A thesis entitled

" Investigations on some Reactive Aromatic Halides"

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ROY GRICE

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Armstrong Laboratory,
Imperial College,
London, S.W.7.

R. Grice,
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Abstract

A range of monosubstituted benzyl halides has been synthesised including the nearly completely new series of methylmercapto- and acetoxy-benzyl chlorides and bromides, and the new N-acetylaminobenzyl bromides. New routes were devised to obtain the N-acetylamino-benzyl chlorides and some aldehydo-derivatives, while the methoxybenzyl chlorides and bromides were obtained by more efficient processes than those hitherto described.

The majority of these halides were synthesised via the appropriately substituted benzyl alcohol, itself obtained by lithium aluminium hydride reduction of the nuclear substituted methyl benzoate. A number of acetoxybenzyl halides were obtained by selective halogen replacement of the benzyl acetate grouping in the acetoxybenzyl acetates.

The object of this work was to provide a range of compounds for use in kinetic experiments to assess the influence of the various nuclear substituents on the reactivities of the side chain halogen atoms. By designing these experiments to emulate physiological

Abstract (cont.)

conditions it was possible to correlate the reaction rates with toxicities when these compounds were assessed (by Professor J.F. Danielli) for toxicity and anti--tumour effects on rats.

Exploratory investigations were also begun on the preparation of intermediates in the synthesis of monosubstituted xylylene dihalides, bifunctional analogues of the benzyl halides. In those routes starting with the appropriate nitroxylene, it was possible to isolate 4-nitro-o-xylylene dibromide and 2-nitro-p--xylylene drbromide in pure crystalline form, from which the corresponding aminophthalyl alcohols, potential intermediates for other substituted xylylene dihalides, were prepared.

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HISTORICAL INTRODUCTION

HISTORICAL INTRODUCTION

Chemotherapy of Cancer

Chemotherapy is an attempt by chemical means selectively to remove or destroy a parasite species with the minimum effect on the host. In cancerous species the differences existing between them and the host are very small and selective destruction of the former is difficult. Furthermore any selective cytotoxicity is often overcome by the ability of the tumour to develop drug resistance. For drug testing it is therefore desirable to manufacture as many drugs of a given design as possible so that as drug resistance is noted with one, treatment may be continued with another. Danielli[1,2] has stated that selective action by a drug may be promoted by increasing the number of variables on which it relies for its activity. The modern trend in drug design has therefore been to take a relatively simple chemical molecule of known anti-cancer activity and to elaborate it chemically leaving the active centre intact. The majority of compounds used for the chemotherapeutic treatment of cancer fall into three main groups: the antimetabolites,

hormones and biological alkylating agents. There are many comprehensive studies on chemotherapy of which those by Stock[3] and Farber et al.,[4] on general chemotherapy and Ross[5] on alkylating agents are examples.

The antimetabolites include mainly folic acid, purine and pyrimidine antagonists and are largely derivatives of the parent metabolite. Their action probably depends upon their ability to block certain metabolic processes for which the parent compounds are essential.

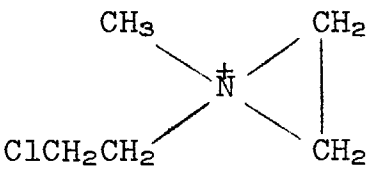
Hormone treatment has been limited largely to cortisone and related steroids. The activity of these compounds is thought to be due to the oxygen function at C_{11}.

By far the most widely synthesised and tested compounds are the alkylating agents. This group includes sulphonic esters of simple diols and of sugars; the apparent requirement for activity is that the diester groupings should be at opposite extremities of the molecule. Other members include polyepoxides, polyethyleneimines, and, by far the largest series, the nitrogen mustards. This last class, of which hundreds have been synthesised, rely for their activity on the N-dihaloethyl grouping.

