307. *The Mobility of Groups in 4-Chloro-2-nitrodiphenylsulphones.*

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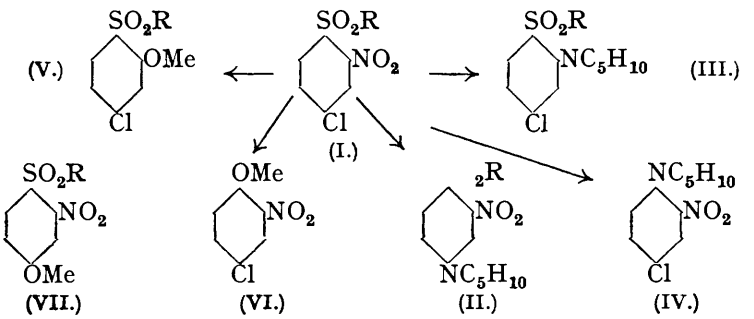
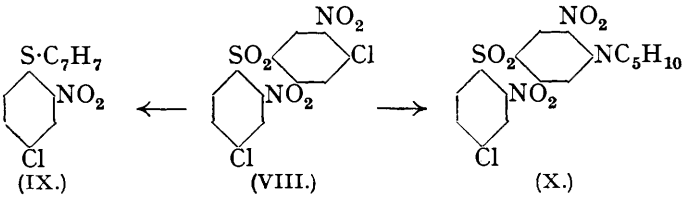
Further instances are recorded of the different preferential replacements effected by various reagents in reaction with compounds of type (I), and it is found that such replacements are largely independent of the nature of the group R. A note is appended on the preparation of sulphonyl chlorides by the action of chlorine on disulphides and on compounds having the character of acylated thiols.

It has previously been recorded (Loudon and Robson, J., 1937, 242) that each of the three substituent groups in the benzene nucleus of (I, R = *p*-tolyl) is mobile and may be replaced in preference to the other two by the action of specific reagents. Apparently the relative reaction speeds at the three reactive centres are subject to wide variation consequent upon a change of reagent and, in a favourable case, the simultaneous formation of all three possible products may be anticipated. This has in fact been demonstrated for the reaction between (I) and piperidine: the production of (II) and (III) has already been noted (*loc. cit.*) and we have now isolated small quantities of (IV). A similar case is probably provided by the interaction of (I) with sodium methoxide (and ethoxide): (V) and (VI) were isolated and the presence of chloride ions indicated the formation also of (VII).



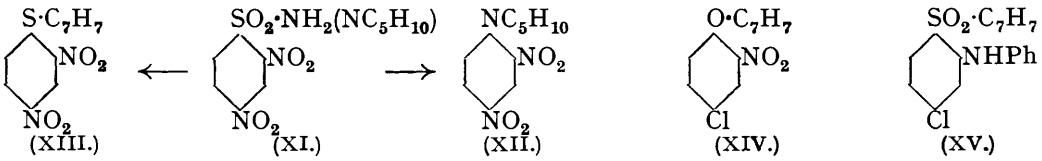
With most of the reagents examined, however, the attack was largely confined to a single centre, as is illustrated by replacement of the sulphonyl group with reagents of sulphide character. For instance, good yields of the corresponding *4-chloro-2-nitrophenyl thioethers* were obtained by the action of the sodium salts of thiophenol, *p*-thiocresol and 2 : 5-dichlorothiophenol upon (I), and with sodium mono- and di-sulphides, bis-4-chloro-2-nitrophenyl monosulphide and disulphide were respectively produced. The replacement of sulphonyl by a thio-group is also favoured in the reaction between (VIII) and alkaline *p*-thiocresol (1 mol.) (VIII ⟶ IX) despite the fact that in (VIII) a chlorine atom is jointly activated by two powerful cationoid groups (NO_2 and SO_2) and is, moreover, exclusively replaced (VIII ⟶ X) by the action of piperidine (2 mols.).



(IX.) (VIII.) (X.)

