THE MOBILITY OF GROUPS IN SUBSTITUTED AROMATIC NUCLEI

T H E S I S

presented by

CEDRIC W. N. HOLMES

for the Degree of Doctor of Philosophy in the Faculty of Science, University of Glasgow.

- - - - - - - - -

March, 1941

ProQuest LLC.
789 East Eisenhower Parkway
P.O. Box 1346
Ann Arbor, MI 48106 – 1346

ACKNOWLEDGEMENTS

The author wishes to express his deepest appreciation for the thoughtful assistance and understanding tendered to him by his supervisor, Dr. J. D. Loudon, in the years during which this work was carried out.

Grateful acknowledgement is also made to The Carnegie Trustees for a Research Scholarship, to the Medical Research Council for a Grant, and to Mr J. M. L. Cameron who performed the analyses of most of the compounds herein described.

- - - - - - - - - - - -

THE MOBILITY OF GROUPS IN SUBSTITUTED AROMATIC NUCLEI

- - - - - - - - - - - - -

PUBLICATIONS

THE MOBILITY OF GROUPS IN CERTAIN BENZONITRILES

PREFACE

- - - - - - - -

In Part I of this work the mobility of groups in substituted benzonitriles (Chapter I), thioxanthone dioxides (Chapter II) and benzoic acids (Chapter III) analogous in structure to the 2-nitro-4-chloro- and 2-chloro-4-nitrodiphenyl sulphones of Loudon and Robson (J.C.S., 1937, 242) is described. The reactivities of these four types of compound are compared, and the bearing of the main results on cationoid reactivity, from the point of view of group mobility, is discussed in relation to the views up to the present held on it.

Part II deals with the application of group mobility of this type to the synthesis of bactericidal drugs similar to the "prontosils". Syntheses of a number of sulphur and nitrogen containing derivatives utilising some interesting reactions are described.

- - - - - - - - - - - - -

INDEX

- - - - - -

PART I

THE MOBILITY OF POTENTIAL ANIONS IN CATIONOID AROMATIC NUCLEI

PART I.

THE MOBILITY OF POTENTIAL ANIONS IN CATIONOID AROMATIC NUCLEI.

Historical Introduction.

The transition of the halogen atom from a state of comparative inertness to one of great activity when nitro-groups are introduced into suitable positions in the nucleus of an aromatic halogeno-compound, is an aspect of cationoid reactivity which has been the subject of considerable attention since the middle of the 19th century. The first record of uncatalysed* halogen replacement was made in 1854 by Pisani[1], who noted the replacement of the chlorine atom of picryl chloride by an amino-group when this compound was treated with dry ammonium carbonate. Although Pisani's discovery seems to have had no immediate repercussions, we find an increasing number of similar examples as time went on.

---

* Replacements of this type must be distinguished from such catalysed replacements as that of the chlorine atom from ortho-chlorobenzoic acid in the presence of copper-bronze.

During the succeeding twenty years, the incidence of mobility in halogeno-benzenes following the insertion of nitro-groups in the ortho- and para-positions seems to have become accepted gradually. Its acceptance, however, was due rather to an accumulation of individual cases noted in the course of other investigations, than to any effort to define the circumstances of its origin or the limits of its applicability. For instance, by 1874 its possibilities, both from a synthetic and a diagnostic point of view, appear to have been appreciated by Körner[2], who utilised replacement reactions between ammonia and such compounds as 3:4-dinitrochlorobenzene, 2:6-dinitrochlorobenzene and others as a means, on the one hand, of preparing compounds normally difficult of access, and on the other, of orienting the groups present.

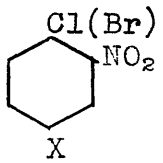
Apparently, then, the first attempt at a coordinating investigation on the subject of group-mobility (now not necessarily halogen) in "negatively"* sub-

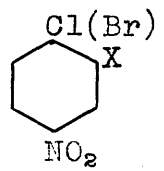
---

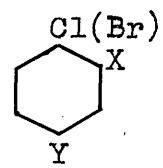
* The word "negative", when referring to nuclei or to substituents, is used in its old sense and is retained for clarity in discussing early conceptions regarding this type of reactivity.

stituted benzenes was made during the years 1876-82 by Laubenheimer[3]. Laubenheimer's researches were made on replacement reactions between ortho-dinitro-compounds (o-dinitrobenzene and 3:4-dinitrobromo-benzene) and various reagents such as caustic alkali, sodium alcoholates, alcoholic ammonia and amines and sodium sulphite. Probably the most noteworthy discovery arising from this work was that of the great reactivity of 3:4-dinitrobromobenzene as compared with ortho-dinitrobenzene.

In 1889 began the study of a new and wider aspect of the problem opened by Schöpff and his coworkers[4]. Whereas, in previous years, nitro-halogenobenzenes alone had been examined, the study was now extended to compounds having meta-directing substituents other than the nitro-group. Schöpff's investigations were made on the types shown below.







Where X and Y = CN, CO.R, CHO, CO.OH, SO_3H.

As a result of his work, Schöpff was able to enunciate the following rule:-

"A halogen atom in the benzene nucleus is rendered mobile by the simultaneous presence in the ortho- and para-positions of two meta-directing substituents which may or may not be identical. If only one such substituent be present,no replacement takes place except that substituent be the nitro-group."

All researches concerning group-mobility since this period have been performed with compounds conforming closely to the above types,with the exception that other potential anions (e.g. NO_2, SO_2R) have been employed in the place of halogen. Investigators in this field have been concerned mainly with the theoretical side of the question,and have sought proof of their hypotheses in the study of analogous rather than of fresh and different configurations. True,certain apparently anomalous cases of group-mobility have been observed,as,for example,the mobility of the nitro-group in 2-chloro-4-nitrobenzaldehyde[5]. These appear,however,to have excited little comment.

In 1914 the subject was finally summarised by Kenner[6],who put forward the first connected hypothesis regarding replacement reactions of this type. The ideas presented by this author centred

round the superiority of the nitro-group as an activating agent, such superiority arising from a strong tendency to form additive complexes with anionoid reagents. Reaction was thus regarded as being facilitated by the attraction and retention (as an additive complex) of the reagent, which was thereby placed in a favourable position to attack substituents at reactive centres. Reactive centres were situated in the ortho- and para-positions to meta-directing groups or in the meta-positions to ortho-para-directing groups and were characterised by a loosening of the attachment of potential anions present as substituents at such points. Interference with the ease of reaction might be occasioned by steric hindrance either to the formation of additive compounds or to the subsequent interaction between the retained reagent and a substituent. In certain cases accumulation of "negative" groups might result in the activation of the nucleus as a whole, and under these conditions potential anions situated in the meta-positions to meta-directing groups might be rendered mobile. The impossibility of predicting, with certainty, which of a number of potentially mobile groups would be replaced by a reagent, led Kenner to make the final proviso that, in some

unknown way, the course of the reaction was influenced by the nature both of the reagent and of the substituent to be replaced.

Summarising the main points of this hypothesis, we have:

(a) The loosening effect of meta-directing groups on substituents in the ortho- or para-positions.

(b) The corresponding effect of ortho-para-directing groups on substituents in the meta-positions.

(c) The superiority of the nitro-group due to its ability to form additive compounds - a property not shared by other meta-directing groups to any extent.

(d) Steric hindrance to the formation of additive compounds or to subsequent interaction between reagent and substituent.

(e) The "negative condition" of the nucleus.

(f) The influence of the reagent and of the group to be replaced.

In the main, these suggestions are still acceptable. On the other hand, in spite of the fact that additive compounds are most certainly formed between nitro-compounds and anionoid reagents, and

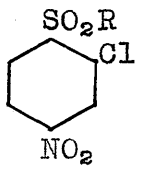
that examples of these have actually been isolated[7], a hypothesis based on the assumption that the property is characteristic of the nitro-group alone is open to criticism. It does not, for instance, since it places the nitro-group in a rather unjustifiably unique position, (This does not imply that the nitro-group is not superior in activating power.) adequately interpret the significance of the remaining manifestations listed above. The inadequacy is indicated by the fact that 2:4-dicyanochlorobenzene[8] and 2:4-dimethylsulphonylchlorobenzene[9] approach closely to 2:4-dinitrochlorobenzene in reactivity, and also, as will be seen later, by similar observations made during the present investigation. Further, the nitro-group does not seem to be alone in its capacity for additive complex formation, for it has been shown that additive compounds may be prepared from s-tricyanobenzene and from trimesic acid trichloride[10]. An alternative to, or a modification of Kenner's theory not requiring such a uniqueness of the nitro-group is therefore desirable.

That Kenner's views, adequate as a whole at the time of communication, should still be accepted in their entirity, is largely due to the failure to recognise the potentialities of other

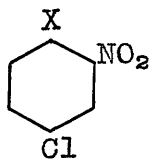
cationoid groups. The preoccupation with the nitro-group has led to a good deal of work on steric effects involved[11] and on further theories of the mechanism of the convertion from initial additive compounds to final condensation products[12], but it has also led to delay in the development of an important aspect of aromatic cationoid reactivity. It is only in recent years[13] that investigations concerning this have been commenced.

It has been mentioned (p. 4) that, in general, Schöpff's types of compound have been adhered to in the study of group mobility. A new type of reactive compound - the chloronitrosulphones represented by A and B below - has, however, been noted[14]. These display a reactivity comparable with 2:4-dinitrochlorobenzene coupled with general mobility of all three substituents.

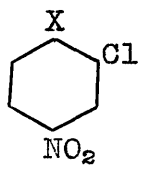
A



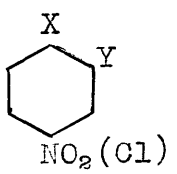
B



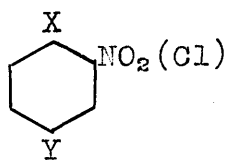
C



D



E



F

With the exception of a few isolated cases such as 2-chloro-4-nitrobenzaldehyde[5] and ortho- and para-nitrobenzonitriles[15], examples of group mobility conferred by a single meta-directing group other than the nitro-group - a state of affairs not covered by Schöpff's Rule - had hitherto been unknown. Considering these examples along with the two sulphone types, A and B, we find that a number of developments, so far unsuspected, are foreshadowed. The most prominent of these is latent in the fact that the nitro-group does not, as is the case with the majority of previously known types, predominate the system entirely, otherwise the sulphonyl group alone would be replaceable. In other words, we have a sulphonyl group exercising almost as powerful an effect on ortho-para-substituents as does the nitro-group itself. If, therefore, this unusually strong influence could be shown to be a property possessed not only by the sulphonyl group, but also by other meta-directing group, it would be possible to put forward a hypothesis explaining the forces here in action as an alternative to that proposed by Kenner. Such a hypothesis would, in contrast to Kenner's, be based merely on a difference in degree of activity between the nitro-group and other meta-directing

groups rather than on a difference in mode of reaction. In pursuance of this aim, various types of "negatively" substituted compounds represented by the structures C - F (X and Y = CN, CO and SO_2R variously situated) were examined.

CHAPTER I.

THE MOBILITY OF GROUPS IN SUBSTITUTED BENZONITRILES.

In extending the study of the effect on group mobility of "negative" substituents to groups other than the sulphonyl group, a fairly wide choice is available. The desirability of specific properties in such a substituent, however, influenced the selection considerably. Thus, the adoption of the cyano-group as being suitable for the purpose was decided upon for the following reasons:-

(a) Its powerful activating influence (c.f. cyanacetic ester, 2:4-dicyanochlorobenzene etc.).

(b) Its freedom from interaction with the reagents used in the investigation.

(c) Its powerful attachment to the nucleus - a property which might be expected to allow of its remaining unattacked.

(d) Its easy convertion to other groups such as amido, carboxylic and carbonyl groups.

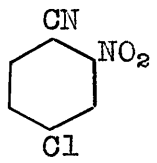
Two reagents - piperidine and alkaline p-thiocresol - were used in the investigation. These yielded, by the replacement of appropriate substit-

uents, piperidino-derivatives and sulphides respectively, and the structures of the reaction products were indicated by the groups replaced. Qualitative tests for anions (Cl, NO_2, etc.) in the reaction mother liquors and quantitative analysis of the reaction products were taken as sufficient for determining structure. In most cases the reaction with alkaline p-thiocresol took place almost instantaneously under the conditions used and hence could not be utilised for comparing reactivities. On the other hand, the rates of reaction with piperidine showed considerable variation and furnished a rough comparison of reactivity.

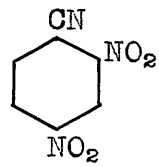
The set of seven benzonitriles examined by these methods is readily subdivided into two series. The first series consists of the three parent chloronitro- and dinitrobenzonitriles (I-III), from which the second series comprising four nitro- and chlorosulphonylbenzonitriles (XI-XIV) was derived.

The first three nitriles - 2-nitro-4-chlorobenzonitrile (I), 2:4-dinitrobenzonitrile (II) and 2-chloro-4-nitrobenzonitrile (III) were readily obtained from the corresponding chloronitro- and dinitroanilines by means of the Sandmeyer Reaction

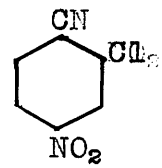
using potassium nickelocyanide.



I



II

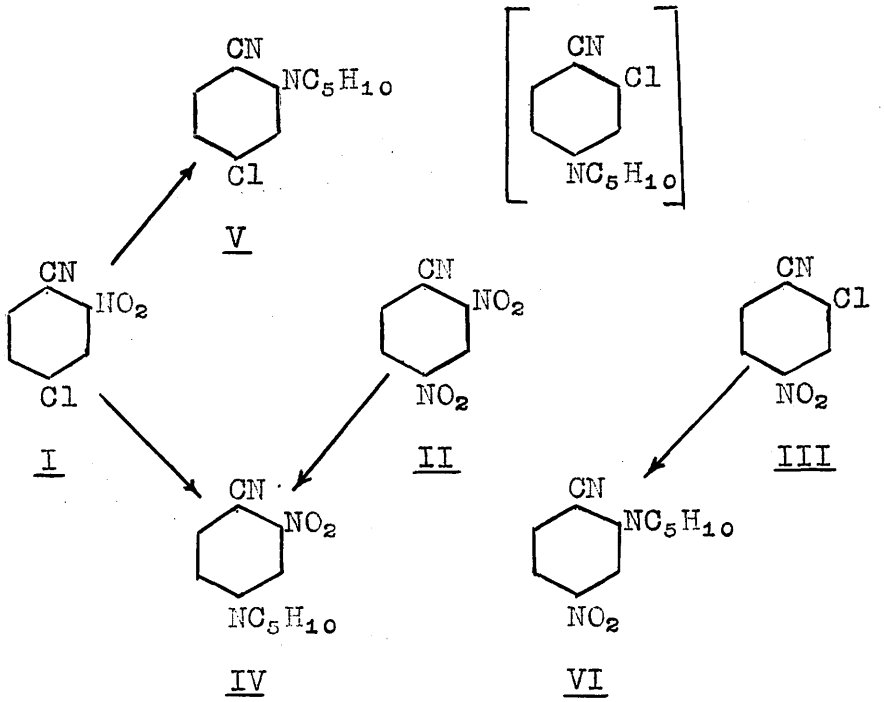


III

Some difficulty in the purification of I and II was encountered but was finally overcome by repeated crystallisation. III was much more readily purified by steam distillation followed by one crystallisation.

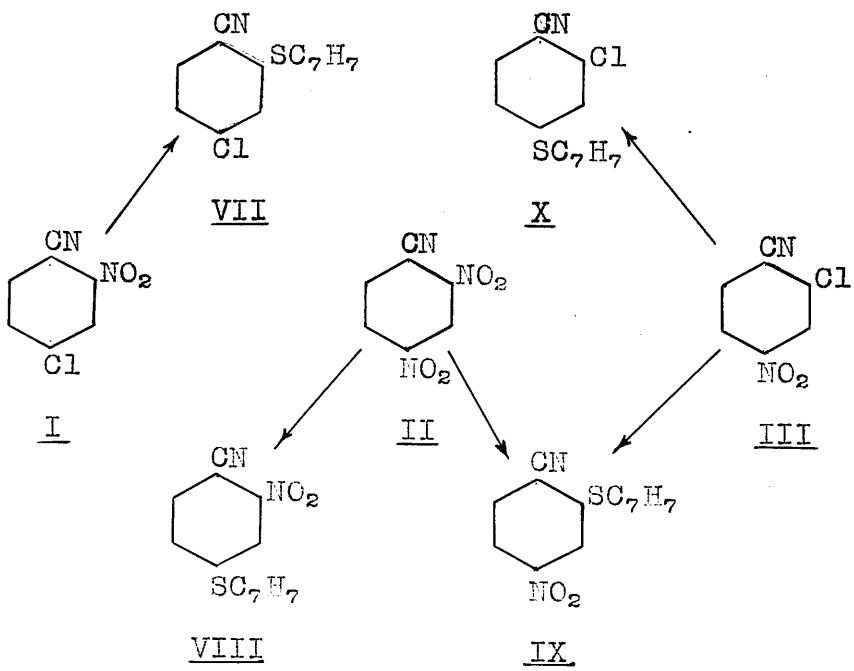
Reactions between these compounds and piperidine proceeded smoothly and rapidly with the replacement of either a chlorine atom or a nitro-group. There were indications that, in each of the three compounds, both substituents other than the cyano-group had been replaced in separate molecules, but only from 2-nitro-4-chlorobenzonitrile were two corresponding reaction products isolable. These were 2-nitro-4-piperidinobenzonitrile (IV) and 2-piperidino-4-chlorobenzonitrile (V). The former was also obtained as the only workable product from 2:4-dinitrobenzonitrile in which case it was accompanied by a considerable quantity of tar. 2-chloro-4-nitrobenzonitrile yielded 2-piperidino-4-nitrobenzo-

nitrile (VI).