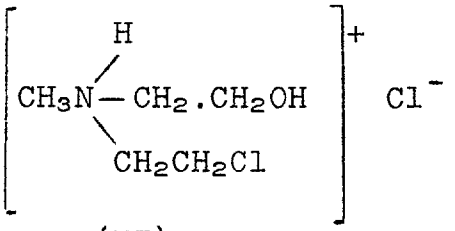
The chemical and biological properties of reactive halides

The efficiency of the nitrogen mustards in the chemotherapy of cancer is believed to be due to their action as alkylating agents. They are known to attack cellular proteins and nucleic acids but their mode of action and the reasons why they selectively attack certain tumours more than normal cells is not known. It is certain however, that two alkylating groups are necessary for cytotoxicity in a compound, thus prompting the theory by Goldacre et al.,[6] that an inter- or intra-molecular bridge system is formed by the nucleophilic attack of one or two protein chains. Although the actual mechanism of reaction has not been determined in living systems it has been thoroughly investigated by Ross et al.,[7,8,9] for aromatic, and Golumbic et al.,[10] and Hanby et al.,[11] for aliphatic nitrogen mustards under normal chemical conditions. For aromatic nitrogen mustards the mechanism of hydrolysis in aqueous acetone is S_N1, the rate determining step being the ionisation of the halide to give a carbonium ion. This mechanism is characterised by simultaneous liberation of halide and hydrogen ion, a

retardation of the reaction on adding the halide ion, an acceleration on adding other nucleophiles and by placing electron repelling substituents on the aromatic ring. When an aliphatic nitrogen mustard e.g. methyl di-2-chloroethylamine, is added to an aqueous medium one equivalent of halide ion is quickly formed but the hydrogen ion is liberated very slowly, the mustard yielding an ethyleneimonium ion (I).



(I)



(II)

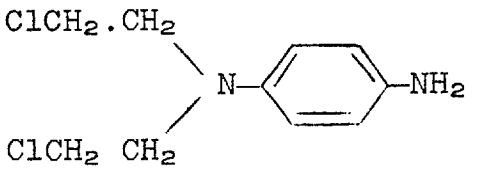
In unbuffered solutions this hydrolysis ceases after one equivalent of hydrochloric acid has been produced due to stabilisation of the chlorohydrin by salt formation (II); as the nitrogen atom carries a positive charge further cyclisation is prohibited. If the solution is buffered the reaction goes to completion. The reactivity of aliphatic nitrogen mustards is thus governed by the pH of the solution and under physiological conditions their action can be restricted.

Because nitrogen mustards attack living tissue indiscriminately extensive work has been carried out to locate them specifically at the tumour site. To accomplish this they must first be 'deactivated' so that little or no reaction occurs in their passage through normal cells and on arrival at the tumour site the active compound must be regenerated so as to attack the neoplastic cells.

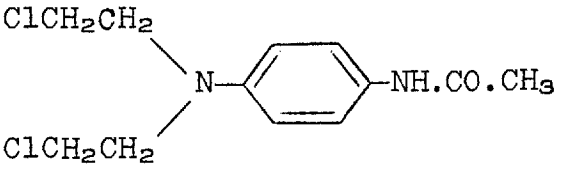
In one method the mustard is attached to a 'carrier molecule', normally a physiologically active molecule such as an α-amino acid or sugar which is able to diffuse more rapidly than others through cell membranes. By attaching the mustard to a 'carrier molecule', essential to the tumour, it would be located at that site and eventually liberated. In another method the enzymes in the host and tumour are assayed and attempts are made to utilise those in the tumour which do not exist in the host for regeneration of the active nitrogen mustard entity from an inactive derivative.

A reverse procedure can also be used; an active drug can be administered which is destroyed or deactivated by the host but not by the tumour, due to enzymic differences from the host. Deactivation of aromatic

nitrogen mustards involves the introduction of electron attracting groups into the aromatic nucleus, normally in the p-position. Thus NN-di-2'-chloroethyl--p-phenylenediamine (I) could be deactivated by acetyla-



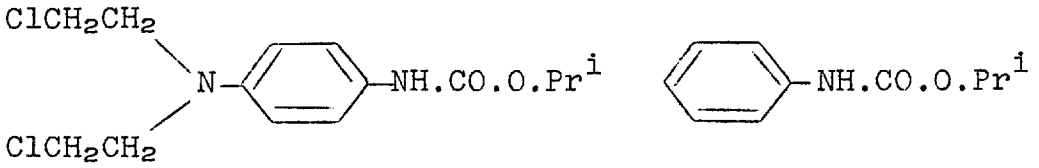
(I)