It appears, therefore, that between such reagents as piperidine and alkaline *p*-thiocresol there exists a markedly different selective capacity for the reactions in question and it became of interest to inquire how, with these reagents, the loci and degree of reactivity are affected by modifying the sulphonyl component of (I). The compounds examined included the *piperidide* and amide (I; R = NC_5H_{10} and NH_2) and a series of four *sulphones* (I; R = Me, Ph, *p*-C_6H_4Me, and 2 : 5-$C_6H_3Cl_2$) representing a range of anionic stability in the sulphonyl groups (cf. Loudon, J., 1935, 537; Gibson and Loudon, J., 1937, 487). A qualitative comparison was made of the times required for reaction and of the relative quantities of pure products isolated. The reactions with the mercaptide were indistinguishably rapid under the conditions used and uniformly resulted in replacement of the sulphonyl substituent (I ⟶ IX). With piperidine the three possible products (I ⟶ II, III and IV) were isolable in each case, but whereas the four sulphones reacted with similar rapidity (5 mins.) and yielded approximately corresponding quantities of the products in the order (II)>(III)>(IV), the piperidide and amide required longer treatment (30—45 mins.) and the quantities of products became, (II) approximately equal to (III)>(IV).

In considering these results it is to be recognised that alteration of the radical R in (I) may affect two factors probably concerned in the reactivity of the system, for whilst it modifies the potential anionic stability and hence the mobility of the sulphonyl group, it also influences the contribution of that group to the cationoid character of the nucleus, thereby affecting indirectly the mobility of the nitro- and chloro-substituents. The gross effect may therefore be a general increase or decrease in the mobility of each of the three groups, accompanied by comparatively slight readjustments in their relative mobilities. The decreased general reactivity of the sulphon-amide and -piperidide compared with the sulphones is consistent with the weaker " acidifying effects " of these amido-groups (cf. Arndt and Martius, *Annalen*, 1932, **499**, 228), and the fact, incidentally observed, that they are themselves capable of replacement was confirmed by the behaviour of the 2 : 4-dinitrophenyl compounds (XI ⟶ XII and XIII). As a whole, however, the results indicate that the reactivity of a system such as (I) is much more sensitive to changes in the attacking reagent than it is to alteration of its sulphonyl component.



(XIII.) (XI.) (XII.) (XIV.) (XV.)

Two further replacements are referred to here because of the contrast they provide to the facile intramolecular replacement of sulphonyl in 2-hydroxy- and 2-amino-2′-nitrodiphenylsulphone structures (Smiles and colleagues, J., 1932, 2774; 1934, 422; 1935, 131).

The intermolecular analogies selected were the reactions of (I, R = *p*-tolyl) with sodium *p*-tolyloxide and with aniline. The conditions necessary for these reactions were, however, much more intense than those sufficing for the intramolecular type and particularly with the latter reagent difficulty was experienced in isolating the product. Moreover, although with cresol the product (XIV) did indeed correspond to sulphonyl replacement, the *diphenylamine* isolated contained the sulphonyl group intact (XV).

Note on the Preparation of Sulphonyl Chlorides.

In the course of this research, having need of certain nitrobenzenesulphonyl chlorides, we applied the methods of Zincke (*Annalen*, 1918, **416**, 93) and Riesz (*Monatsh.*, 1928, **50**, 263) based on the chlorination of disulphides dissolved or suspended in dilute acetic acid. The method, however, failed with bis-2 : 4-dinitrophenyl disulphide, but, since the first stage in the reaction would appear to be formation of the sulphenyl chloride and since Fries (*Annalen*, 1927, **454**, 258) obtained 2 : 4-dinitrobenzenesulphenyl chloride by chlorinating 2 : 4-dinitrophenyl thiolbenzoate, we combined the two procedures in a successful preparation of the required sulphonyl chloride from the thioester. We had applied our procedure to a number of benzoylated thiols, to thiolsulphonic esters and to ethyl ethylxanthate when a publication by Douglass and Johnson (*J. Amer. Chem. Soc.*, 1938, **60**, 1486), developing their work on *iso*thioureates, anticipated in principle our results. From both sources, however, agreement may be expressed with the conclusion that sulphonyl chlorides are readily prepared by chlorinating in an aqueous medium compounds having the character of acylated thiols.

Experimental.

To avoid unnecessary repetition the experimental procedure is largely referred to two processes A and B, and the formation by process A of 4-chloro-2-nitrophenyl *p*-tolyl sulphide (IX), found with all sulphones and sulphonamides of type (I) in reaction with *p*-thiocresol, is not further mentioned. Formation of the piperidino-compound (IV), found in quantities indicating about 2% conversion, is implied in referring to process B.

Process A.—A solution of the sulphone or chloronitro-compound (1 mol.) and the thiol (1 mol.) in alcohol or alcoholic dioxan was treated with sodium hydroxide (1 mol., 10% aqueous solution) and thereafter warmed for 5 minutes. The product which separated on cooling was crystallised from acetic acid.