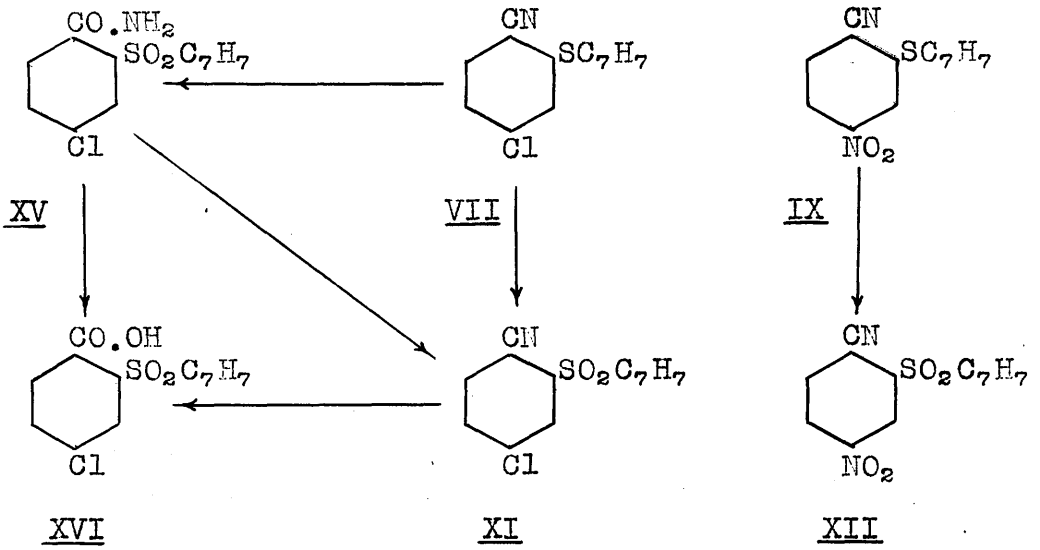
With alkaline p-thiocresol, also, reaction was very rapid, but reduction reactions involving the nitro-group interfered to some extent, particularly with 2-chloro-4-nitrobenzonitrile (III). Under the standard conditions this compound was reduced quickly and completely to the corresponding azoxy-derivative, no appreciable replacement of groups being effected. By suitable alterations to the conditions - lowering of temperature, use of a defficiency of alkali and use of a minimum of alcohol as solvent - replacement reactions were finally brought about, 2-p-tolylthio-4-nitrobenzo-

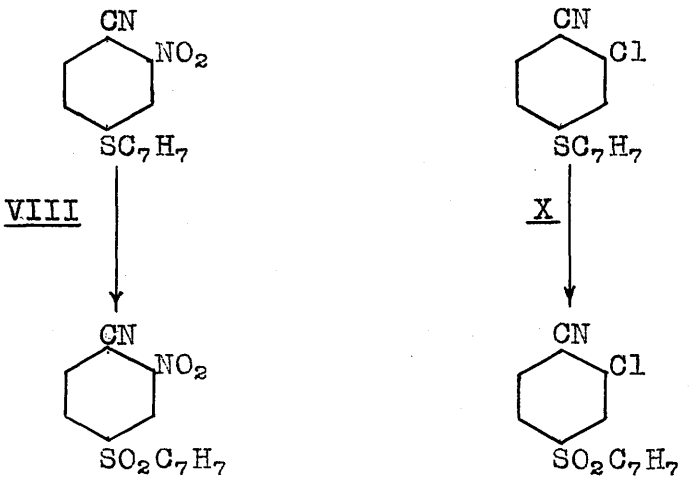
nitrile (IX) and 2-chloro-4-p-tolylthiobenzonitrile (X) being produced in approximately equal quantities. 2-Nitro-4-chlorobenzonitrile (I), likewise, showed a tendency toward reduction, made evident by a relatively poor yield of 2-p-tolylthio-4-chlorobenzonitrile (VII), the sole replacement product isolated, and by the formation of di-p-tolyl disulphide, a compound which always accompanies such reduction reactions. The yield of VII, however, was sufficiently high to make any change in experimental conditions unnecessary. 2:4-Dinitrobenzonitrile (II) reacted with no indication of reduction to give both 2-p-tolylthio-4-nitrobenzonitrile (IX) and 2-nitro-4-p-tolylthiobenzonitrile (VIII). The former was in great preponderance.



The second series of nitriles - 2-p-tolylsulphonyl-4-chlorobenzonitrile (XI), 2-p-tolylsulphonyl-4-nitrobenzonitrile (XII), 2-nitro-4-p-tolylsulphonylbenzonitrile (XIII) and 2-chloro-4-p-tolylsulphonylbenzonitrile (XIV) - was derived by oxidising the respective sulphides (VII - X above) with 30% hydrogen peroxide in glacial acetic acid. In the main these oxidations proceeded without complication, but the reaction product from 2-p-tolylthio-4-nitrobenzonitrile (VII) consisted of a mixture of two compounds m.p.'s 187° and 196°C respectively. The higher melting material was shown to be the amide (XV), first by dehydrating to the nitrile (XI, the lower melting material) with phosphorus pentoxide, and secondly by converting to the acid (XVI) by treating with nitrous acid. The nitrile (XI), in turn, was hydrolysed, with some difficulty, to the acid using 60% sulphuric acid. It follows, therefore, that oxidation to the cyano-sulphone (XI) is not likely to be the first stage in the formation of the amido-sulphone (XV), since the prevailing conditions can scarcely be compared with those necessery to effect hydrolysis of XI. It is more probable that the cyano-sulphide (VII) is hydrolysed to an amido-sulphide which is then oxid-

ised to the amido-sulphone (XV)





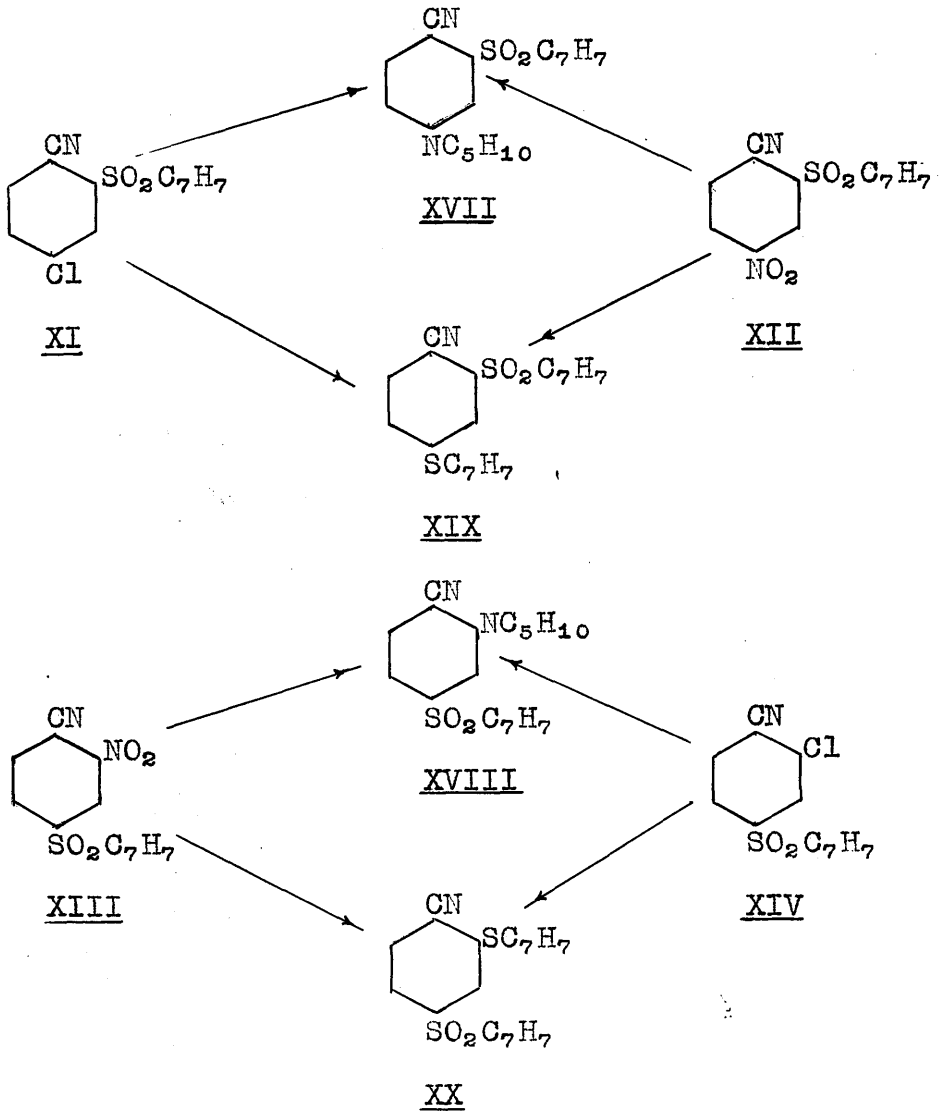
The sulphones (XI - XIV above), when examined by the methods used for the chloronitro- and dinitrobenzonitriles mentioned previously, behave in a similar manner to the latter. There are, however, two

interesting points in which their behaviour differs from that of the preceding nitriles. Firstly, and most significantly from the point of view of this work, the reactivity of the two chlorosulphones (XI and XIV), as revealed by speed of reaction with boiling piperidine, is considerably less than that of the chloronitro- and dinitrobenzonitriles as well as that of the two nitrosulphones (XII and XIII). At the same time, however, a high order of reactivity is maintained despite the fact that nitro-groups are entirely absent. Secondly, whereas the chloronitrodiphenylsulphones, mentioned in the introduction (p. 8), display mobility of all three substituents, and whereas the chloronitro- and dinitrobenzonitriles show mobility of both substituents other than the cyano-group, only one group - the nitro-group or the chlorine atom and never the cyano or the sulphonyl group - was replaceable in each of the sulphonylnitriles (XI - XIV). Although at first sight this appears to be at variance with the general tendency as noted so far, it is reasonably explained by assuming a fairly stable linkage between the sulphonyl group and the nucleus. Such a linkage might be unable to withstand the loosening effect of an ortho- or para-situated nitro-group and hence

its attack in the 2-nitro-4-chloro- and 2-chloro-4-nitrodiphenylsulphones,but it might sufficiently resist the loosening effect of an ortho- or para-cyano-group to allow of the attack of another centre of reactivity which would bring about the neutralisation of the whole system. A similar state of affairs is apparent in certain chloro- and nitrothioxanthone-S-dioxides mentioned in Chapter II. The same explanation is applicable with a greater degree of certainty to the cyano group which in no case is replaced. Here the attachment to the nucleus is so powerful that not even the combined effects of two nitro-groups is sufficient to impart mobility (c.f. 2:4-dinitrobenzonitrile,pp. I3 and I5)

As a consequence of the immobility of the sulphonyl group the reaction products from 2-p-tolylsulphonyl-4-chloro- and 2-p-tolylsulphonyl-4-nitrobenzonitriles (XI and XII) were identical as were those from the remaining pair of nitriles (XIII and XIV). That is,with piperidine XI and XII both yielded 2-p-tolylsulphonyl-4-piperidinobenzonitrile (XVII) and XIII and XIV both yielded 2-piperidino-4-p-tolylsulphonylbenzonitrile (XVIII). The chloro-compounds (XI and XIV) required twenty minutes and the nitro-compounds (XII and XIII) five minutes to

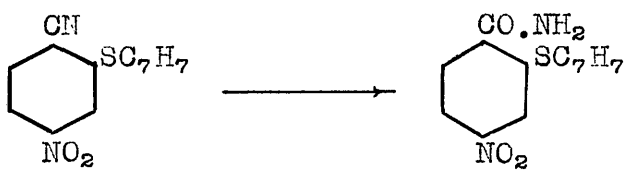
react with boiling piperidine



With alkaline p-thiocresol, likewise, XI and XII both gave 2-p-tolylsulphonyl-4-p-tolylthiobenzonitrile (XIX), and XIII and XIV gave 2-p-tolylthio-4-p-tolylsulphonylbenzonitrile (XX). Reactions with the chloro-compounds were slightly

slower than those with the nitro-compounds, ten and five minutes being required respectively.

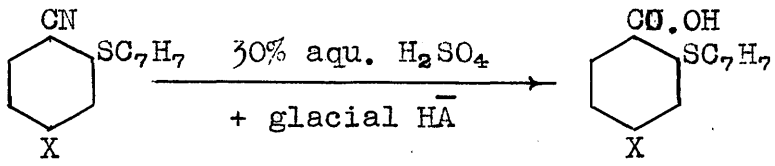
As a final experiment in the benzonitrile series 2-p-tolylthio-4-nitrobenzonitrile (VII) was treated with alkaline p-thiocresol in the hope of effecting the replacement of the nitro-group. This expectation, which was based on the simultaneous replacement of all three bromine atoms of 2-4-6-tribromonitrobenzene by alkaline p-thiocresol (discussed in Part II, p. 86), was, however, not fulfilled, the cyano-group being hydrolysed to an amido-group with the formation of 2-p-tolylthio-4-nitrobenzamide (XXI)



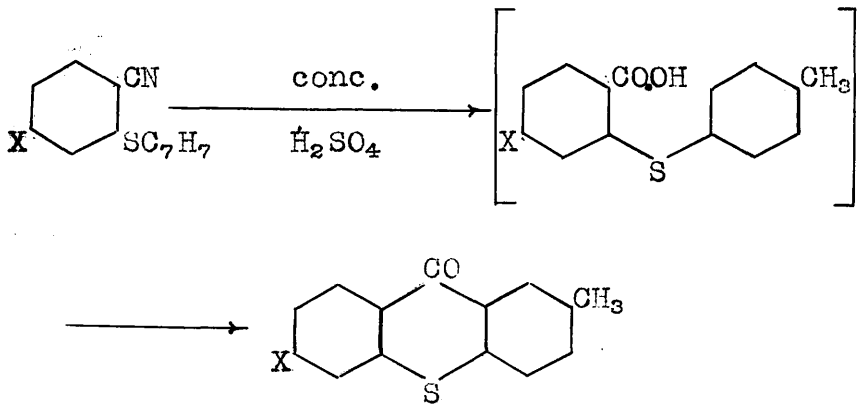
VII XXI

In conclusion, a reaction peculiar to the ortho-thio-derivatives and leading to the formation of thioxanthones is noted here in view of its use for confirming the structure of the ortho-thioethers. While regulated hydrolysis of these thio-compounds with 30% sulphuric acid in presence of sufficient glacial acetic acid to bring about solution results in the production of the correspond-

ing carboxy-acid (reaction A below), the use of concentrated sulphuric acid alone yields a 2:7-di-substituted thioxanthone by condensation of the carboxy-group with the adjacent nucleus (reaction B below).



Reaction A



Reaction B

Thioxanthones obtained from reaction B have been utilised for the preparation of thio-xanthone dioxides, the subject of the next chapter.

The high degree of reactivity displayed by the chloronitrosulphones (A and B p. 8) is, therefore, retained in analogous benzonitriles. The distribution of mobility between the various sub-

stituents in each of the two types of compound is, generally speaking, also comparable. The main differences between the benzonitriles and the chloronitrosulphones lie in the immobility of the cyano-group and of the sulphonyl group in the former. As has already been suggested (p. I8), this is probably due to the strength of the bonds between these groups and the nucleus, and is quite to be expected in the case of the cyano-group. With the sulphonyl group the question is a little more obscure, especially since this group is readily replaceable in the chloronitrosulphones; but, on the one hand, the sulphonyl group comes under the directive influence of the cyano-group and, on the other, under the directive influence of the nitro-group. The known difference in activating power between the two latter groups is therefore probably sufficient to account for the mobility of the sulphonyl group in the chloronitrosulphones and its immobility in the chloro- or nitrosulphonylbenzo-nitriles.

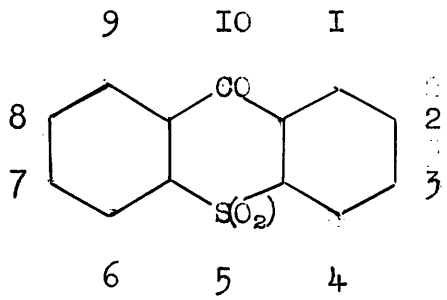
- - - - - - - - - - - - - - - - - - -

CHAPTER II.

THE MOBILITY OF GROUPS IN SUBSTITUTED THIOXANTHONE DIOXIDES.