(II)

ting the free p-amino group to give NN-di-2'-chloroethyl--p-N'-acetylphenylenediamine (II) converting an electron donating to an electron attracting unit. Regeneration of the active mustard at the tumour site would require an enzyme capable of cleaving an amide linkage. Danielli[13] has suggested that if the tumour were previously treated with a simple non-mustard compound possessing that linkage, it would form an adaptive enzyme capable of splitting this in its attempts to destroy the compound. Thus acetanilide could be used to 'potentiate' acetylated NN-di-2'-chloroethyl-p-phenylenediamine, the adaptive enzyme produced to nullify the effects of the former regenerating the latter in its active free amine form. By this method Benn[14] potentiated (III) with

(IV), a policy pursued later by White.[15]



(III) (IV)

It has been shown that other alkylating agents of the methanesulphonyl type like 'Myleran' possess anti--tumour activity, and their reaction mechanism may be of the S_N2 type as opposed to the S_N1 exhibited by the nitrogen mustards. The object of the present work was to investigate other types of reactive halides which might react by either of these mechanisms. Compounds of this class include benzyl halides, α-haloketones, α-haloesters, alkyl halides and some aliphatic nitro compounds like chloropicrin. Coupled with these essentially monofunctional compounds there are bifunctional analogues of the αα'-dihalodiketone, αα'-dihalodiester and the xylylene dihalide type. Biologically, most of these are potent lachrymators, the more important members of which have been reviewed by Jackson and Jackson.[16]

A survey conducted by Mackworth[17,18] revealed that enzyme systems which were dependent on thiol groups for

their activity were strongly and irreversibly inhibited by low concentrations of lachrymators. Iodoacetic acid, although not classed as a lachrymator because of its inactivity towards some thiol-containing enzymes, has furnished many details of the mode and mechanism of the lachrymator-thiol reaction. Dickens[19] using sodium iodoacetate, in reactions utilising cysteine and glutathione as the thiol source, conducted a series of experiments under physiological conditions of pH and temperature. The reactions, carried out in the presence of sodium bicarbonate, were followed by measuring the amount of carbon dioxide evolved. From the results he was able to compare the effect of different halogen substituents on the reaction rate and at the same time establish that the reaction was second order. For the three mono-halogenoacetic acids he obtained the following results:

pH 7.4, $t = 37^{\circ}$, glutathione as nucleophile.

$CH_2I.CO_2H$ > $CH_2Br.CO_2H$ > $CH_2Cl.CO_2H$

$k_I = 15$ $k_{Br} = 8.5$ $k_{Cl} = 0.15$

k is in 1. $mole^{-1}$ $min.^{-1}$

By isolating the product from the simpler reaction with cysteine he established that a sulphide was produced. As iodoacetic acid was not considered a true lachrymator, Dixon[20] applying similar techniques conducted a series of experiments using a true lachrymator. He found that, at neutral pH, reactions with cysteine and other thiols were complete within a few minutes, an excess of thiol being detected by the sodium nitroprusside test. Using a wider range of compounds including non--lachrymators, Morgan and Dixon[21] showed that only those which exhibited lachrymatory properties were reactive towards thiols. Bacq et al.,[22,23,24] independently investigating the same problem reached the same conclusions; he treated denatured protein with lachrymators, including chloropicrin and phenacyl chloride, at different values of pH. The higher the pH the more potent was the thiol as a nucleophile and the faster was the reaction. Using a system with a preponderance of thiol groups he established that lachrymator and thiol combined in a 1:1 ratio. For lachrymators the rate of reaction with cysteine or glutathione was faster than with the denatured protein. If however halogenoacetic acids were used the findings were reversed. This rather unusual

effect, explained by Dixon as possibly due to poisoning, prompted investigations into whether the analogy drawn for lachrymators with iodoacetic acid in the actual products formed was justified. Desreux, Fredericq and Fischer[25] had shown that chloropicrin, a recognised lachrymator, oxidised cysteine to cystine, no sulphide being formed, showing that anomalous results might be due to disulphide formation. Dixon[20] obtained completely reduced muscle powder by treating the normal material with glutathione and cyanide. This material was then treated with various lachrymators and the reaction product reduced with cyanide. In all cases, except where chloropicrin was used, no free thiol was detected by the sodium nitroprusside test, indicating that sulphide rather than disulphide formation was the preferred reaction.

Kinetic Work on Benzyl Halides

This review deals mainly with work which surveys the influence exerted by mono-substituents in various positions of the aromatic nucleus on the reactivity of the halogen atom in the side chain.

