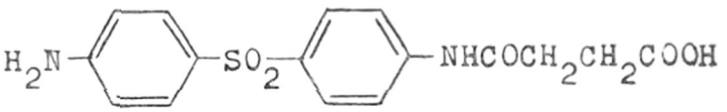
Of the several succinic acid derivatives tested[157] against experimental tuberculosis in guinea pigs, 4-amino-4′succinimidodiphenyl sulphone (LIX) was about as effective as promin but inferior to 4-amino-4′-n-propylaminodiphenyl sulphone. Compound (LX) was also equally effective. These compounds along



(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].

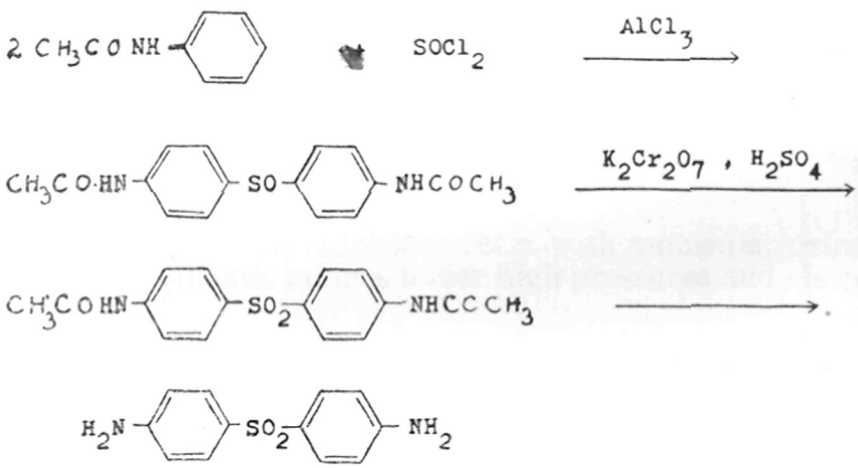
Several aromatic aldehydes have been condensed with bis-(p-aminophenyl) sulphone and some of the resulting anils showed activity. Sulphetrone was derived by the addition of sodium bisulphite to the dianil from cinnamaldehyde[137]. Of the other Schiff's bases, bis-(p-phenylpropylideneaminophenyl) sulphone[160] 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 [161]. 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[159] 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].

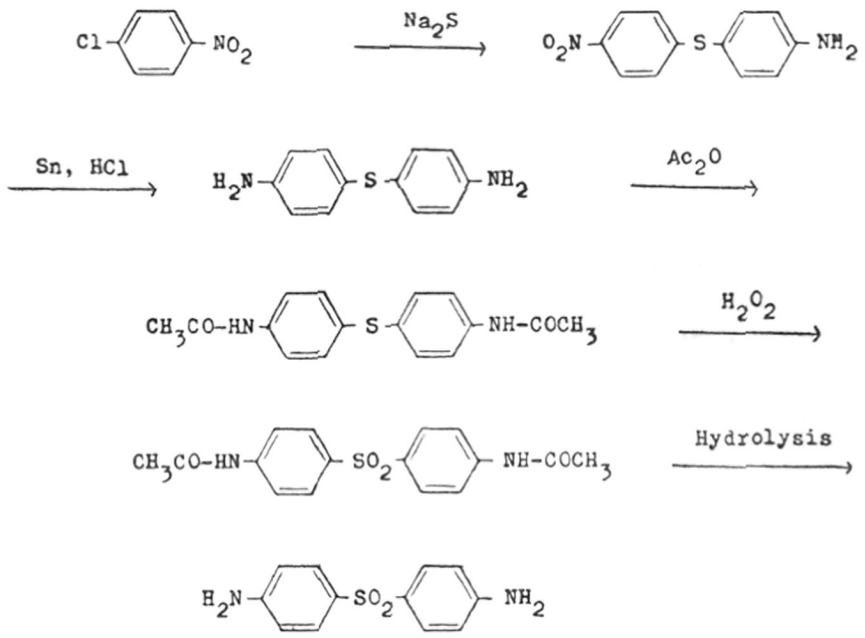
It seemed desirable to prepare more nuclear-substituted bis-(aminoaryl) sulphones and study their therapeutic potentialities. Sugasawa and Sakurai[166] prepared bis-(p-aminophenyl) sulphone by condensing acetanilide with thionyl chloride in presence of anhydrous aluminium chloride, oxidising the resulting 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