The thioxanthone dioxides were chosen for the continuation of studies in group mobility partly for reasons of convenience (two of the five compounds examined were readily obtained from ortho-thiobenzonitriles - Chapter I,p. 22),but more especially for the interest attached to the carbonyl group and to the disposition of substituents throughout the system (see diagram below for numbering). For instance,it was expected that,in view of their general analogy with the foregoing nitriles in possessing one cationoid substituent which was not likely to be replaceable (the carbonyl group) and two potential anions of which one at least was a cationoid group,the thioxanthone dioxides would be most suitable for investigation. Benzophenones corresponding in structure to either the nitriles I,II and III (p. I3) or the thioxanthone dioxides of the following pages might well have been utilised for examining the influence of the carbonyl group, but it was considered that the thioxanthone dioxides

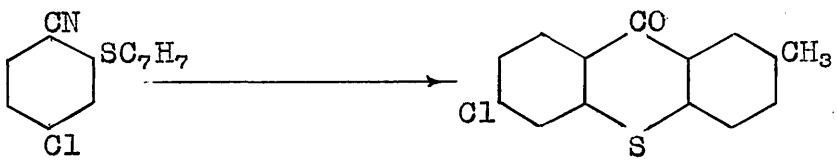
might provide some interesting results by virtue of the inclusion of the carbonyl and sulphonyl groups in a heterocyclic nucleus. This expectation has been more than fully realised, some interesting and unforeseen results having been obtained.



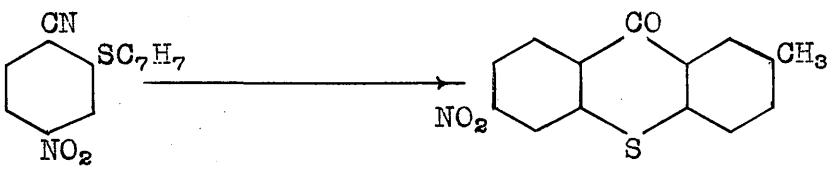
Thioxanthone (dioxide)

The thioxanthone dioxides described hereafter are all 7- or 8-chloro- and nitro-derivatives. The parent thioxanthones from which they were obtained were generally prepared by the internal condensation of ortho-thiobenzoic acids or the corresponding benzonitrile through the agency of concentrated sulphuric acid. 2-Methyl-7-chloro- and 2-methyl-7-nitrothioxanthones (XXII and XXIII) having already been obtained in this manner from 2-p-tolylthio-4-chloro- and 2-p-tolylthio-4-nitrobenzonitriles (VII and IX) respectively, the intention was to keep the 2-methyl group present throughout the whole series and to prepare 2-methyl-8-

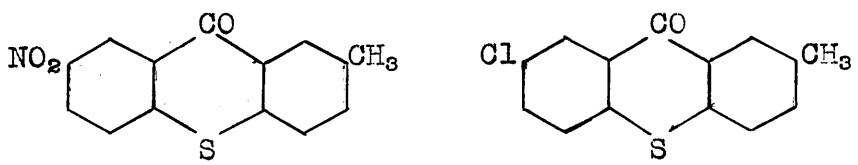
chloro- and 2-methyl-8-nitrothioxanthones (G and XXIV).



VII XXII

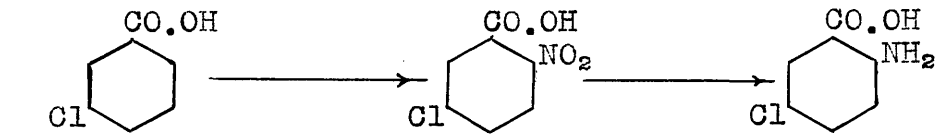


IX XXIII

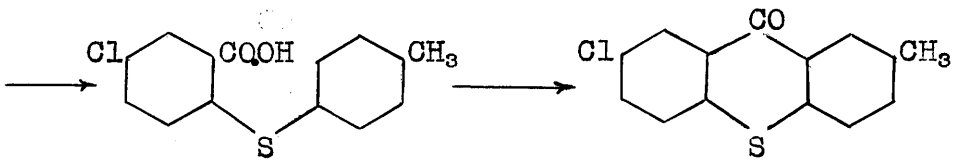


XXIV G

The nitro-derivative (XXIV) was readily obtained from 2-p-tolylthio-5-nitrobenzoic acid, but the chloro-derivative (G), the synthesis of which was attempted as shown below, could not be prepared owing to shortness of material at stage of conversion of 2-amino-5-chlorobenzoic acid (M) to 2-p-tolylthio-5-chlorobenzoic acid (K).

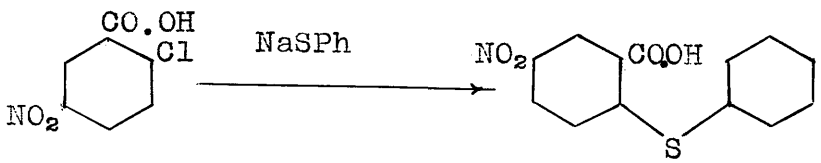


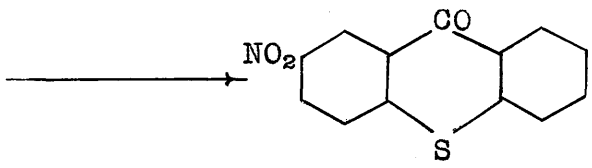
H



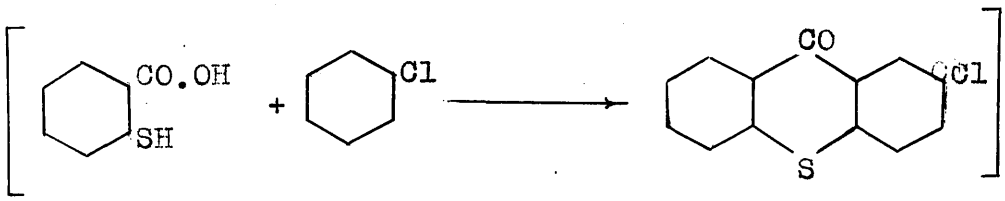
K G

Since this end could not be realised and since it was desirable to maintain the analogy between the two 7-substituted and between the two 8-substituted derivatives in order to keep a check on the products obtained with each reagent, the methyl group was ommited from the latter type. Accordingly, 8-(2)-chlorothioxanthone (XXV) being obtainable from outside sources, 8-(2)-nitrothioxanthone (XXVI) was prepared in the following manner:





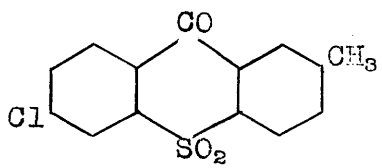
XXVI



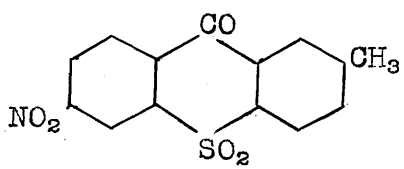
XXV

2-methyl-8-nitrothioxanthone (XXIV), having been prepared already by the same method as that used for 8-(2)-nitrothioxanthone (XXVI), was retained in the series for comparison with the latter.

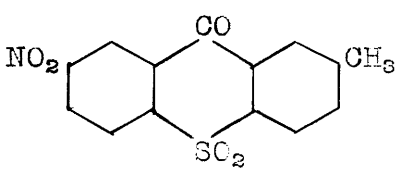
Oxidation of the thioxanthones XXII, XXIII, XXIV, XXV and XXVI yielded the respective dioxides XXVII, XXVIII, XXIX, XXX and XXXI.



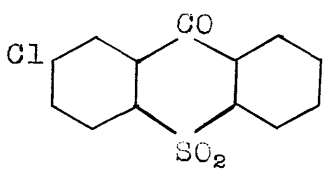
XXVII



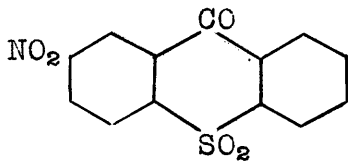
XXVIII



XXIX



XXX



XXXI

Oxidation by the usual method consisting of refluxing the thioxanthone in glacial acetic acid solution with 30% hydrogen peroxide until all colour is discharged proceeded readily enough, but required a period of about one hour for completion. The observation that 2-methyl-7-nitrothioxanthone in concentrated sulphuric acid was oxidised very rapidly on the addition of a few drops of 30% hydrogen peroxide led to a useful oxidation method for thioxanthones. This consisted in dissolving the thioxanthone in concentrated sulphuric acid with a little glacial acetic acid to aid solution and to temper the violence of the reaction and adding 30% hydrogen peroxide a few drops at a time until all colour was discharged. The resulting dioxide precipitated completely on the addition of water. The reaction appears to be peculiar to the thioxanthones, for little success accompanied attempts to apply it to other types of compounds which were known to be difficult to oxidise. For example, comparison with

the standard method showed a slight increase in speed of reaction with 2:2':4:4'-tetranitrodiphenyl-sulphide, little or no increase in speed of reaction with 2:2':4:4':6-pentanitrodiphenylsulphide and complete failure with 2:2':4:4':6:6'-hexanitro-diphenylsulphide.

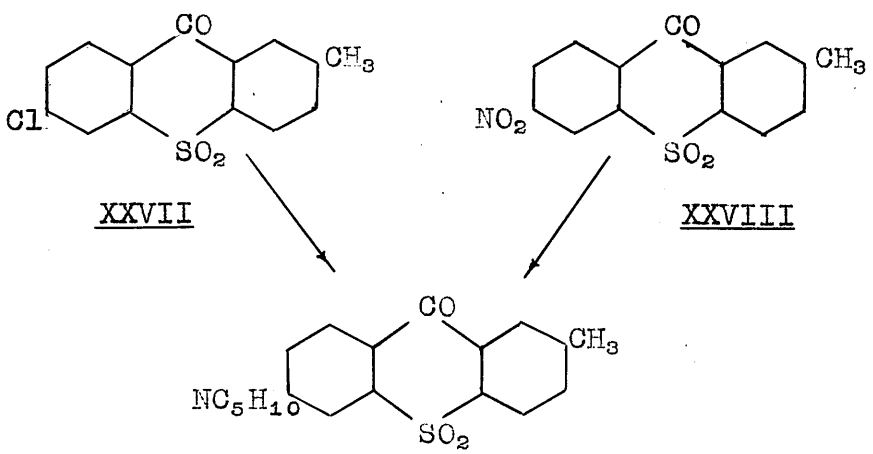
As the degree of mobility of a substituent has been found to be considerably influenced by the position which it occupies in the molecule of a thioxanthone dioxide, the derivatives described in the following pages have been divided into two sections according to their structure. Section I consists of 7-substituted thioxanthone dioxides in which a chlorine atom ar a nitro-group is directly activated by the carbonyl group. Section II consists of 8-substituted thioxanthone dioxides in which a chlorine atom or a nitro-group is directly activated by the sulphonyl group.

- - - - - - - -

SECTION I

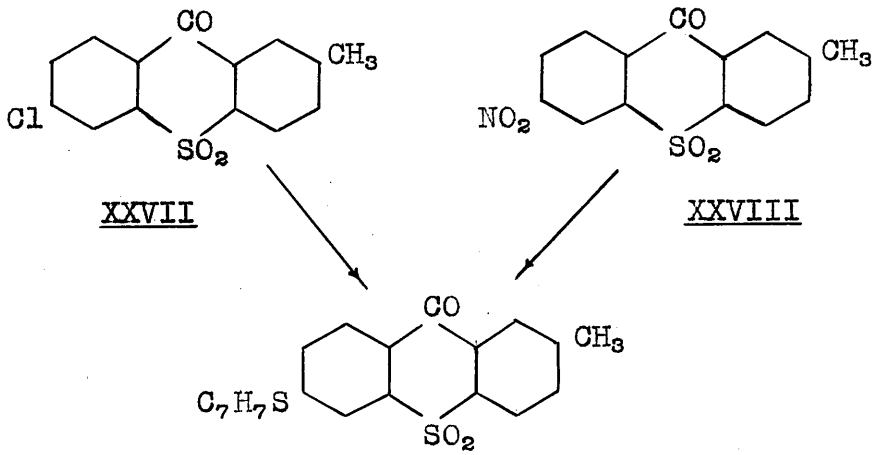
2-Methyl-7-chloro- and 2-methyl-7-nitro-thioxanthone-S-dioxides

Reactions between these two compounds and piperidine proceeded readily with the replacement of the chlorine atom of the one and the nitro-group of the other. 2-Methyl-7-chlorothioxanthone-S-dioxide (XXVII) reacted in twenty minutes and 2-methyl-7-nitrothioxanthone-S-dioxide (XXVIII) in five minutes and both yielded the same product, 2-methyl-7-piperidinothioxanthone-S-dioxide (XXXII). With alkaline p-thiocresol reaction followed the same course. Both compounds reacted in from five to ten minutes and gave identical products - 2-methyl-7-p-tolylthio-thioxanthone-S-dioxide (XXXIII).



XXVII XXVIII

XXXII



XXVII XXVIII

XXXIII

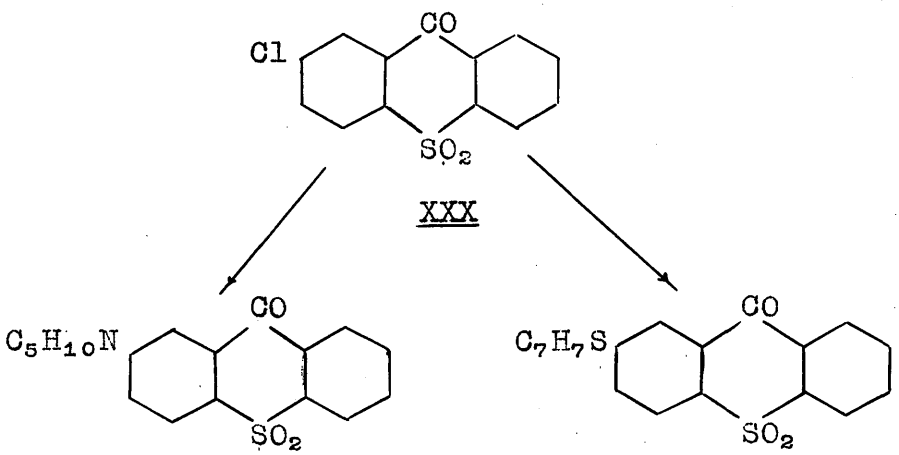
SECTION II

8-(2)-chloro- and 8-(2)-nitrothioxanthone- and 2-methyl-8-nitrothioxanthone-S-dioxides

In contrast to the 7-nitrothioxanthone-S-dioxides the 8-nitrothioxanthone-S-dioxides show little or no mobility of the nitro-group when treated with piperidine or alkaline p-thiocresol. Instead, the sulphonyl group which is situated in the para-position to the nitro-group is replaced with the production of a sulphinic acid. The 8-chloro-derivatives, however, have a replaceable halogen atom as do the 7-chloro-derivatives.

8-(2)-chlorothioxanthone-S-dioxide (XXX) reacted with piperidine in 120 minutes and with

alkaline p-thiocresol in I20 minutes to give 8-(2)-piperidino- and 8-(2)-p-tolylthio-thioxanthone-S-dioxides (XXXIV and XXXV) respectively.



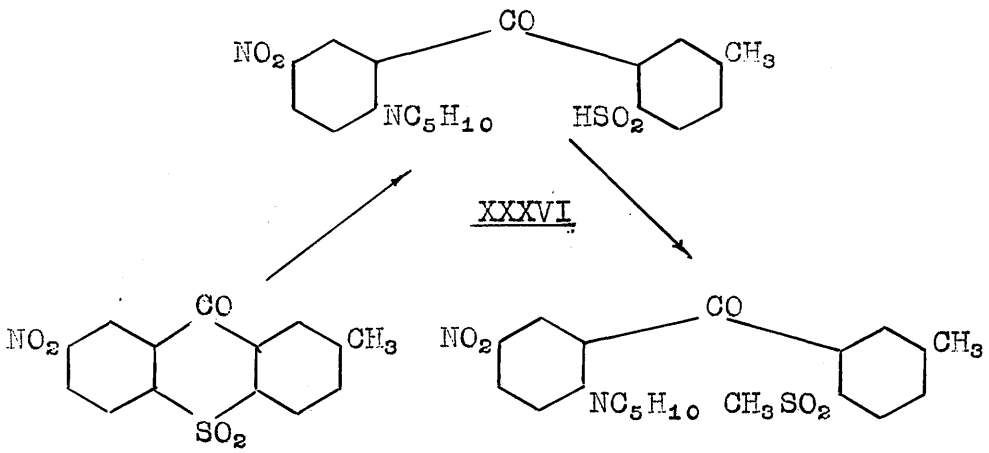
XXX

XXXIV

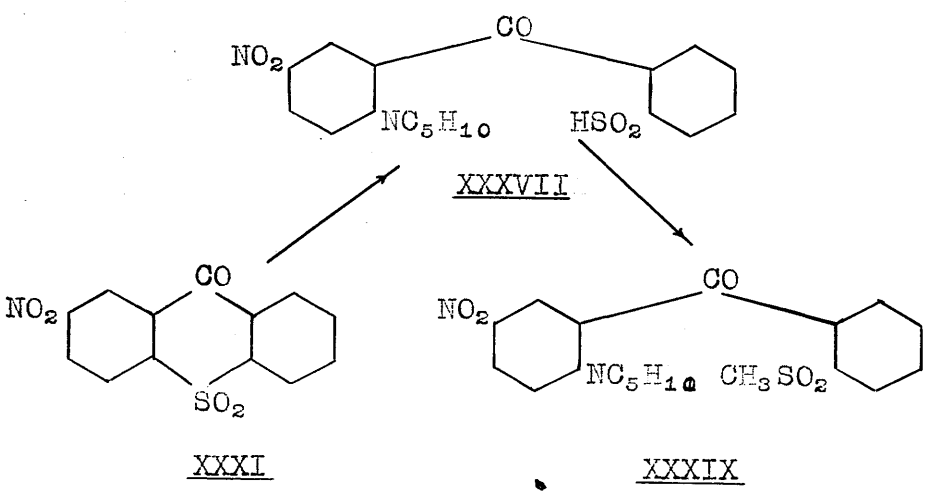
XXXV

As has been mentioned already 2-methyl-8-nitrothioxanthone-S-dioxide and 8-(2)-nitrothio-xanthone-S-dioxide (XXIX and XXXI) reacted with piperidine to give sulphinic acids. In both cases this reaction required 45minutes for completion and the respective sulphinic acids (XXXVI and XXXVII) resulted. The latter,being very difficult to isolate in a pure condition,were identified as the corresponding methyl sulphones (XXXVIII and XXXIX) to which they were converted by treatment of their sodium salts with methyl iodide. A small quantity of an uncrystallisable basic material which,in the case of

8-(2)-nitrothioxanthone-S-dioxide, was suspected of being 8-(2)-piperidinothioxanthone-S-dioxide (XXXIV) was also isolated. This could not be identified with the product from 8-(2)-chlorothioxanthone-S-dioxide (XXX) nor could it be converted to a hydrochloride or picrate capable of purification.