Reaction mechanisms

Benzyl halides can undergo substitution reactions by two types of mechanism. The first is the S_N1 type of reaction where the product is formed in a two stage process. Initially there is a breaking of the carbon--halogen bond to give a carbonium ion, a slow rate determining step, followed by the relatively fast reaction with the nucleophile.

$$RCH_2X \longrightarrow RCH_2^{+} + X^{-}$$

$$RCH_2^{+} + Y^{-} \longrightarrow RCH_2Y$$

This reaction is facilitated by nuclear substituents which release electrons to the side chain. It will occur more readily in polar solvents which aid the charge separation and stabilise the intermediates and it will be more likely to occur if the nucleophile is weak. A strong nucleophile would tend to effect an S_N2 process, the second type of mechanism. Here a one step reaction occurs with simultaneous bond breaking

$$RCH_2X + Y^{-} \longrightarrow RCH_2Y + X^{-}$$

and formation. The conditions for this reaction are more complex in relation to the substituents. The bond breaking process will be aided, as before, by electron

donating groups, but the nucleophilic attack will be facilitated by electron withdrawing groups. The actual order of reactivity of compounds is difficult to predict but it can be stated that as the effect on reactivity in the S_N2 mechanism is the sum of two opposing effects the range of reactivities of compounds participating in reactions of this type will not be so large as in the S_N1 type. Unlike the S_N1 case, S_N2 reactions occur more readily in non polar solvents.

These two reaction mechanisms are just the limits of a spectrum. Between these limits there can be an infinite number of mechanisms composed of varying proportions of the two. In many cases reactions occur by both mechanisms at once, the predominant one being the one measured.

Survey of kinetic work.

Although, for many of the early kinetic observations, no mechanism was postulated, it is proposed to deal first with that kinetic work conducted in highly polar solvents using weak nucleophiles, which conforms to the S_N1 conditions.

The first extensive study of the reaction rates of benzyl halides under such conditions was carried out by Olivier[26,27,28,29] who determined them for a wide range of nuclear substituted benzyl chlorides with water as the nucleophile at a number of different temperatures. Using a large excess of equal volumes of water and ethanol he first[26] compared the unimolecular reaction constants of benzyl chloride with the isomeric chlorobenzyl, nitrobenzyl and monomethylbenzyl chlorides. The reactions were followed by extracting and estimating the chloride ion formed (by Volhard's method). Later he extended his investigations to include the bromobenzyl chlorides,[27] and the iodo and carboxylic acid derivatives.[28] Later realising that he was estimating a combination of two reactions, a pure hydrolysis and an alcoholysis, he repeated his earlier work replacing ethanol by acetone.[29] The numerical values for the rate constants were smaller but the order of reactivity of compounds remained unchanged. Using the new method he also investigated the three isomeric cyanobenzyl chlorides and two α-chlorotoluamides.[29] Some representative results can be seen in Table I. No mention is made of the reaction

mechanism involved but from the conditions employed he was probably measuring an essentially S_N1 process. As would be expected of such a process, the electron--donating methyl substituents produce the fastest reaction, while the electron-attracting nitro and cyano groups have a retarding effect. Shoesmith et al.,[30,31,32] using the same solvolytic conditions

Table I

$T = 60^{\circ}$ Acetone-water k in $min.^{-1}$

Substituent	$k \times 10^3$	Substituent	$k \times 10^3$
p-Me	4.0	H	0.46
o-Me	1.89	m-CO_2H	0.132
m-Me	0.55	p-CO_2H	0.086
p-Cl	0.268	m-NO_2	0.051
o-Cl	0.137	o-NO_2	0.045
m-Cl	0.093	p-NO_2	0.046
p-Br	0.234	m-$CONH_2$	0.203
o-Br	0.129	p-$CONH_2$	0.146
m-Br	0.093	m-CN	0.062
p-I	0.215	p-CN	0.058
o-I	0.123	o-CN	0.049
m-I	0.089		