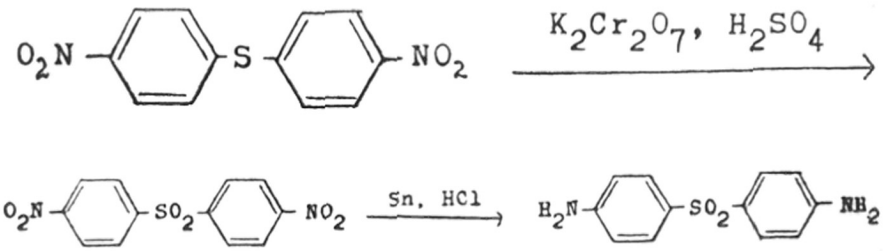
examine the possibilty of preparing new bis-(aminoaryl) sulphones by this method. If the reaction of acet-toluidides with thionyl chloride takes the expected course, it should be possible to get several bis-(aminoaryl) sulphones whose antituberculous and antileprous activities would be worth examining.

DISCUSSION

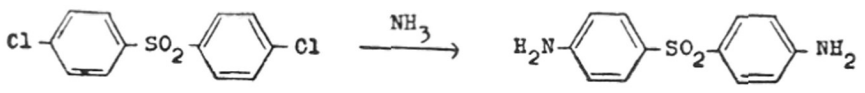
There are several methods of preparing bis-(p-aminophenyl) sulphone. In one method[167,168], bis-(p-acetamidophenyl) sulphide, obtained according to the scheme given below, is oxidised to bis-(p-acetamidophenyl) sulphone and the latter is then deacetylated.



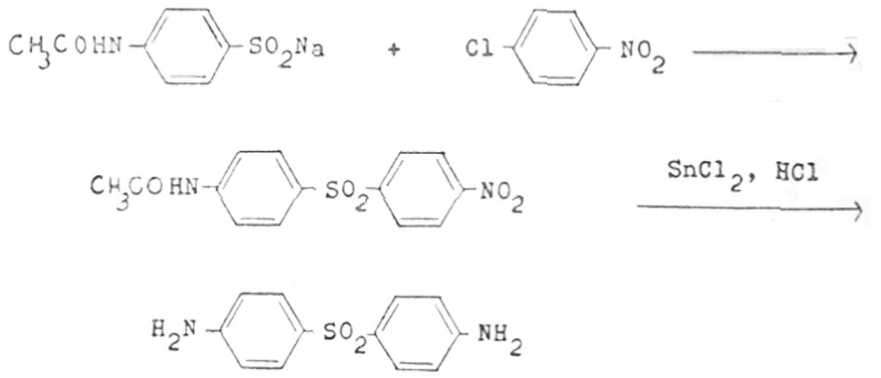
In another method[124] bis-(p-nitrophenyl) sulphide, obtained from p-chloronitrobenzene and sodium sulphide, is oxidised to the sulphone and then reduced.



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



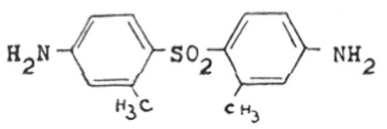
Reaction of sodium p-acetamidobenzenesulphinate with p-chloronitrobenzene and reduction of the resulting nitro sulphone also give the diamino sulphone[170,171].