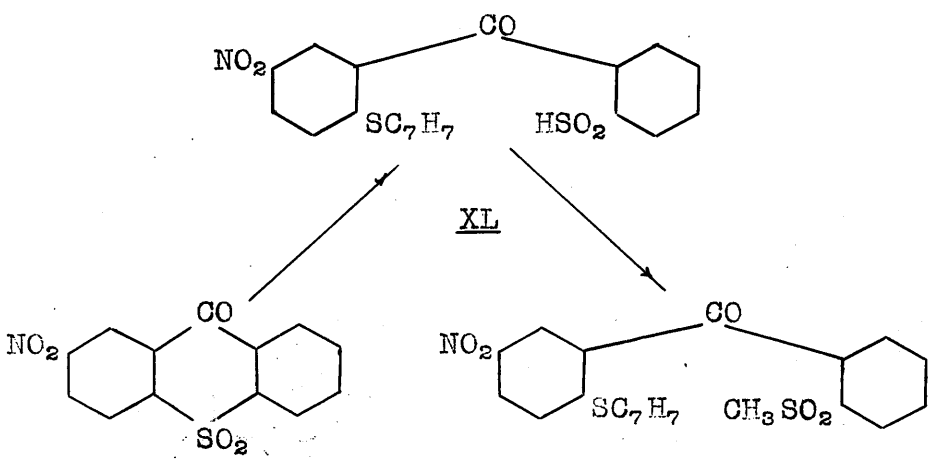
XXIX XXXVIII



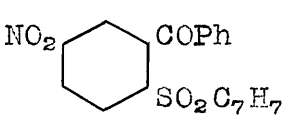
XXXI XXXIX

2-methyl-8-nitrothioxanthone-S-dioxide was

not treated with mercaptide. 8-(2)-Nitrothioxanthone-S-dioxide (XXXI), however, was examined with this reagent and reaction which required 40 minutes was found to take the same course as that with piperidine. The sulphinic acid (XL) again was not isolated as such, but was identified after methylation as 2-p-tolylthio-5-nitro-2'-methylsulphonylbenzophenone (XLI)



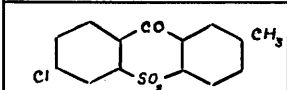
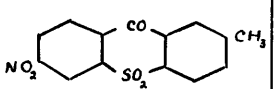
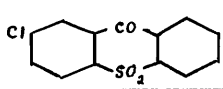
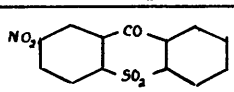
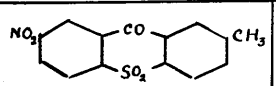
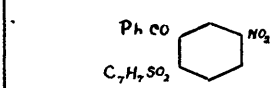
XXXI XLI



XLII

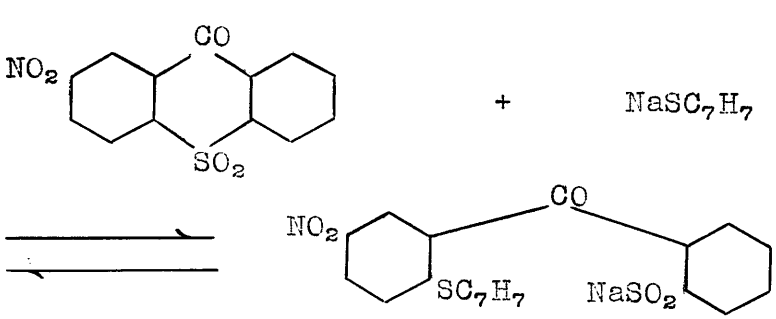
The thioxanthone dioxides of Section I, it will be seen, display a reactivity (based on the speed of reaction with piperidine) comparable with

the analogous benzonitriles (2-p-tolylsulphonyl-4-chloro- and 2-p-tolylsulphonyl-4-nitrobenzonitriles, XI and XII, pp. I8-20), but those of Section II are relatively inactive. A comparative experiment with analogous 2-p-tolylsulphonyl-5-nitrobenzophemone (XLII) shows the latter to be ten times as reactive (approximately) as 8-(2)-nitro- or 2-methyl-8-nitro-thioxanthone-S-dioxides (XXXI or XXIX). The table below showing reaction times (qualitative only) with boiling piperidine and alkaline p-thiocresol makes the position clearer.

Compound	Time of Reaction	
	Piperidine	p-Thiocresol
	20 mins.	5-I0 mins.
	5 "	5-I0 "
	I20 "	I20 "
	45 "	40 "
	45 "	40 "
	5 "	not taken

From a study of compounds examined up to this point it might be reasonably expected that

8-(2)-nitrothioxanthone-S-dioxide, if normal effects were functioning, would be more reactive than 2-methyl-7-chlorothioxanthone-8-dioxide and at least to be just as reactive as 2-p-tolylsulphonyl-5-nitrobenzophenone (XLII), whereas, in the first instance, the reverse is the case, and, in the second, the thioxanthone dioxide is not so reactive as the benzophenone. Clearly in the thioxanthone dioxides there is some influence, absent from or merely latent in other types of compound, making itself evident by depressing the reactivity. What this influence may be has not as yet been explained. The possibility of a reversible reaction in the case of the nitro-derivative (see equation below) in which the sulphonyl linkage is ruptured, while explaining the sluggishness of the particular example under consideration, does not account for the still slower reaction of 8-(2)-chlorothioxanthone-S-dioxide for which no such mechanism is possible.



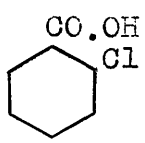
In general, then, the thioxanthone dioxides behave in a similar manner to the benzonitriles of Chapter I, the reactivity being of a high order, especially in the 7-substituted derivatives in which the carbonyl group directly activates the mobile groups. In view of the tendencies so far noted, the restriction of mobility to the chlorine atoms and nitro-groups in all cases except the 8-nitro-derivatives is not altogether surprising, and the analogy between the chloronitrosulphones mentioned in the introduction and the 8-nitro-derivatives is sufficient justification for the expectation that the sulphonyl linkage would be ruptured in the latter compounds. Comparison beyond this point is, however, impossible. The change of structure from the 7- to the 8-substituted derivatives appears to introduce further factors, so far unencountered, resulting in considerable difference in reactivity and not readily explainable by such external influences as that excercised by reagents. The main importance of the results of this chapter, however, lies in the observation that the carbonyl group has an effectiveness comparable with that of the cyano and sulphonyl groups.

- - - - - - - - - - - - - - - - - -

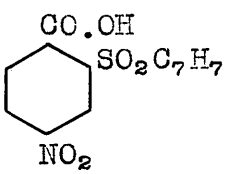
CHAPTER III.

THE MOBILITY OF GROUPS IN SUBSTITUTED BENZOIC ACIDS.

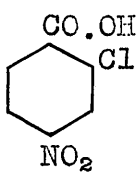
Certain substituted benzoic acids were prepared during the foregoing investigations. Since this material was on hand it was decided to include it in the examination for comparative purposes. The acids XLIII, XLIV, XLV, XLVI and XVI shown below were therefore treated with piperidine and alkaline p-thiocresol.



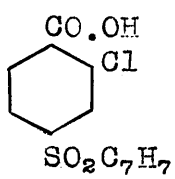
XLIII



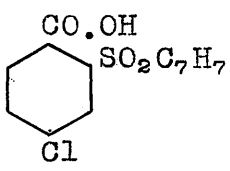
XLV



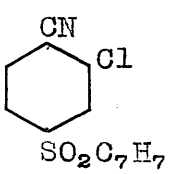
XLIV



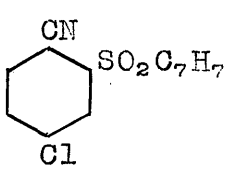
XLVI



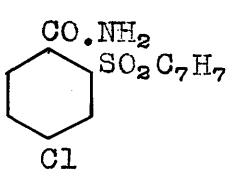
XVI



XIV



XI

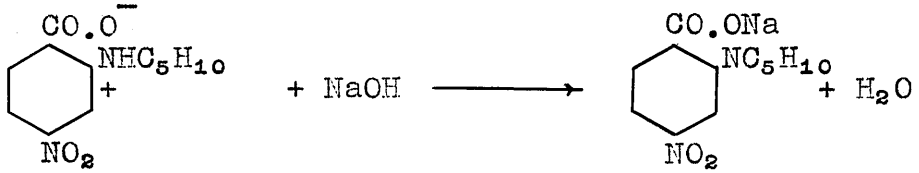


XV

2-p-tolylsulphonyl-4-nitrobenzoic acid (XLV) was prepared by the action of sodium p-toluenesulphinate on sodium 2-chloro-4-nitrobenzoate in the presence of copper-bronze. 2-Chloro-4-p-tolylsulphonylbenzoic acid (XLVI) and its isomer (XVI) were obtained by the hydrolysis of the respective nitriles (XIV) and (XI). The latter was also prepared from 2-p-tolylsulphonyl-4-chlorobenzamide (XV) by the action of nitrous acid.

Unlike the benzonitriles and the thioxanthone dioxides, the benzoic acids showed little or no reactivity (except in the presence of catalysts). The sulphonyl derivatives, XLV, XLVI and XVI failed to react with piperidine even when refluxed for eight hours. o-Chlorobenzoic acid (XLIII), after refluxing for six to seven hours, yielded a minute quantity of a high melting material which may have been 2-piperidinobenzoic acid. 2-Chloro-4-nitrobenzoic acid (XLIV) alone showed any definite reactivity. When refluxed with piperidine for four to five hours, this compound gave a high melting product with properties resembling those of 2-amino-4-nitrobenzoic acid. It dissolved in alkali to give a red-brown solution from which it was reprecipitated as a colourless solid by dilute acid. In hot alcoholic

solution a yellow-brown colour was developed which disappeared on cooling. The latter colour change was probably due to the dissociation of an internal salt, and the former to a complete breaking up of the internal salt according to the equation:



Colourless internal salt

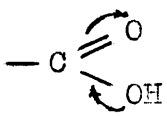
Red nitro-amine

Although the analysis of the compound was not conclusive for the 2-piperidino-4-nitro-benzoic acid structure, the presence of chloride ions in the reaction mother liquors coupled with the foregoing changes and the high melting point - 212°C points to the probability of its being this.

Alkaline p-thiocresol failed to react with 2-chloro-4-nitrobenzoic acid and also with 2-p-tolylsulphonyl-4-nitro- and 2-chloro-4-p-tolyl-sulphonylbenzoic acids. For this reason the reactions between alkaline p-thiocresol and the remaining two acids were not attempted.

The low order of reactivity observed in the substituted benzoic acids is not

altogether unexpected. The carboxyl group possesses certain peculiarities of structure which are not shared by the cyano, sulphonyl or carbonyl groups and which have led to its being regarded as an internally neutralised system represented thus:



Such an internal neutralisation must reduce the tendency, as compared with the carbonyl group of a ketone, either to induce a "negative" condition in an attached nucleus or to exert within that nucleus an electromeric effect. Further, when the conditions of reaction are powerfully basic, as is the case with those dealt with throughout this work, the carboxyl group will be present as the anion $-CO.O^-$ and its value as an activating agent will thereby be further reduced.

- - - - - - - - - - - - - - -

GENERAL DISCUSSION.

- - - - - -

Kenner's theory (p. 6), it will be remembered, was criticised on the ground that, since it attributed a unique property (additive complex formation) to the nitro-group, it did not interpret the full significance of the data. In view of more recent observations, and especially of those contained in the foregoing description, it is possible to suggest an alternative which postulates similarity rather than dissimilarity in behaviour between the nitro-group and other cationoid groups.

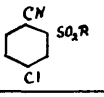
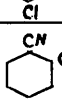
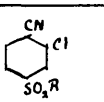
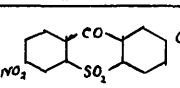
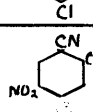
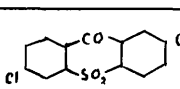
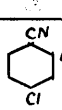
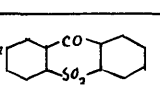
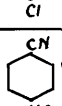
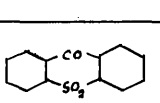
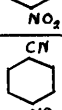
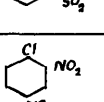
One relevant possibility is that cationoid groups in general, under certain conditions, are capable of imitating the nitro-group with respect to the formation of additive complexes. This must not be dismissed as being unlikely, for, as mentioned before (p. 7), additive compounds of s-tricyano-benzene and of trimesic acid trichloride have been isolated. Until further evidence is available, however, no more can be said concerning this question. On the other hand, there is an alternative theory, based on another of Kenner's concepts - the

"negative condition" of the nucleus -,capable of a much fuller discussion.

Kenner based the idea of a "negative condition" of the nucleus on an observation,made by Lobry de Bruyn[16],that s-trinitrobenzene and m-dinitrobenzene have nitro-groups replaceable by sodium methoxide. This replaceability,being unexplainable by the directive influence of the nitro-groups upon each other,he attributed to a distributed influence resulting in activation at all centres of the nucleus. The hypothesis,however,does not appear since to have been referred to,and until the present work,which again brings it to the fore,was undertaken there was little further evidence in support of it.

Referring to the table below (all reactions were carried out on a qualitative basis and results are not strictly quantitative) we have:

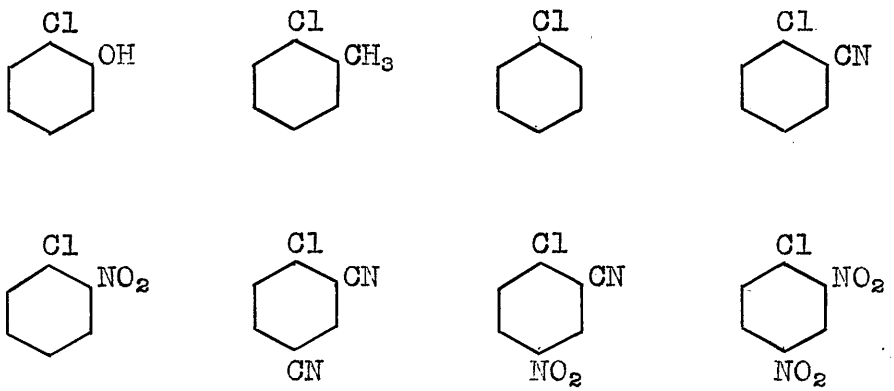
Ortho- and para-chlorobenzonitriles inactive; 2-nitro-4-cyano- and 4-nitro-2-cyanochlorobenzenes (Schöpff) very reactive; and 3-nitro-4-cyano- and 3-nitro-6-cyanochlorobenzenes practically as reactive as the latter.

Compound	Mobile Groups	Reactivity	Compound	Mobile Groups	Reactivity
	(Cl)	almost nil		Cl	moderate
	(Cl)	almost nil		Cl	moderate
	Cl	high		NO_2	very high
	Cl	high		Cl	moderate
	NO_2, Cl	fairly high		SO_2R	fairly low
	NO_2, Cl	fairly high		Cl	fairly low
	NO_2	very high		Cl	very high
	NO_2	very high			

Since in the cases of 3-nitro-4-cyano- and 3-nitro-6-cyanochlorobenzenes the nitro-group cannot directly affect the chlorine atom (or itself), the influence of this group must be distributed throughout the nucleus as a whole, and the actual mobility is imparted mainly by the cyano-group. As a result of this distributed effect the position taken up by the entrant nitro-group plays no very great part in the reactivity of the resulting compound. The reactivity of 2-nitro-4-cyano- and

of 4-nitro-2-cyanochlorobenzenes, being slightly higher than the two last mentioned, requires that the main power of the effect be felt in the ortho- and para-positions. Stated briefly, the influence of the nitro-group, or, as a comparison with the remaining compounds in the above table will show, of any cationoid group is felt generally throughout the nucleus, but has its focal points in the ortho- and para-positions.