Process B.—The compound was heated in excess of piperidine as solvent for 5 minutes (exceptions noted). After steam-distillation to remove 4-chloro-2-nitro-1-piperidinobenzene (IV) (extracted from the distillate with benzene), the residue, which solidified on cooling or on stirring with dilute acid, was fractionally crystallised from alcohol.

4-Chloro-2-nitrophenylmethylsulphone (Zincke, *Annalen*, 1918, **416**, 99) (he gives m. p. 143°; now found 155—156°) reacted with piperidine (process B) to give *2-nitro-4-piperidinophenylmethylsulphone*, m. p. 126° (Found : N, 10·2. $C_{12}H_{16}O_4N_2S$ requires N, 9·9%), and *4-chloro-2-piperidinophenylmethylsulphone*, m. p. 134° (Found : N, 5·2. $C_{12}H_{16}O_2NClS$ requires N, 5·1%).

4-Chloro-2-nitrodiphenylsulphone.—The corresponding *sulphide*, obtained from 2 : 5-dichloronitrobenzene and thiophenol (process A), had m. p. 86° (Found : N, 5·35. $C_{12}H_8O_2NClS$ requires N, 5·3%) and was oxidised with hydrogen peroxide in acetic acid to the required *sulphone*, m. p. 121° (Found : N, 4·7. $C_{12}H_8O_4NClS$ requires N, 4·7%). The latter compound with piperidine (process B) gave *2-nitro-4-piperidinodiphenylsulphone*, orange plates, m. p. 172° (Found : N, 8·3. $C_{17}H_{18}O_4N_2S$ requires N, 8·1%), and *4-chloro-2-piperidinodiphenylsulphone*, colourless needles, m. p. 121° (Found : N, 4·2. $C_{17}H_{18}O_2NClS$ requires N, 4·2%).

4 : 2′ : 5′-Trichloro-2-nitrodiphenylsulphone.—The corresponding *sulphide*, obtained from 2 : 5-dichloronitrobenzene and 2 : 5-dichlorothiophenol (process A), had m. p. 106—107° (Found : N, 4·4. $C_{12}H_6O_2NCl_3S$ requires N, 4·2%) and was oxidised to the *sulphone*, m. p. 131° (Found : N, 3·8. $C_{12}H_6O_4NCl_3S$ requires N, 3·8%). With piperidine (process B) the sulphone yielded *2′ : 5′-dichloro-2-nitro-4-piperidinodiphenylsulphone*, m. p. 172° (Found : N, 6·9. $C_{17}H_{16}O_4N_2Cl_2S$ requires N, 6·75%), and *4 : 2′ : 5′-trichloro-2-piperidinodiphenylsulphone*, m. p. 153° (Found : N, 3·5. $C_{17}H_{16}O_2NCl_3S$ requires N, 3·5%).

4-Chloro-2-nitrobenzenesulphonamide (Riesz, *loc. cit.*), treated with piperidine (45 mins., process B), yielded *4-chloro-2-piperidinobenzenesulphonamide*, m. p. 152° (Found : N, 10·2.

$C_{11}H_{15}O_2N_2ClS$ requires N, 10·2%), and *2-nitro-4-piperidinobenzenesulphonamide*, m. p. 137° (Found: N, 14·9. $C_{11}H_{15}O_4N_3S$ requires N, 14·7%).

4-Chloro-2-nitrobenzenesulphonylpiperidide, obtained by slow addition of piperidine (2 mols.) to a well-cooled solution of the sulphonyl chloride (cf. below) in alcohol, formed colourless crystals, m. p. 138° (Found: N, 9·3. $C_{11}H_{13}O_4N_2ClS$ requires N, 9·2%). From it, *4-chloro-2-piperidinobenzenesulphonylpiperidide*, m. p. 105° (Found: N, 7·9. $C_{16}H_{23}O_2N_2ClS$ requires N, 8·2%), and *2-nitro-4-piperidinobenzenesulphonylpiperidide*, m. p. 121° (Found: N, 12·1. $C_{16}H_{23}O_4N_3S$ requires N, 11·9%), were obtained by the action of piperidine (45 mins., process B).

2 : 4-*Dinitrobenzenesulphonylpiperidide*, m. p. 130° (Found: N, 13·5. $C_{11}H_{13}O_6N_3S$ requires N, 13·3%), prepared from the sulphonyl chloride and piperidine (2 mols.) in cold alcohol, and 2 : 4-dinitrobenzenesulphonamide (Willgerodt and Mohr, *J. pr. Chem.*, 1886, **34**, 124) each yielded (a) 2 : 4-dinitro-1-piperidinobenzene (m. p. and mixed m. p. 92°) when heated for 30 minutes with excess of piperidine, and (b) 2 : 4-dinitrophenyl *p*-tolyl sulphide (m. p. and mixed m. p. 103°) when heated with alkaline *p*-thiocresol (process A).