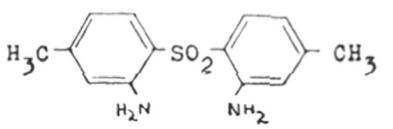
p-Acetamidobenzenesulphonyl chloride reacts with acetanilide in presence of aluminium chloride to give bis-(p-acetamidophenyl) sulphone[172].

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.

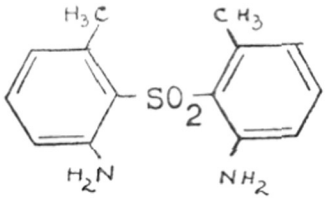
The analytical data of the acetamido sulphoxide, acetamido sulphone and amino sulphone obtained from acet-m-toluidide showed that two molecules of the toluidide had reacted with one molecule of thionyl chloride. Taking the directive influence of methyl and acetamido groups into consideration, the amino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



(LXII)

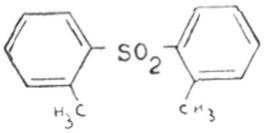


(LXIII)

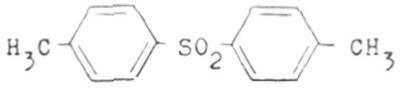


(LXIV)

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-

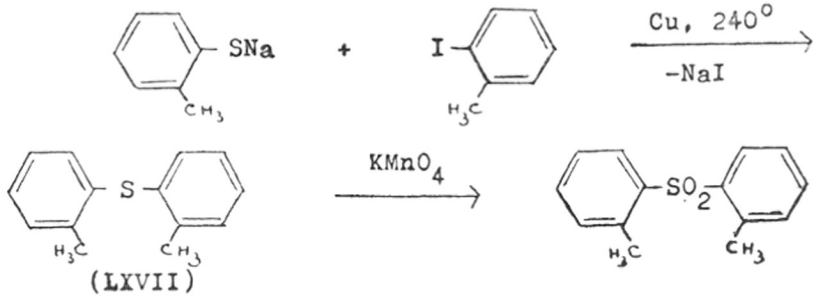


(LXV)



(LXVI)

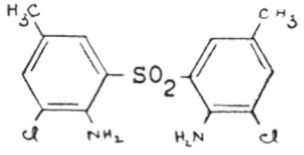
phone was effected with hypophosphorous acid, since ethanol did not give satisfactory results. The analytical data of the sulphone, thus obtained, corresponded with those calculated for a ditolyl sulphone. The compound melted at 103-104.5°. But this did not correspond with the reported melting point 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.



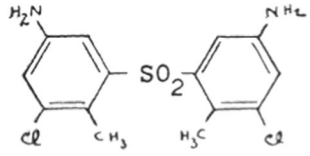
(LXVII)

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.

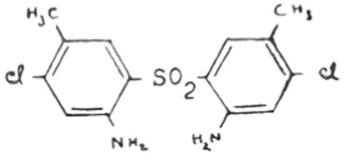
The sulphoxide obtained in the reaction of thionyl chloride with acet-p-toluidide was oxidised to the sulphone which, on hydrolysis, gave a diamino sulphone (A). All the three compounds, the sulphoxide, the diacetamido sulphone and the diamino sulphone contained chlorine. Their analytical data showed 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:



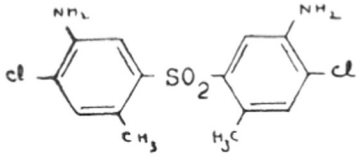
(LXVIII)



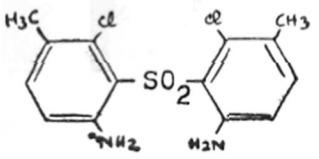
(LXIX)



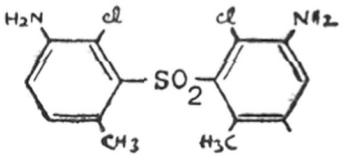
(LXX)



(LXXI)

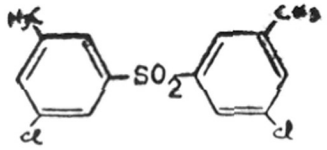


(LXXII)

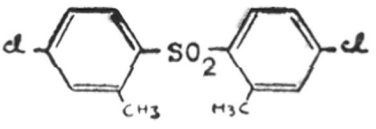


(LXXIII)

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).