To find an explanation for this state of the nucleus a wider selection (see table below) of compounds of differing types must be examined.



Taking nitration as being representative of replacement of hydrogen, and reaction with alcoholic ammonia as being representative of replacement of chlorine in the above compounds, we find that, roughly speaking, the former becomes increasingly

difficult as we proceed from left to right, while the latter becomes correspondingly easier. Now the first of these processes, since it requires the ejection of hydrogen as a cation, also requires, if reaction is to proceed readily, that the nucleus should be willing to accept a negative charge. Conversely the second process, which involves the removal of chlorine as an anion, requires that the nucleus should readily accept a positive charge. That the presence of methyl groups or hydroxyl groups induces the first, and the presence of cyano-groups and nitro-groups the second condition of the nucleus is most simply explained as follows;-

In the unsubstituted state, benzene is essentially anionoid in character; that is, the nucleus is exceedingly reluctant to assume a positive charge which is possible only if hydrogen is removed as an anion. The position is substantially the same with chlorobenzene (and even more so with chlorotoluene and chlorophenol), and we find that the chlorine atom which, being a potential anion, might be expected to undergo replacement, is firmly held except under the most rigorous conditions. The introduction into any positions in the nucleus of meta-directing groups in sufficient number overcomes

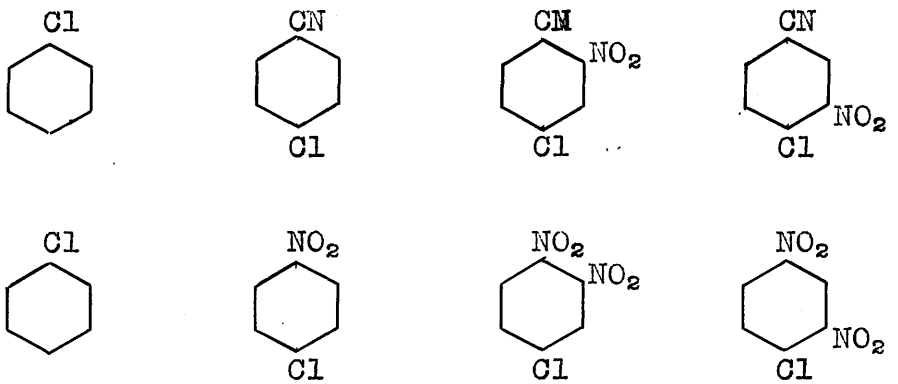
the resistance and the effect becomes apparent in the mobility of potential anions situated in the ortho- or para-positions to any one of these groups. The reactivity increases as more meta-directing groups enter the nucleus. According to contemporary theory, the resistance toward receiving a positive charge is broken down by the tendency of meta-directing groups to withdraw electrons from the nucleus. The withdrawal may be the result of an inductive or of an electromeric effect, but in either case a defficiency of electrons chiefly in the ortho- and para-positions is caused thereby loosening the attachment of potential anions at these points and creating a general tendency to make good the deficiency from outside of the molecule. This tendency is satisfied when the molecule is attacked by an anionoid reagent which replaces a cationoid group.

In the structure adhered to - I:2:4-trisubstituted benzenes - in this work, each substituent, which is a cationoid group, is situated in either the ortho- or the para-position to one or two of the remaining substituents. Consequently all are activated, and those groups capable of becoming stable anions on replacement are rendered mobile. The

degree of mobility of any one group depends on the cumulative influence of several factors such as the stability of the anion produced on replacement, the number and power of the groups directly activating it and the nature of the reagent employed. For example, in the chloronitrodiphenylsulphones (A and B, p. 8) all groups may become stable anions on replacement, the sulphonyl group is activated by the nitro-group and the nitro-group and chlorine atom are each activated by the sulphonyl group giving a fairly well balanced activation between all three groups. With sodium mercaptide the sulphonyl group is replaced, with piperidine the chlorine atom is mainly replaced and with sodium methoxide mainly the nitro-group. Again, in the chloronitrobenzonitriles (I and II, p. 13) conditions are the same with the exception that the cyano-group becomes an anion only with considerable difficulty and is never replaced. Sodium mercaptide replaces mainly the nitro-group and piperidine mainly the chlorine atom.

Now let us consider the relative position of the nitro-group amongst meta-directing groups in general from the point of view of nuclear resistance toward acceptance of a positive charge. The resistance, as such, must have some limiting value

which is, generally speaking, exceeded by the influence of a single nitro-group or by the joint influence of two or more meta-directing groups which may or may not be nitro-groups. Commencing with chlorobenzene which is inactive we may introduce a cyano- or a nitro-group in the para-position, say. p-Chlorobenzonitrile is inactive - p-chloronitrobenzene is reactive; that is, the nitro-group overcomes the resistance, but the cyano-group does not do so effectively.



On the other hand, the introduction of a further nitro-group into p-chlorobenzonitrile and p-chloronitrobenzene (Ist pair above), either in the ortho- or in the meta-position with respect to the chlorine atom, results in both cases in a pair of compounds of roughly comparable reactivity (2nd

or 3rd pair above). In other words, from a comparison of p-chlorobenzonitrile and p-chloronitrobenzene, it would seem that the nitro-group far outweighs the cyano-group in activating power, while, from a comparison of 3-nitro-4-cyanochlorobenzene with 3:4-dinitrochlorobenzene, or of 2-nitro-4-cyanochlorobenzene with 2:4-dinitrochlorobenzene, the activating power of the nitro-group appears to be only slightly in excess of that of the cyano-group. These facts are by no means irreconcileable with each other, and indeed the latter, taken in conjunction with fact that p-chloronitrobenzene is comparatively feebly reactive justifies the proposal that the nitro-group is just able to overcome nuclear resistance, while other meta-directing groups fail to do so; or, otherwise staded, that the nitro-group is not so greatly superior to other meta-directing groups as has hitherto been believed. Regarding, in this way, the superiority of the nitro-group as due merely to a difference in degree and independent of other characteristics, it appears pointless to adhere to the suggestion that addition compounds play a fundamental part in contributing to this superiority. As has already been stated, such addition compounds do exist and are almost certainly formed -

deep colourations which fade are always observed when nitro-compounds are treated with anionoid reagents - but although they might even take part in reactions, there now seems no reason why the nitro-group per se should not be able to produce the degree of reactivity observed.

The data discussed in the preceding pages do not, of course, preclude the possibility, suggested on page 43, that the similarity in behaviour between the nitro-group and other cationoid groups is due to the ability of the latter to form additive complexes in a suitable environment. The lack of knowledge as regards this issue shows the necessity for further investigation, and until more data are available the matter must remain controversial. Regardless of which theory is the more correct, however, one fact remains outstanding, namely, that, in a favourable environment, the effects of all cationoid groups are similar, and the mode of activation by the nitro-group differs in no way from that by other cationoid groups.

- - - - - - - - - - - - - -

EXPERIMENTAL

- - - - - - - - - - - - -

2-nitro-4-chloroaniline

In the nitration of p-chloroacetanilide carried out with pure fuming nitric acid (d. = 1·53)[17] difficulty was encountered during precipitation and the product tended to gum with occlusion of acid which later brought about decomposition. It was found better to use (for 14 g. of amine) a mixture of fuming nitric acid (50 cc. d. = 1·49) and concentrated sulphuric acid (20 cc.). In this way 2-nitro-4-chloroacetanilide was obtained as a pale yellow powder with no difficulty[18]. The hydrolysis of the acetyl derivative with hot conc. sulphuric acid yielded the required amine.

2:4-dinitroaniline

This was prepared from 2:4-dinitrochlorobenzene by the action of alcoholic ammonia.

2-chloro-4-nitroaniline

The nitration of o-chloroacetanilide yielded a mixture of 4-nitro- and 6-nitro-derivatives[19]. Since fractional crystallisation of these compounds was slow, an improved method of separation was de-

vised. The well dried mixture of isomers (25 g.) was warmed at about 60°C on the water bath for fifteen minutes with benzene (100 cc.), the suspension being well stirred throughout the process. It was then filtered rapidly through a cold funnel. The residue was almost entirely 2-chloro-6-nitroacetanilide. The filtrate which had deposited a quantity of solid was again filtered without delay through a second funnel and the resulting filtrate allowed to stand. The residue on the second funnel was a mixture of isomers which was set aside for extraction with a further batch. A solid consisting almost entirely of 2-chloro-4-nitroacetanilide was gradually deposited from the mother-liquors of the two filtrations. One crystallisation from alcohol yielded a sufficiently pure product which on hydrolysis gave the required amine.

As this method of preparation proved to be somewhat impracticable - the mixture of isomers containing only 59% of 4-nitro-derivative, some of which was also lost in the separation - a new method of nitration of p-tolylsulphonyl-o-chloroanilide,[20] (dilute aqueous nitric acid had previously been used) based on that used by Morgan,[21] was employed. The anilide (60 g.), prepared by heating p-tolyl-

sulphonyl chloride (I mol.) and o-chloroaniline (2 mols.), was dissolved in glacial acetic acid (600 cc.). Bench conc. nitric acid (I8 - I9 cc., making a I·5% solution containing I mol. of nitric acid) was added to the hot solution which was then raised to the boiling point. No reaction took place at this stage, but on allowing the solution to cool without disturbance, a violent reaction, which was preceded by the appearance of a yellow-brown patch at the surface of the liquid, set in within a few seconds. When all energetic reaction had ceased the solution was boiled to remove oxides of nitrogen and then diluted to about one litre with hot water. On cooling, the 2-chloro-4-nitroanilide crystallised out in an almost pure state, and this, when hydrolysed with conc. sulphuric acid, yielded the required amine.

Further dilution of the reaction mother-liquors with water gave a small amount of a second material. This was readily separated from the above compound by crystallisation from alcohol in which it was much the more soluble of the two. It was found to be p-tolylsulphonyl-2-chloro-4:6-di-nitroanilide, m.p. I4I°C (Found: N, II·3I. $C_{13}H_{10}O_6N_3ClS$ requires N, II·34%). On hydrolysis an amine m.p. I57°C was obtained. This corresponded to 2-chloro-4:6-di-

nitroaniline[22].

2-nitro-4-chloro-,2-4-dinitro-,and 2-chloro-4-nitrobenzonitriles (I,II and III)

These were all obtained from the respective anilines by the standard method which is here described for the hitherto unknown

2-chloro-4-nitrobenzonitrile

A solution of 2-chloro-4-nitroaniline (6·9 g.) in glacial acetic acid (40 cc.) was cooled to about 0°C and diazotised by pouring gradually into a solution of sodium nitrite (3·1 g.) in conc. sulphuric acid (22 cc.) cooled in ice. The temperature of diazotisation was kept below 25°C. Meanwhile a nickelocyanide solution was prepared as follows: Nickel chloride (6·6 g.) in hot water (40 cc.) was treated with a hot solution of potassium cyanide (14 g.) in water (60 cc.). The resulting clear red-brown solution was cooled in ice and sodium carbonate (38 g.) in water (200 cc.) added. The diazo-solution which had been filtered free from sodium sulphate was added gradually over a period of one hour to the nickelocyanide solution. The mixture was thereafter heated to 70°C slowly and maintained at this temperature for 30 minutes and then allowed to cool. After filtering and washing first with dilute

caustic soda and then with cold water, the residue was steam distilled. Crystallisation of the solid distillate from alcohol yielded the pure nitrile m.p. 81°C (Found: N, 15·34. $C_7H_3O_2N_2Cl$ requires N, 15·27%).

Steam distillation did not prove very satisfactory with the other two nitriles, although after several crystallisations 2-nitro-4-chlorobenzonitrile appeared to benefit by it. Fractional crystallisation, however, proved to be the best method for purifying the latter and 2:4-dinitrobenzonitrile.

REACTION A (the piperidine reaction)

One standard method was used in all cases described below and was carried out as follows:-

The nitrile (about 0·5 g.) was refluxed gently with excess piperidine (about 2 cc.) for a period depending on the reactivity. The reaction products were precipitated with water and after filtering or, in the case of unsolidified products, decanting, triturated with dilute hydrochloric or sulphuric acid. Alcohol or glacial acetic acid were the crystallising agents generally employed.

REACTION B (the mercaptide reaction)

Except in one specific case (see below)

this reaction was carried out as follows:-

The nitrile (I mol.) and the mercaptan (I mol.) were dissolved in excess of a suitable solvent (alcohol or dioxan). To this hot solution sodium hydroxide (I mol. in IO% aqueous solution) was added a few drops at a time. When addition was complete the mixture was refluxed gently for a short time (about five to ten minutes). The products usually began to separate while the mixture was still hot and could be completely precipitated by adding more water. Crystallising agents were usually alcohol or glacial acetic acid.

Special mercaptide reaction with 2-chloro-4-nitrobenzonitrile

Under the above conditions 2-chloro-4-nitrobenzonitrile failed to give replacement reactions,but instead,the reduction of the nitro-group was effected with the production of a red compound which appeared to be an azoxy-compound contaminated with azo-compounds. The same product was obtained by treating the nitrile in alcoholic solution with benzoin and a few drops of sodium methoxide[28] - one method of preparing azoxy-compounds.

Replacement reactions,however, were finally effected by using the following quantities

and conditions:-

The nitrile (I mol.) and the mercaptan (I·5 mols.) were dissolved in a slight excess of alcohol at 40°C. Sodium hydroxide (I·2 mols. in I0% aqueous solution) was added a few drops at a time. The dark colour produced at each addition was allowed to disappear completely before further addition was made. The end of the reaction was marked by the sudden appearance of a deep crimson colour which usually accompanied reduction reactions, and any further addition of sodium hydroxide failed to increase the yield. In this manner no precipitation of azoxy-compounds was observed, but an oil, consisting of a mixture of two sulphides, separated on cooling.

Oxidation of Sulphides

All sulphides of this series were readily oxidised to sulphones by the following method:

The sulphide was dissolved in excess of glacial acetic acid and 30% hydrogen peroxide (I0 cc./g. of sulphide) added a little at a time to the gently refluxing solution. Refluxing was continued for a few minutes after all colour had disappeared, the whole process in the present cases requiring about five to ten minutes. The reaction products either crystallised out on cooling or were

precipitated with water.

2-p-tolylthio-4-nitrobenzamide

This was obtained instead of replacement products when 2-p-tolylthio-4-nitrobenzonitrile was treated with alkaline p-thiocresol. After precipitation from the reaction mixture it was crystallised from alcohol from which it separated as fine yellow needles m.p. 219°C. (Found: C,58·38,H,4·30. $C_{14}H_{12}O_3N_2S$ requires C,58·33,H,4·17%).

2-methyl-7-chloro- and 2-methyl-7-nitrothioxanthones

2-methyl-7-chlorothioxanthone was the sole product from the treatment of 2-p-tolylthio-4-chlorobenzonitrile with 95% sulphuric acid at about 100°C for five to ten minutes. Purification was effected by washing with caustic soda followed by water and then crystallising from acetic acid. Colourless needles m.p. 212°C. (Found: C,64·3.H,3·2. $C_{14}H_9OSCl$ requires C,64·5,H,3·4%).

2-methyl-7-nitrothioxanthone (obtained from outside sources in quantity) was likewise produced from 2-p-tolylthio-4-nitrobenzonitrile. M.p. 275°C.

8-(2)-nitrothioxanthone

2-phenylthio-5-nitrobenzoic acid was prepared by treating sodium 2-chloro-5-nitrobenzoate

(I mol.) with sodium thiophenate (I mol.) in aqueous solution. The resulting product was treated with hot conc. sulphuric acid for ten minutes and the thioxanthone thus obtained precipitated with water and purified as above.

2-phenylthio-5-nitrobenzoic acid crystallised as pale yellow needles m.p. 224°C. (Found: C,56·8I, H,3·3. $C_{13}H_9O_4NS$ requires C,56·72,H,3·27%).

8-(2)-nitrothioxanthone crystallised as colourless needles m.p. 22I°C

2-methyl-8-nitrothioxanthone

This was prepared in the same manner as 8-nitrothioxanthone using 2-p-tolylthio-5-nitrobenzoic acid instead of 2-phenylthio-5-nitrobenzoic acid. It was obtainable from outside sources.

(8-(2)-chlorothioxanthone was obtainable from outside sources.)

All dioxides were prepared from the respective thioxanthones by oxidising with 30% hydrogen peroxide in glacial acetic acid (IO cc. peroxide/g. of thioxanthone).

2-methyl-7-chlorothioxanthone-S-dioxide

Colourless needles from glacial acetic acid m.p. 240°C. (Found: C,57·2,H,3·0. $C_{14}H_9O_3SCl$ requires C,57·4,H,3·I%).

2-methyl-7-nitrothioxanthone-S-dioxide

Colourless plates from acetic acid m.p. 293°C.

2-methyl-8-nitrothioxanthone-S-dioxide

Pale yellow needles from acetic acid m.p. 281°C.

8-(2)-nitrothioxanthone-S-dioxide

Colourless needles from dioxan m.p. 264°C. (F. Mayer[24] gives m.p. 254°C.)