4 : 4′-*Dichloro*-2 : 3′-*dinitrodiphenylsulphone*.—4 : 4′-*Dichloro-2-nitrodiphenyl sulphide*, m. p. 158°, obtained from 2 : 5-dichloronitrobenzene and *p*-chlorothiophenol (process A) (Found: N, 4·8. $C_{12}H_7O_2NCl_2S$ requires N, 4·7%), was oxidised to 4 : 4′-*dichloro-2-nitrodiphenylsulphone*, m. p. 133° (Found: N, 4·3. $C_{12}H_7O_4NCl_2S$ requires N, 4·2%). The latter compound, nitrated in cold concentrated sulphuric acid solution by addition of potassium nitrate (1 mol.), yielded the required *sulphone*, m. p. 162° (Found: N, 7·6. $C_{12}H_6O_6N_2Cl_2S$ requires N, 7·4%). A solution of this sulphone in dioxan, when treated at room temperature with piperidine (2 mols.) and kept for a few hours, yielded, in addition to piperidine hydrochloride, only 4-*chloro*-2 : 3′-*dinitro*-4′-*piperidinodiphenylsulphone*, m. p. 140° (Found: N, 9·9. $C_{17}H_{16}O_6N_3ClS$ requires N, 9·9%). The constitution of this piperidino-derivative was proved by the formation of the sulphide (IX) from it (process A).

Reactions of 4-*Chloro*-2-*nitrophenyl*-p-*tolylsulphone*.—(a) The reaction with sodium methoxide (Loudon and Robson, *loc. cit.*) was re-examined. Steam-distillation of the products effected a separation of 4-chloro-2-nitroanisole (representing about 5% conversion), which was extracted from the distillate with benzene and was identified by comparison with an authentic specimen (m. p. and mixed m. p. 96—97°).

(b) A similar reaction with sodium ethoxide gave 4-chloro-2-nitrophenetole, separated by steam-distillation, and 4-*chloro*-2-*ethoxyphenyl*-p-*tolylsulphone*, m. p. 105°, isolated by crystallisation of the residue from alcohol (Found: C, 57·5; H, 4·9. $C_{15}H_{15}O_3ClS$ requires C, 57·9; H, 4·8%).

(c) 4-Chloro-2-nitrophenyl *p*-tolyl ether (m. p. and mixed m. p. 100°; cf. Fox and Turner, J., 1930, 1115) was obtained when the sulphone was heated with sodium *p*-tolyloxide dissolved in *p*-cresol.

(d) 5-*Chloro*-2-p-*toluenesulphonyldiphenylamine* (XV) was obtained by refluxing a solution of the sulphone in aniline for 5 hours. The dark oil obtained by treatment with dilute acid solidified slowly and was repeatedly crystallised from acetic acid (charcoal). It formed colourless crystals, m. p. 121° (Found: N, 4·2. $C_{19}H_{16}O_2NClS$ requires N, 3·9%).

Preparation of Sulphonyl Chlorides.—The procedure (Riesz, *loc. cit.*) consisted in saturating with chlorine a solution or suspension of the compound in acetic acid containing 10% of water (about 10 c.c. of liquid to 2 g. of solid). The product either separated on standing or was precipitated by cautious addition of water.

2 : 4-Dinitrobenzenesulphonyl chloride, m. p. 102°, was obtained in 50—60% yield from 2 : 4-dinitrophenyl thiolbenzoate (*Ber.*, 1899, **32**, 3532) or from the disulphide by chlorinating a suspension in concentrated sulphuric acid, followed by dilution with acetic acid and water.

4-Chloro-2-nitrobenzenesulphonyl chloride (most conveniently prepared from the disulphide; Riesz, *loc. cit.*) was formed in 80—90% yield from 4-*chloro*-2-*nitrophenyl thiolbenzoate*. The latter, prepared by the Schotten–Baumann method from the thiol, had m. p. 124° (Found: N, 4·8. $C_{13}H_8O_3NClS$ requires N, 4·8%).

High yields of the corresponding sulphonyl chlorides were obtained from *p*-tolyl, *o*-nitrophenyl, and benzyl disulphoxides. Ethyl ethylxanthate gave a good yield of ethanesulphonyl chloride (fraction, b. p. 174—177°), which was extracted with benzene after dilution of the reaction solution with water.

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