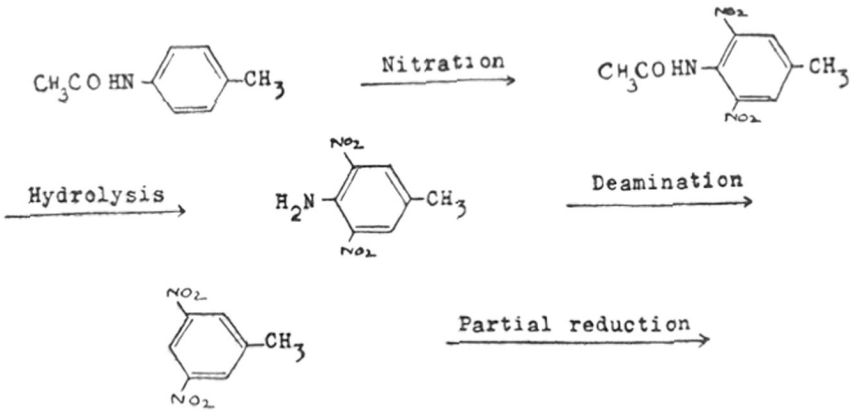


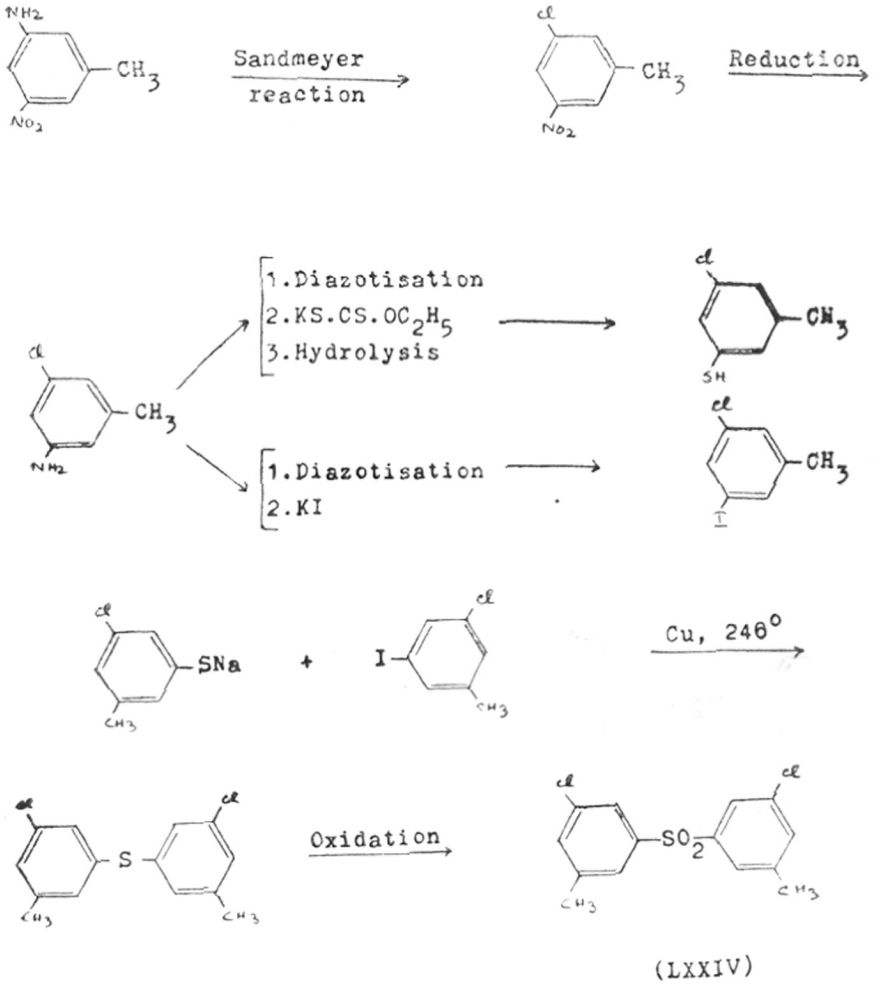
(LXXIV)