8-(2)-chlorothioxanthone-S-dioxide

Lustrous colourless needles from dioxan-alcohol m.p. 226°C.

Methylation of sulphinic acids

The acid, purified partially by solution in carbonate and reprecipitation with dilute acid, was dissolved in dilute sodium hydroxide and refluxed with a good excess of methyl iodide for six to eight hours, during which time the colour became transferred from the aqueous to the methyl iodide layer. The methyl iodide layer, after separation and washing, was evaporated to dryness and the residue taken up in a little alcohol or acetic acid. The solution was treated with animal charcoal and the partially purified product precipitated with water, filtered and drained dry. The methyl sulphone thus

obtained was finally crystallised from the requisite solvent.

2-p-tolylsulphonyl-4-nitrobenzoic acid

2-chloro-4-nitrobenzoic acid (2 g. = I mol.) was dissolved in caustic soda (I mol. in 20 cc. water) and sodium p-toluenesulphinate (I mol.) added. The solution was transferred to a Carius tube, a little copper-bronze added and the tube sealed. The mixture was heated to I35°C. for three hours, cooled and, after opening the tube, decolourised with animal charcoal. The acid was precipitated and purified further by solution in carbonate, re-precipitation, and crystallisation from aqueous alcohol. Colourless prisms m.p. 217°C. (Found: C, 52·32, H, 3·28. $C_{14}H_{11}O_6NS$ requires C, 52·34, H, 3·42%). The same material was obtained by hydrolysis of 2-p-tolylsulphonyl-4-nitrobenzonitrile in the same manner as described under (a) of the next paragraph.

2-p-tolylsulphonyl-4-chlorobenzoic acid

(a) 2-p-tolylsulphonyl-4-chlorobenzonitrile was refluxed gently with 60% sulphuric acid for about one hour. The resulting acid was purified by solution in carbonate, reprecipitation, and crystallisation from acetic acid. Snow white plates m.p. I55°C. (Found: C, 54·2, H, 3·35. after drying at I00°C. in vacuo for

one and a half hours. $C_{14}H_{11}O_4ClS$ requires C,54·I,H 3·5%).

(b) 2-p-tolylsulphonyl-4-chlorobenzamide (I mol.) was dissolved in the least amount of hot 20 - 30% sulphuric acid, and sodium nitrite (2 mols. in 5 -I0% aqueous solution) added slowly through a pipette extending to the bottom of the liquid. The acid separated on cooling and was purified as above.

Piperidine and Mercaptide Reaction Products from Benzonitriles, Thioxanthone Dioxides and Benzoic Acids.

In the description of these compounds experimental conditions are referred to Reactions A or B (reaction A is with piperidine and reaction B is with mercaptide, and the procedure, which is described on pp. 57 and 58, is the same for all cases with one exception noted in the text). The only other details noted are the time of reaction and the analytical data.

2-nitro-4-piperidinobenzonitrile (IV)

From both 2-nitro-4-chloro- and 2:4-dinitrobenzonitriles by Reaction A. Time - 5 mins.

and 3 mins. respectively. Red needles m.p. 143°C. (Found: N,18·21. $C_{12}H_{13}O_2N_3$ requires N,18·18%).

2-piperidino-4-chlorobenzonitrile (V)

From 2-nitro-4-chlorobenzonitrile by Reaction A. Time 5 mins. Yellow plates m.p. 71°C. (Found: N,12·84. $C_{12}H_{13}N_2Cl$ requires N,12·8%).

2-piperidino-4-nitrobenzonitrile (VI)

From 2-chloro-4-nitrobenzonitrile by Reaction A. Time 5 mins. Yellow plates m.p. 107°C. (Found: N,18·15. $C_{12}H_{13}O_2N_3$ requires N,18·18%).

2-p-tolylthio-4-chlorobenzonitrile (VII)

From 2-nitro-4-chlorobenzonitrile by Reaction B. Time 5 - 10 mins. Colourless thick needles m.p. 117°C. (Found: N,5·61. $C_{14}H_{10}NClS$ requires N,5·59%).

2-p-tolylthio-4-nitrobenzonitrile (IX)

From both 2-chloro-4-nitro- and 2:4-dinitrobenzonitriles by Reaction B. Time for dinitro-compound 5 - 10 mins.,for chloronitro-compound see p. 58 for special conditions. Pale yellow fine needles m.p. 156°C. (Found: N,10·7. $C_{14}H_{10}O_2N_2S$ requires N,10·4%).

2-nitro-4-p-tolylthiobenzonitrile (VIII)

From 2:4-dinitrobenzonitrile by Reaction B. Time 5 - 10 mins. Pale yellow plates

m.p. 115°C. (Found: N,10·54. $C_{14}H_{10}O_2N_2S$ requires N,10·4%).

2-chloro-4-p-tolylthiobenzonitrile (X)

From 2-chloro-4-nitrobenzonitrile by special reaction for this compound with mercaptide - see p. 58. Colourless thick needles m.p. 95°C. (Found: C,64·78,H,3·83. $C_{14}H_{10}NClS$ requires C,64·73, H,3·85%).

By oxidation of the four preceding sulphides the following products were obtained:-

2-p-tolylsulphonyl-4-chlorobenzonitrile (XI)

From VII. Colourless plates m.p. 187°C. (Found: N,4·9. $C_{14}H_{10}O_2NClS$ requires N,4·8%).

2-p-tolylsulphonyl-4-chlorobenzamide (XV)

From VII along with XI above. colourless plates m.p. 196°C. (Found: N,4·6. $C_{14}H_{12}O_3NClS$ requires N,4·52%).

2-p-tolylsulphonyl-4-nitrobenzonitrile (XII)

From IX. colourless plates m.p. 176°C. (Found: C,55·37,H,3·45. $C_{14}H_{10}O_4N_2S$ requires C,55·63, H,3·31%).

2-nitro-4-p-tolylsulphonylbenzonitrile (XIII)

From VIII. Colourless needles m.p. 201°C. (Found: C,55·4,H,3·37. $C_{14}H_{10}O_4N_2S$ requires C,55·63,H,3·31%).

2-chloro-4-p-tolylsulphonylbenzonitrile (XIV)

From X. Colourless plates m.p. 175°C. (Found: C,56·6I,H,3·6I. $C_{14}H_{10}O_2NClS$ requires C,56·32, H,3·43%).

2-p-tolylsulphonyl-4-piperidinobenzonitrile (XVII)

From 2-p-tolylsulphonyl-4-chloro- and 2-p-tolylsulphonyl-4-nitrobenzonitriles by Reaction A. Respective times 20 and 3 minutes. Colourless plates m.p. 198°C. (Found: N,8·23. $C_{19}H_{20}O_2N_2S$ requires N,8·4%).

2-piperidino-4-p-tolylsulphonylbenzonitrile (XVIII)

From 2-chloro- and 2-nitro-4-p-tolylsulphonylbenzonitriles by Reaction A. Respective times 20 and 3 minutes. Colourless needles m.p.150°C. (Found: N,8·38. $C_{19}H_{20}O_2N_2S$ requires N,8·4%).

2-p-tolylsulphonyl-4-p-tolylthiobenzonitrile (XIX)

As XVII above by Reaction B. Time for Chloro-compound 10 - 15 mins. and for nitro-compound 5 - 10 mins. Creamy prisms m.p. 132°C. rising to 136°C. on standing some months. (Found: N,3·96. $C_{21}H_{17}O_2NS_2$ requires N,3·7%).

2-p-tolylthio-4-p-tolylsulphonylbenzonitrile (XX)

As XVII above by Reaction B. Time for

chloro-compound 10 - 15 mins and time for nitro-compound 5 10 mins. Colourless needles m.p. 170°C. (Found: C,66·56,H,4·59. $C_{21}H_{17}O_2NS_2$ requires C,66·49, H,4·59%).

2-methyl-7-piperidinothioxanthone-S-dioxide (XXXII)

From 2-methyl-7-chloro- and 2-methyl-7-nitrothioxanthone-S-dioxides by Reaction A. Time for chloro-compound 20 mins. and for nitro-compound 5 mins. Deep yellow needles m.p. 158°C. (Found: C, 66·91,H,5·4. $C_{19}H_{19}O_3NS$ requires C,66·85,N,5·57%).

8-(2)-piperidinothioxanthone-S-dioxide (XXXIV)

From 8-(2)-chlorothioxanthone-S-dioxide by Reaction A. Time 120 mins. Orange-brown needles m.p. 175°C. (Found: N,4·2. $C_{18}H_{17}O_3NS$ requires N,4·28%).

2-piperidino-5-nitro-2'-methylsulphonylbenzophenone (XXXIX)

From 8-(2)-nitrothioxanthone-S-dioxide by Reaction A (after methylation of the resultant sulphinic acid). Time 45 mins. Yellow prisms m.p. 203°C. (Found: C,58·8,H,5·18. $C_{19}H_{20}O_5N_2S$ requires C,58·76,H,5·14%).

2-piperidino-5-nitro-2'-methylsulphonyl-5-methylbenzophenone (XXXVIII)

From 2-methyl-8-nitrothioxanthone-S-

dioxide by Reaction A (after methylation of the resultant sulphinic acid). Time 45 mins. Yellow prisms m.p. 2II°C. (Found: C,59·9,H,5·5I,N,7·05. $C_{20}H_{22}O_5N_2S$ requires C,59·7,H,5·47,N,6·96%).

2-piperidino-5-nitrobenzophenone

From 2-p-tolylsulphonyl-5-nitrobenzophenone by Reaction A. Time 5 mins. Yellow plates m.p. IOI°C. (Found: N,9·09. $C_{18}H_{18}O_3N_2$ requires N,9·03%).

2-methyl-7-p-tolylthio-thioxanthone-S-dioxide (XXXIII)

From 2-methyl-7-chloro- and 2-methyl-7-nitrothioxanthone-S-dioxides by Reaction B. Time 5 - IO mins for both. Colourless prisms m.p. 2I4°C. (Found: C,66·I6,H,4·36. $C_{21}H_{16}O_3S_2$ requires C,66·3I,H,4·2I%).

8-(2)-p-tolylthio-thioxanthone-S-dioxide (XXXV)

From 8-(2)-chlorothioxanthone-S-dioxide by Reaction B. Colourless plates m.p. I9I°C. (Found: C,65·63,H,3·78. $C_{20}H_{14}O_3S_2$ requires C,65·57, H,3·82%).

2-p-tolylthio-5-nitro-2'-methylsulphonylbenzophenone (XLI)

From 8-(2)-nitrothioxanthone-S-dioxide by Reaction B (after the methylation of the

resultant sulphinic acid). Time 40 mins. Colourless plates m.p. 184°C. (Found: C,56·85,H,4·36. $C_{21}H_{17}O_5NS_2.H_2O$ requires C,56·62,H,4·27%. There was no loss of weight when heated in vacuo,however).

2-piperidino-4-nitrobenzoic acid

From 2-chloro-4-nitrobenzoic acid by Reaction A. Time 4 - 5 hours. Colourless plates m.p. 212°C (decomp).

- - - - - - - - - - -

P A R T I I

- - - - - - - - - - -

THE SYNTHESIS OF BACTERICIDAL

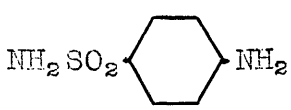
DRUGS

- - - - - - -

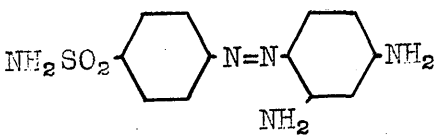
PART II.

THE SYNTHESIS OF BACTERICIDAL DRUGS.

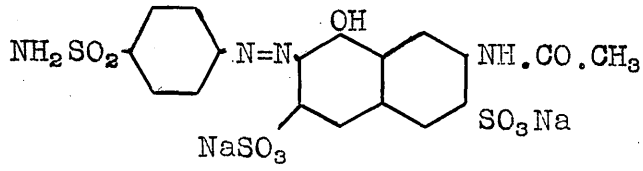
The increasing interest attracted by the bactericidal properties of aromatic sulphur compounds has led to the very rapid development of that branch of chemotherapy concerned with the cure of infections caused by such micro-organisms as streptococci, staphilococci, pneumococci, etc. The large amount of work performed with such compounds since their first use in Germany some five or six years ago (the prontosils, I, II and III below being the earliest types) has resulted in the accumulation of aonfusing data from which no laws correlating chemical structure with bactericidal activity, the ultimate aim of all chemists engaged on such investigations, can be derived.



I



II

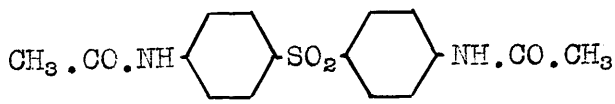


III

Mietzsch[25], however, after collecting a considerable amount of material, has been able to put forward a few empyricisms which define certain wide limits within which the chemical structure of compounds displaying bactericidal properties must lie. These are

(a) Although in the early examples the sulphur-containing substituent was a sulphonamido-group and the nitrogen-containing substituent an amino-, acetyl-amino- or azo-group, any sulphur or nitrogen-containing substituents may (theoretically) be used. A large number of compounds having various sulphur and nitrogen-bearing substituents other than those mentioned above are now known to have powerful bactericidal activity.

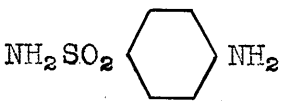
eg.



IV

(b) Where only one sulphur-containing group is present, this must be situated in the para-position to a nitrogen-containing group, otherwise no activity is displayed.

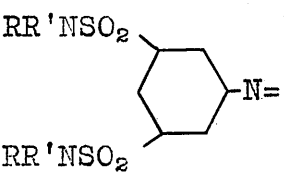
eg.



I

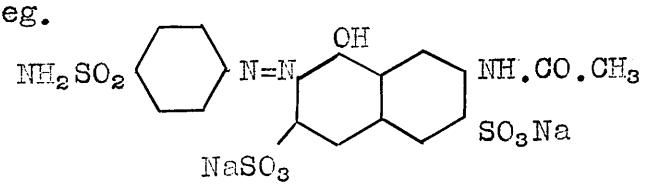
(c) Where more than one sulphur-containing group is present, activity may be displayed with any arrangement of groups.

eg.



(d) Where solublising groups such as SO_3Na or CO.ONa are present, activity cannot be displayed except these groups be situated in any part of the molecule other than in the nucleus bearing the sulphur and nitrogen-containing groups.

eg.



III

It was considered that chemically reactive compounds such as are described in Part I should, by virtue of the ease with which they undergo replacement reactions with amines, thiols and sulphinates, provide a useful source for the synthesis of drugs analogous to those mentioned above. A number of compounds, therefore, were derived in this manner and submitted for examination for bactericidal properties.

As regards the mode of attack, it was found expedient to prepare one or two of a series of compounds of analogous chemical structure and to submit these for examination for bactericidal activity. Where no promise of the latter was exhibited, study of the series was, in general, not pursued, but, where any form of chemical interest was indicated during the preparation of these preliminary compounds, further investigations were made regardless of the physiological properties of the products. The compounds described in the following pages are thus divided into two main sections according to the parent compounds. The derivatives included in each section are then further subdivided into small series consisting of one, two or three compounds of analogous structure or successively derived from

each other. Section I describes derivatives of 3-nitro-4-chlorophenylsulphones consisting of pyridinium chlorides, dimethyl- and diethylamino-compounds, benzimidazolones, polythio- and polysulphonyl compounds and hydroxy compounds. Section II describes derivatives of 2:4:6-tribromonitrobenzene consisting of triphenylthio- and triphenylsulphonyl-compounds containing amino-, piperidino- and hydrazino-groups in the I-position.

- - - - - - - - - - - -

SECTION I

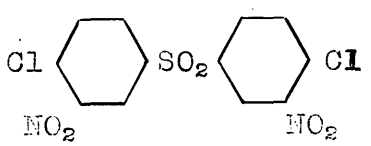
Derivatives of 3-nitro-4-chlorophenylsulphones

The 3-nitro-4-chlorophenylsulphones, the parent substances from which the compounds described in this section were derived, are highly reactive and have readily replaceable chlorine atoms. On treatment with thiols and amines, therefore, 2-nitro-4-sulphonyl-sulphides and 2-nitro-4-sulphonyl-amines are produced. The latter themselves have all been examined for bactericidal activity, but, since the presence of the nitro-group is, as a whole, undesirable on account of the toxic action usually

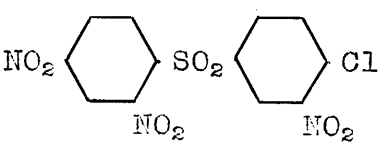
exercised by it, various means for replacing it with other groups have been used. Apart from the straightforward process of reduction, two reactions, both involving the condensation of the nitro-group with a second substituent in the ortho-position, were investigated. These reactions are discussed fully in the series to which they were applied (Series IV and V).

Series I. Pyridinium chlorides

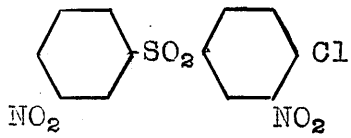
In the search for suitable solvents to replace ethylene glycol as reaction medium in the preparation of the sulphanilic acid condensate of Series II, pyridine was found to react rapidly with 3-3'-dinitro-4-4'-dichlorodiphenylsulphone (V). Since, in general, sulphones have not been found to react easily with pyridine, it was decided to investigate the effect on reaction speeds of variation in the sulphonyl constituent of 3-nitro-4-chlorophenyl sulphones. Accordingly the following compounds were treated with pyridine under standard conditions:



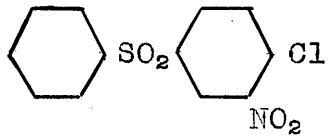
V



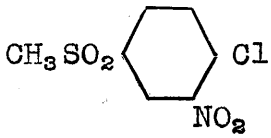
VI



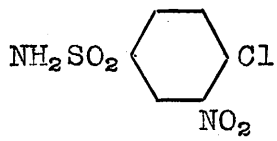
VII



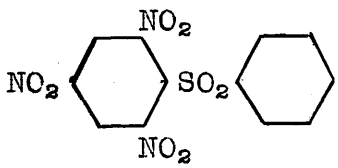
VIII



IX



X



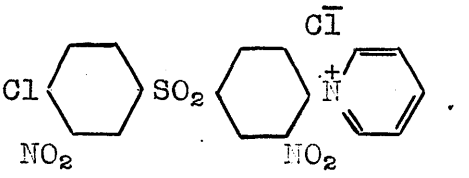
A

As had been expected there was a general decrease in reactivity from V - X, but V, IX and X alone gave crystallisable reaction products (XI, XII and XIII below, respectively). The reaction speeds of the remainder could only be judged from the rate of separation of tar. On this qualitative basis we have the following order of reactivity (times of reaction in brackets).

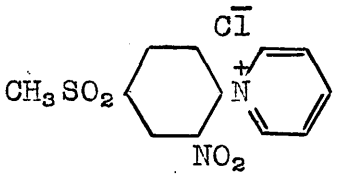
V(20) $\gg$ VI(80) $\doteq$ VII(80) $>$ VIII(100) $>$ IX(120) $>$ X(180).

In A, which was included for comparison, the sulphonyl linkage was ruptured giving pyridine

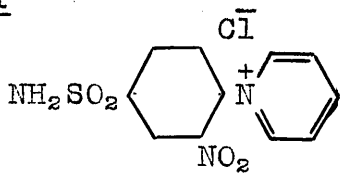
picrate. Reaction required 5 - 10 minutes.



XI



XII

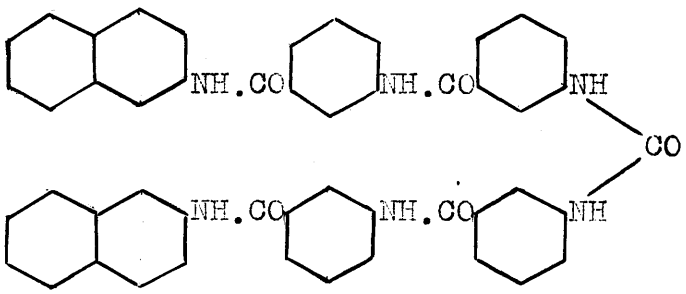


XIII

The above pyridinium salts (XI,XII and XIII) were all readily soluble in water and crystallised with one,two or three molecules of water of crystallisation. They were,however,without bactericidal action.

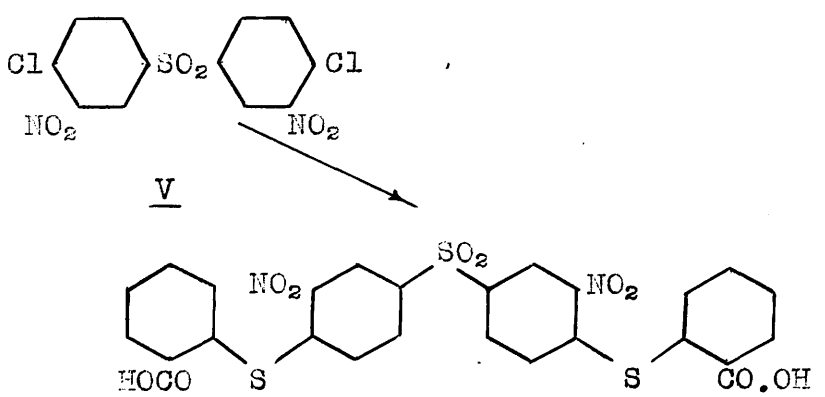
Series II. Polythio-derivatives

The synthesis of this group of compounds was commenced with the ultimate object of producing polythio-derivatives analogous to "Bayer 205",the skeleton of which is shown below. The simplest method available at the time appeared to be the condensation of thiols with polynuclear sulphones having reactive chlorine atoms in both distal nuclei, as,for example, in 3-3'-dinitro-4-4'-dichlorodiphenylsulphone (V).

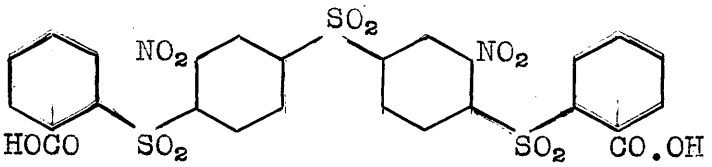


Skeleton of "Bayer 205"

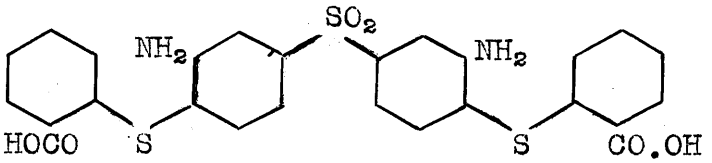
3-3"-Dinitro-4-4'-dichlorodiphenylsulphone (V) was therefore treated with o-thiolbenzoic acid and sodium carbonate in xylene as reaction medium. 3-3'-Dinitro-4-4'-bis(o-carboxyphenylthio)-diphenyl-sulphone (XIV) was obtained as had been expected. This compound, when oxidised with 30% hydrogen peroxide, gave the corresponding trisulphone (XV). Reduction of XIV was also attempted by treating its ammoniacal solution with ferrous sulphate, but, although the product appeared to be the expected amino-acid (XVI), it did not analyse correctly for this.



XIV

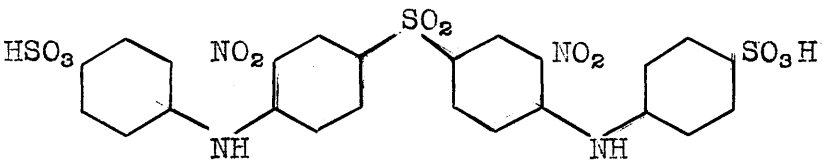


XV

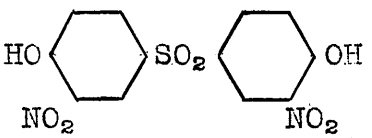


XVI

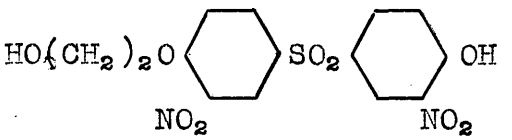
A slightly different type of compound was obtained by condensing 3-3'-dinitro-4-4'-dichlorodiphenylsulphone (V) with sulphanilic acid. As xylene could not be used for a reaction medium in this condensation, a number of other solvents were tested. Of these, only ethylene glycol was found in any way suitable, and it was observed that even with this solvent side reactions interfered. Thus, although the required condensate (XVII) was obtained it was usually accompanied with a mixture of the diphenol (XVIII), the phenol-ether (XIX) and the diether (XX) in proportions depending on the temperature. The phenol-ether was the by-product usually obtained at the temperature at which the condensation with sulphanilic acid was carried out (about 180°C).



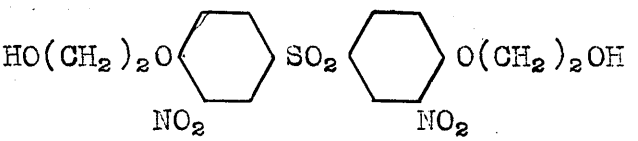
XVII



XVIII



XIX



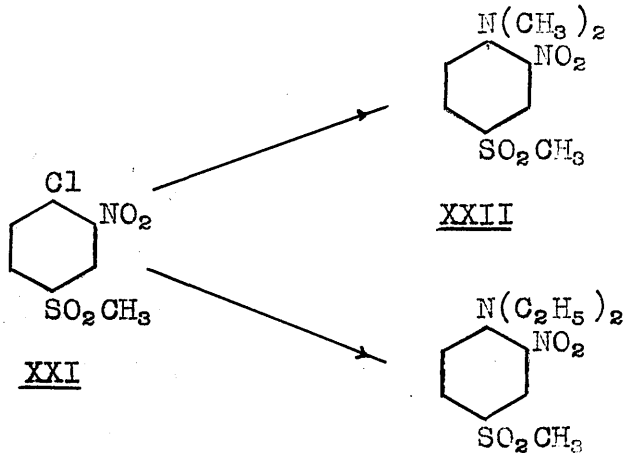
XX

The polythio-compounds described above have water-soluble alkali salts which are neutral to litmus, but they are without bactericidal action.

Series III. Dimethyl- and Diethylamino-compounds

3-Nitro-4-chlorophenylmethylsulphone (XXI) and 3-3'-dinitro-4-4'-dichlorodiphenylsulphone (V) react readily with dimethylamine and diethylamine in alcoholic suspension to give 3-nitro-4-dialkylamino-derivatives. 3-Nitro-4-dimethyl- and 3-nitro-4-diethylaminophenylmethylsulphones (XXII XXIII respectively) were obtained from 3-nitro-4-

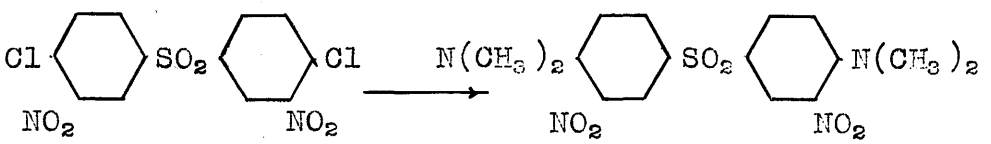
chlorophenylmethylsulphone (XXI) and 3-3'-dinitro-4-4'-tetramethyldiaminodiphenylsulphone (XXIV) from 3-3'-dinitro-4-4'dichlorodiphenylsulphone (V).



XXII

XXI

XXIII



V

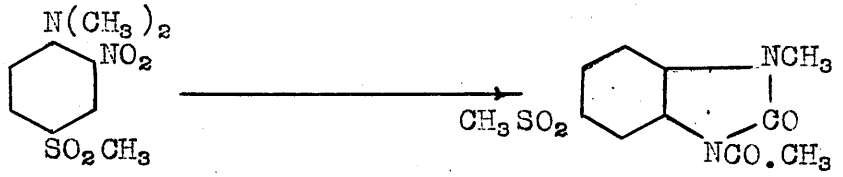
XXIV

The dimethyl- and diethylamino-compounds, which were prepared mainly as intermediates in the synthesis of benzimidazolones and quinoxalines described in the next series, were themselves submitted for examination for bactericidal properties. They were, however, found to be inactive in this respect.

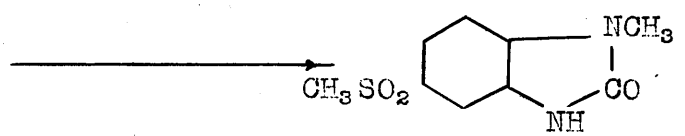
Series IV. Benzimidazolones and Quinoxalines

It has been observed by Van Romburgh[26] that ortho-nitrodimethylamino- and ortho-nitrodiethylamino-compounds yield acetylated benzimidazolones and quinoxalines respectively when treated with zinc chloride and acetic anhydride. Such a reaction, which not only effects the removal of the nitro-group but at the same time introduces a fresh type of nitrogen-containing substituent into the para-position to the sulphonyl group, might be expected to give some interesting derivatives when applied to the dimethylamino- and diethylamino-compounds of Series III. 3-Nitro-4-dimethylamino- and 3-nitro-4-diethylaminophenylmethylsulphones (XXII and XXIII) and 3-3'-dinitro-4-4'-tetramethyldiaminodiphenylsulphone (XXIV) were accordingly treated with zinc chloride and acetic anhydride. From 3-nitro-4-dimethylaminophenylmethylsulphone a readily purified product was obtained. This was I-methyl-3-acetyl-5-methylsulphonylbenzimidazolone (XXV) which on hydrolysis with caustic soda gave the alkali-soluble I-methyl-5-methylsulphonylbenzimidazolone (XXVI). The reaction products from 3-nitro-4-diethylaminophenylmethylsulphone and 3-3'-dinitro-4-4'-tetramethyldiaminodiphenylsulphone were not obtained in

a pure state.



XXII XXV



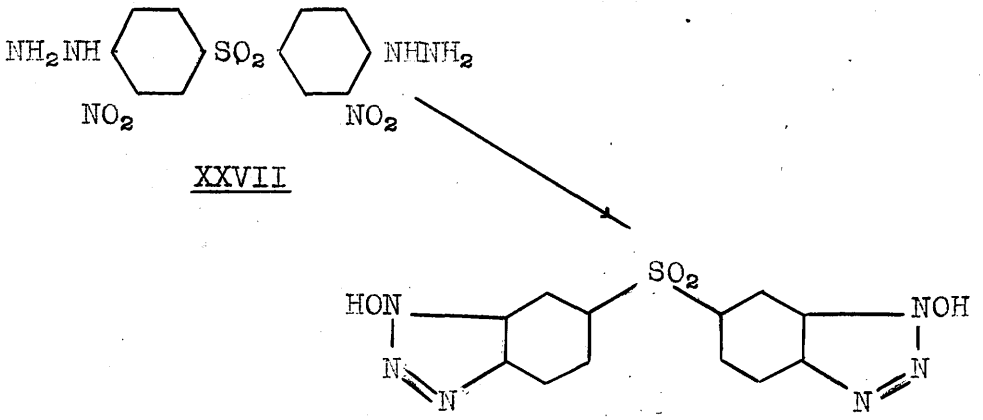
XXVI

Neither I-methyl-5-methylsulphonyl-benzimidazolone nor its 3-acetyl-derivative had any bactericidal action.

Series V. Hydroxy-triazoles

A reaction leading to a similar removal of the nitro-group and introduction of a different nitrogen-containing substituent is that of a base on ortho-nitrophenylhydrazines (c.f. McBeth and Price[27]). This reaction, which yields hydroxy-triazoles by condensation of the nitro-group with the hydrazino-group, was attempted with the dihydrazine (XXVII). An alkali-soluble product which exploded on heating was obtained, but, although this had a high nitrogen content as would be displayed by the ditriazole

(XXVIII), it did not analyse correctly for this.



XXVII

XXVIII

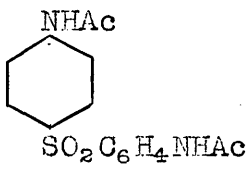
Since the composition of this compound was uncertain, it was not examined for bactericidal action.

- - - - - - - - - - - -

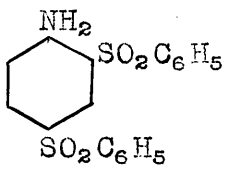
SECTION II

Derivatives of 2:4:6-tribromonitrobenzene

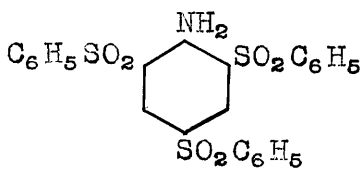
Amino- and acetylamino-derivatives of diphenylsulphone being known to have definite bactericidal properties (c.f. XXIX) and 2:4-bis-phenylsulphonylaniline (XXX) having been found also to have a certain activity, it became of interest to examine the properties of 2:4:6-trisulphonyl-derivatives such as XXXVI.



XXIX

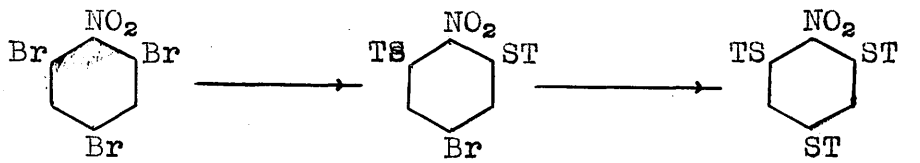


XXX



XXXVI

The trisulphonyl-derivatives were synthesised by utilising a recently observed reaction between 2:4:6-tribromonitrobenzene and alkaline p-thiocresol[28]. All three bromine atoms of tribromo-nitrobenzene may be replaced successively by the latter reagent, and indeed the tendency to form the trithioether (C) is only limited by the low solubil-ity of the bisthioether (B) which in ordinary concentrations is precipitated before reaction reaches the final stage.