(LXXV)

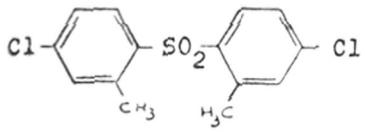
Bis-(3-chloro-5-methylphenyl) sulphone (LXXIV) was synthesised unequivocally according to the following scheme:



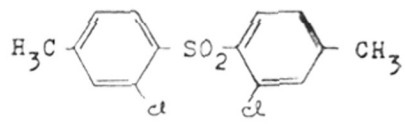


(LXXIV)

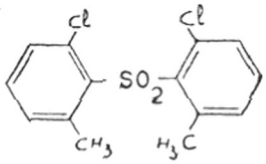
The sulphone (LXXIV), thus obtained, melted at 163.5-164.5° whereas, the bis-(chlorotolyl) sulphone (B) obtained by deamination melted at 134-135°. Since both these compounds were not indentical, bis-(4-chloro-2-methylphenyl) sulphone (LXXV) was sought to be obtained by the reaction of m-chlorotoluene 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.

SUMMARY

1. Dialkyl sulphones, benzyl phenyl sulphone, bis-(phenylsulphonyl)-methane and tris-(phenylsulphonyl)-methane fail to undergo the Mannich reaction.

2. Arylsulphonylacetic acids undergo the Mannich and the Knoevenagel reactions. Phenylsulphonylacetic acid and p-tolylsulphonylacetic acid condense with aromatic aldehydes and ammonia or aliphatic primary amines furnishing *β*-amino and *α, β-unsaturated sulphones.*

3. An aldol-type condensation resulting in the formation of a *β*-hydroxy sulphone has been found to occur in the reaction of p-tolylsulphonylacetic acid with chloral.

4. *α*-p-Tolylsulphonylpropionic acid also undergoes the Mannich and the Knoevenagel reactions, but it is less reactive than p-tolylsulphonylacetic acid.

5. In the reaction of ethyl phenylsulphonylacetate with an aromatic aldehyde and ammonia, an *α, β*-unsaturated sulphone is got; no Mannich base is obtainable.

6. Phenylsulphonylacetonitrile condenses with aromatic aldehydes in presence of ammonium acetate giving *α, β*-unsaturated sulphones in excellent yield.

7. The reaction of ω -phenylsulphonylacetophenone with ammonia and some aromatic aldehydes gives *α, β*-unsaturated sulphones and basic compounds. However, with other aromatic aldehydes only *α, β*-unsaturated sulphones are obtained.

8. *α, α*-Bis-(benzoylphenylsulphonylmethyl)-ethane is formed when ω-phenylsulphonylacetophenone condenses with acetaldehyde-ammonia.

9. A mechanism has been suggested for the Mannich and the Knoevenagel reactions.

10. The Friedel-Crafts reaction of the three isomeric acettoluidides with thionyl chloride has been investigated. No product can be isolated in the case of acet-o-toluidide. Both acet-m- and acet-p-toluidides give sulphoxides. The sulphoxides are oxidised to the corresponding sulphones and then hydrolysed to the amino sulphones. The structures of the amino sulphones are established by deamination and synthesis of the deaminated sulphones.

11. Di-o-tolyl sulphone reported in the literature is shown to be a different compound by synthesising it unequivocally in the present work.

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