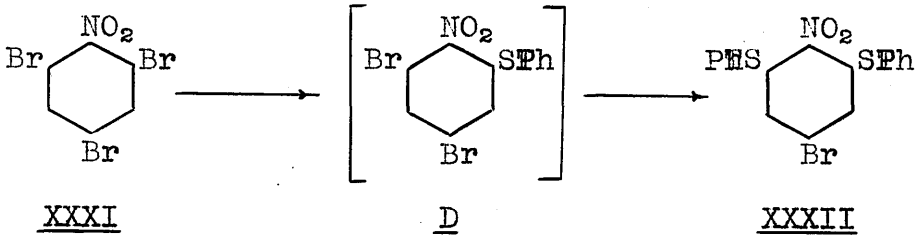


XXXI B C

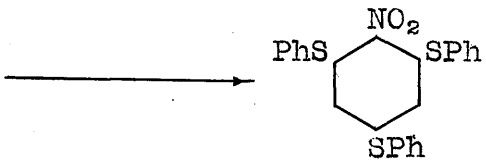
(T = p-tolyl. The monothioether is first formed but is not included in the above)

To maintain the analogy with the mono- and bis-sulphonyl-derivatives (XXIX and XXX) the present investigation was carried out with thiophenol instead of p-thiocresol. In this case the solubility relationships between the mono-,bis- and trithioethers were different,the bis-thioether (2-6-bis-phenylthio-4-bromonitrobenzene,XXXII) being very readily soluble in the reaction medium and the trithioether (2:4:6-triphenylthionitrobenzene,XXXIII) being practically insoluble. This resulted in the predominance of the trithioether (XXXIII) under all conditions of reaction. 2-6-Bis-phenylthio-4-bromo-nitrobenzene (XXXII) was consequently difficult to isolate,being produced only in small quantity when two molecules of thiophenol were used in conjunction with the least possible volume of solvent. The mono-thioether (B) was in no case isolated. Whenever less than three molecules of thiol were used considerable quantities of unchanged tribromonitrobenzene were

returned along with the reaction products.



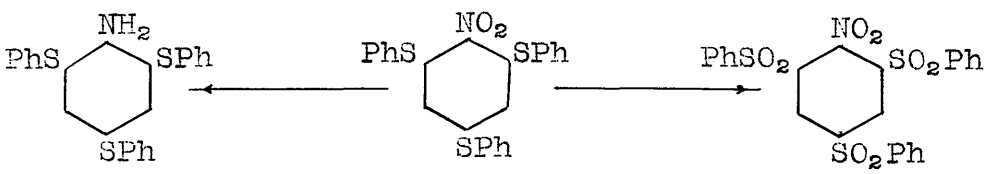
XXXI D XXXII



XXXIII

(Ph = phenyl)

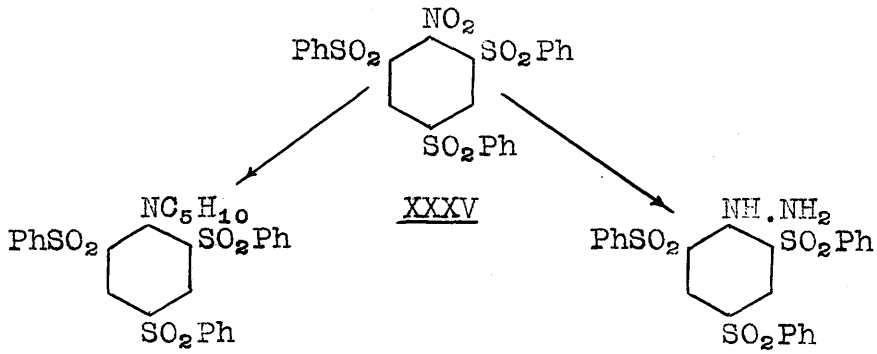
2:4:6-triphenylthionitrobenzene (XXXIII) was reduced with stannous chloride in glacial acetic acid saturated with dry hydrogen chloride to 2:4:6-triphenylthioaniline (XXXIV) and oxidised with 30% hydrogen peroxide in glacial acetic acid to 2:4:6-triphenylsulphonylnitrobenzene (XXXV). The latter was in turn reduced in the above manner to 2:4:6-triphenylsulphonylaniline (XXXVI).



XXXIV XXXIII XXXV

XXXV XXXVI

2:4:6-Triphenylsulphonylnitrobenzene (XXXV) was not so reactive as might be expected considering the number and effectiveness of the electron restraining substituents present. The nitro-group, however, was readily attacked by piperidine and hydrazine hydrate, the respective products being 2:4:6-triphenylsulphonylpiperidinobenzene (XXXVII) and 2:4:6-triphenylsulphonylhydrazinobenzene (XXXVIII).



XXXV

XXXVII XXXVIII

All the derivatives of this section except 2:6-bis-phenylthio-4-bromonitrobenzene (XXXII) and 2:4:6-triphenylsulphonylhydrazinobenzene (XXXVIII) have been examined for bactericidal action but none

has been found to be active.

- - - - - - - - - - - - - -

EXPERIMENTAL

- - - - - - - - - - - - - -

Pyridinium Chlorides

To the reactive chloro-compound (5 g.) was added benzene (10 cc.) and pyridine (30 cc.). The solution was refluxed until no more solid was observed to separate. The reaction mixture was occasionally filtered to avoid excessive bumping due to accumulation of precipitate. The material thus gathered was washed free from pyridine with benzene and then crystallised from water using charcoal.

3-3'-dinitro-4-chlorodiphenylsulphone-4'-pyridinium chloride (XI)

From 3-3'-dinitro-4-4'-dichlorodiphenylsulphone with 20 minutes' refluxing. Colourless prisms m.p. 170°C (decomp.). (Found: C,44·5,H,2·88. $C_{17}H_{11}O_6N_2SCl_2$ requires C,44·7,H,2·42).

2-nitro-4-methylsulphonylphenylpyridinium chloride (XII)

From 3-nitro-4-chlorophenylmethylsulphone with

I20 minutes' refluxing. Thick colourless plates m.p. 226°C (Softens 90 - II0°,froths I65 -I70° and again at m.p.)

2-nitro-4-sulphonamidophenylpyridinium chloride (XIII)

From 3-nitro-4-chlorobenzenesulphonamide with I80 minutes' refluxing. Colourless needles m.p.255°C (decomp.).(Found: after heating in vacuo 3·645 - 3·475 equivalent to I mol. H_2O from $C_{11}H_{10}O_4N_3SCl.2H_2O$, C,4I·I,H,3·8. $C_{11}H_{10}O_4N_3SCl.H_2O$ requires C,40·9, H,3·6I).

3-3'-dinitro-4-4'-bis(o-carboxyphenylthio)-diphenyl sulphone (XIV)

3-3'-Dinitro-4-4'-dichlorodiphenylsulphone (I mol.) and thiosalicylic acid (2 mols.) were dissolved in hot xylene and solid sodium carbonate (2 mols.) added a little at a time. The precipitated disodium salt of the required product was filtered as free from xylene as possible and then dissolved in water and boiled with animal charcoal to remove last traces of xylene. The acid was finally precipitated with dilute HCl and crystallised from glacial acetic acid. Yellow platelets m.p. 245°C.

3-3'-diamino-4-4'-bis(o-carboxyphenylthio)-diphenyl-sulphone (XVI)

The above nitro-acid (5 g.) was dissolved

in ammonia (20 cc. ·880 d. + aq.). A concentrated solution of ferrous sulphate (28 g. crystals) was added a little at a time with alternate shaking. At the end of the reaction the blackish precipitate of ferrous hydroxide ceased to turn red-brown due to convertion to ferric hydroxide. The mixture, at this point, was warmed and then filtered. The residue was extracted with sodium hydroxide, filtered and the combined filtrates precipitated with dilute acid. The precipitated acid was crystallised from alcohol using charcoal. Short needles m.p. 246°C (decomp.).

3-3'-dinitro-4-4'-disulphanilyldiphenylsulphone (XVII)

3-3'-Dinitro-4-4'-dichlorodiphenylsulphone (I mol.) and sulphanilic acid (2 mols.) were dissolved in hot ethylene glycol and solid sodium carbonate (2 mols.) added a little at a time. The acid was precipitated with dilute H_2SO_4 and crystallised from acetic acid. Pale yellow powder m.p. 231°C.

3-3'-dinitro-4-hydroxy-4'-β-hydroxyethoxydiphenylsulphone (XIX)

During the above reaction ethylene glycol condensed with 3-3'-dinitro-4-4'-dichlorodiphenylsulphone to give the present compound which was obtained directly from these two reagents in the presence of sodium carbonate at about 120°C. After

precipitation with dilute acid the phenol was crystallised from acetic acid using charcoal. Pale yellow plates m.p. 229°C. (Found: C,43·75,H, 2·75. $C_{14}H_{12}O_9N_2S$ requires C,43·75,H,3·1%).

Dialkylamino-derivatives

The reactive chloro-compound was suspended in hot alcohol and the amine (dimethyl- or diethylamine - 2 mols.) added in several portions. The solution turned orange-yellow and undissolved starting material went into solution. Gentle refluxing was continued for 5 - 10 minutes. On cooling the reaction product either crystallised out or was precipitated with water.

3-nitro-4-dimethylaminophenylmethylsulphone (XXII)

From 3-nitro-4-chlorophenylmethylsulphone and dimethylamine. Orange plates from alcohol m.p. 138°C. (Found: N,11·66. $C_9H_{12}O_4N_2S$ requires N,11·46%).

3-nitro-4-diethylaminophenylmethylsulphone (XXIII)

From 3-nitro-4-chlorophenylmethylsulphone and diethylamine. Yellow needles from alcohol m.p. 88°C. (Found: N,10·45. $C_{11}H_{16}O_4N_2S$ requires N,10·29%).

3-3'-dinitro-4-4'-tetramethyldiaminodiphenyl-sulphone (XXIV)

From 3-3'-dinitro-4-4'-dichlorodiphenyl-sulphone with dimethylamine. Orange prisms from acetic acid m.p. 169°C. (Found: N,14·28. $C_{16}H_{18}O_6N_4S$ requires N,14·21%).

Benzimidazolones

1-methyl-3-acetyl-5-methylsulphonylbenzimidazol-one (XXV)

3-Nitro-4-dimethylaminophenylmethylsulphone (2 g.) and zinc chloride (1 g.) were dissolved in acetic anhydride (4 cc.) and refluxed gently for five hours. On cooling the reaction mixture was diluted with about its own bulk of alcohol and then poured into 50 cc. water. The black precipitate was filtered off, dried and extracted with benzene in a Soxhlet apparatus. The required product separated out gradually in the flask. On crystallising from acetic acid using charcoal it was obtained as colour-less prisms m.p. 245°C (Found: N,10·25. $C_{11}H_{12}O_4N_2S$ requires N,10·45%).

1-methyl-5-methylsulphonylbenzimidazolone (XXVI)

The above 3-acetyl-derivative was suspended in boiling water and conc. sodium hydr-

oxide (bench) added gradually until all solid had dissolved. Heating was continued for a few minutes and the mixture then allowed to cool. The product was precipitated with dilute hydrochloric acid, filtered off and washed with water. Colourless plates from aqueous alcohol m.p. 285°C. (Found: C,47·94,H,4·57. $C_9H_{10}O_3N_2S$ requires C,47·78,H,4·43%).

- - - - - - - - - -

The nitration of s-tribromobenzene

An improved method of nitration is as follows:-

Tribromobenzene (8 g.) was treated with bench conc. nitric acid (I6 cc.) and fuming nitric acid (I6 cc. d = I:5I). The mixture was warmed gently until all was in solution and the temperature just maintained there for 2 - 3 minutes. 2:4:6-tribromo-nitrobenzene separated on cooling and was completely precipitated with water. This method avoids the formation of the dinitro-compound which is formed in other methods. Tribromonitrobenzene crystallised from alcohol in short needles m.p. I25°C.

The action of alkaline thiophenol on 2:4:6-tri-bromonitrobenzene

Tribromonitrobenzene (I mol.) was dissolved in excess of hot alcohol and thiophenol (3 mols.)

added. Sodium hydroxide (3 mols. in 10% aqueous solution) was added gradually to the hot solution which was refluxed for a few minutes after the final addition. The reaction product which had commenced to precipitate during the addition of alkali separated almost completely on cooling.

2:4:6-triphenylthionitrobenzene (XXXIII) was the sole reaction product obtained thus. It crystallised from acetic acid as yellow needles m.p. 150°C. (Found: C,64·39,H,3·83. $C_{24}H_{17}O_2NS_3$ requires C,64·43,H,3·8%).

A second reaction using 2 mols of thiophenol and a smaller volume of solvent was carried out. The product from this was crystallised from the smallest volume of acetic acid possible. The first crop of crystals were identical with above,but,on filtering and allowing the filtrate to stand,a second crop consisting of a mixture of tri- and bis-sulphides separated slowly. The mixture was crystallised first from a deficiency and then twice from an excess of alcohol.

2:6-bis-phenylthio-4-bromonitrobenzene (XXXII) was obtained as pale yellow needles m.p. 105°C. (Found: C,51·99,H,3·3. $C_{18}H_{12}O_2NS_2Br$ requires C,51·68, H,2·87%).

2:4:6-triphenylsulphonylnitrobenzene (XXXV)

2:4:6-Triphenylthionitrobenzene was dissolved in excess glacial acetic acid and refluxed with 30% hydrogen peroxide (30 cc./g.) until all colour was discharged. The trisulphone separated on cooling. Colourless plates from acetic acid m.p. 203°C. (Found: C,53·1,H,3·36. $C_{24}H_{17}O_6NS_3$ requires C,53·04, H,3·13%).

2:4:6-triphenylthioaniline (XXXIV)

2:4:6-Triphenylthionitrobenzene (0·5 g.) was heated with a mixture of stannous chloride in glacial acetic acid saturated with dry hydrogen chloride (containing a slight excess of $SnCl_2$). A colourless crystalline solid began to separate on cooling. The mixture was then treated with water and the oil which resulted allowed to solidify when it was filtered off and washed with sodium hydroxide. The required amine crystallised from acetic acid as colourless needles m.p. 89°C. (Found: C,69·1,H,4·7. $C_{24}H_{19}NS_3$ requires C,69·07,H,4·7%).

2:4:6-triphenylsulphonylaniline (XXXVI)

Obtained from 2:4:6-triphenylsulphonylnitrobenzene in the same manner as above. Colourless needles m.p. 241°C. (Found: C,56·0,H,3·9. $C_{24}H_{17}O_6NS_3$ requires C,56·14,H,3·7%).

2:4:6-triphenylsulphonylpiperidinobenzene (XXXVII)

2:4:6-triphenylsulphonylnitrobenzene was refluxed with excess piperidine for ten minutes. The reaction product was precipitated with water and the oil washed with dilute HCl. On solidifying this was dissolved in hot acetic acid from which it crystallised as yellowish prisms m.p. 215°C. (Found: C,60·05,H,4·9. $C_{29}H_{27}O_6NS_3$ requires C,59·9,H,4·65%).

2:4:6-triphenylsulphonylhydrazinobenzene (XXXVIII)

2:4:6-triphenylsulphonylnitrobenzene (1 g.) was heated with hydrazine hydrate (0·6 g. = 4 mols. in dioxan). The reaction product precipitated while the solution was still hot and on cooling was filtered off. Colourless needles from dioxan-alcohol m.p. 196°C. (Found, after heating in vacuo: C,54·83,H,3·86,N,5·34. $C_{24}H_{20}O_6N_2S_3$ requires C,54·55,H,3·79,N,5·3%).

- - - - - - - - -

BIBLIOGRAPHY

[1]) Pisani, Annalen, I854, 92, 326.

[2]) Körner, Gazz., Chim., It., I874, 4, 305.

[3]) Laubenheimer, Ber., I876, 9, I826; I878, II, II56;

[4]) Schöpff and co-workers,Ber., I89I, 24, 3784 et seq.

[5]) Tiemann, Ber., I89I, 24, 704.

[6]) Kenner, J.C.S., I9I4, 27I7.

[7]) Bamberger, Ber., I900, 33, I02.

[8]) Baudet, Rec., Trav., Chim., I924, 43, 707.

[9]) Heppenstall and Smiles, J.C.S., I938, 899.

[10]) Bennett and Wain, J.C.S., I936,II08.

[11]) Kenner and Witham, J.C.S., I92I, I452.

[12]) Brewin and Turner, J.C.S., I928, 334.

[13]) Loudon and co-workers,J.C.S., I937 et seq.

[14]) Loudon and Robson, J.C.S., I937, 242.

[15]) Reinders and Ringer, Rec., Trav., Chim., I899, I8, 326.

[16]) Lobry de Bruyn, Rec., Trav., Chim., I890, 9, 2I0.

[17]) Claus and Kurz, J. Pr., I888, 37, I96.

[18]) Lobry de Bruyn, Rec., Trav., Chim., I9I6, 36, I27.

[19]) Lobry de Bruyn, Rec., Trav., Chim., I9I6, 36, I39.

[20]) Centralbl., I905, 76, I, 4I5.

[21]) Morgan and Glover, J.C.S., I924, I597.

Bibliography (contd.)

[22]) Ullmann, Ber., I9II, 44, 3734.

[23]) Nisbet, J.C.S., I927, 208I.

[24]) Mayer, Ber., I909, 42, 3055.

[25]) Mietzsch, Ber., I938, 7I, I5.

[26]) Van Romburgh and Huyser, Rec. Trav. Chim., I930, 50, I65.

[27]) McBeth and Price, J.C.S., I937, 982.

[28]) Loudon, J.C.S., I940, I525.

- - - - - - - - - - -

- - - - - -