extended the range to substituted benzyl bromides. Although no rate constants were calculated, by estimating volumetrically the acid formed after given intervals of time, when the bromides were treated with excess water-ethanol, he was able to draw up tables of relative reactivities. He first compared the carboxybenzyl bromides and the nitrobenzyl bromides.[30] He noticed the abnormal reaction of o-bromomethyltoluic acid due to phthalide formation, but the other results conformed to those found by Olivier. Similar hydrolyses of the w-bromoxylenes followed by all the fluoro-, chloro- and bromo-benzyl bromides and azoxybenzyl bromides gave a comprehensive picture of reactivity relationships in isomeric series. The general effected noted was

$$Me > F > Cl > Br > CO_2H > NO_2$$

In the series of nuclear halogen substituents the effect noticed was

$$F > Cl > Br$$

Later Shoesmith[33] measured the reaction rate constants under the same conditions for the m- and p-isomers of tertiarybutylbenzyl bromide:

p-tertiary butyl > m-tertiarybutyl > benzyl bromide

k in hr.$^{-1}$

k x 10^6	333	192	125

As in the initial work of Olivier two simultaneous reactions were occurring, probably of the S_N1 type.

In comparing the reactivities of substituted benzyl chlorides under varying reaction conditions, Bennett and Jones[34] repeated some of Olivier's work in aqueous acetone but included the three nuclear fluorinated benzyl chlorides. Although slightly different temperatures were used, reaction rates could be compared by taking that of benzyl chloride as a standard. Good agreement was obtained and the same general trends in reactivity were noticed (p > o > m in an isomeric series of halogens) for the fluorobenzyl chlorides as for the fluorobenzyl bromides.[32]

Little study has been made of the benzyl iodides because their enhanced reactivity over the benzyl bromides makes their preparation more difficult and their reactions faster. At the other end of the scale however, Bernstein[35] has conducted a survey of substituted benzyl fluorides. Under the conditions used by Olivier[29] and Bennett[34] similar relative reactivities were noted:

p-Me > m-Me > H > p-X > o-X > m-X > m-NO_2 > p-NO_2

The only unusual feature was that the solvolysis of benzyl fluoride is catalysed by hydrogen ions, which can bond with the fluorine atom. Olivier[26] noted that acid had no effect on the solvolysis of benzyl chlorides. Comparison of benzyl fluoride with benzyl chloride by reaction with ethoxide ion (an S_N2 process) showed the chloride to be fifty times as reactive.

Extensive work has been conducted on the kinetics of solvolysis of benzyl chloride itself. Heble and Wheeler[36] measured the reaction rate of this compound with a large excess of formic acid at a number of temperatures while Beste and Hammett[37] measured velocity constants with hydroxyl and acetate ion in a variety of dioxan-water mixtures. Böhme and Henning[38] used the same solvent for a similar set of investigations while Winstein et al.[39] studied the solvolysis in a number of different hydroxylic solvents. Water-dioxan-formic acid mixtures were employed by Fierens et al.[40] in their investigations and later he[41] observed the variation of reaction rate with temperature in dioxan-water mixtures. Dewar and Sampson[42] conductiometrically measured the reaction rate with aqueous formic acid and ethanol and recently Barbieri et al.[43-49] have

extensively studied the solvolysis in aqueous acetic acid at a variety of temperatures.

On substituted benzyl halides the work has not been so extensive. Baker[50] studied the reaction kinetics of a few p-substituted benzyl chlorides and bromides with aqueous ethanol at 30°. Aqueous acetone mixtures at 40° and 60° were employed in investigations by Simonetta and Favini[51] while Fierens[52] conducted reactions on p-methoxybenzyl chloride and p-methylbenzyl chloride in aqueous dioxan and aqueous dioxan-formic acid solutions. Later[53] he calculated unimolecular reaction constants in aqueous dioxan and aqueous acetic acid for the solvolyses of the three chloromethyltoluenes and the chloromethyl-chlorobenzenes. His results of comparative reactivities agreed with the earlier findings of Olivier and Bennett. Clement and Naghizadeh[54] treated p-methylbenzyl chloride and p-tertiarybutylbenzyl chloride with methanol and determined their unimolecular rate constants.

In the preceeding section all the reaction rate constants have been calculated for the unimolecular type of reaction. Many of the bimolecular reaction rate constants of benzyl halides have been determined for

the reaction with amines. The initial work in this field was done by Menschutkin[55] who followed the bimolecular reaction between benzyl bromide and a series of aromatic amines in alcohol at 40°. Peacock,[56] using similar conditions and a four to one ratio of amine to substituted benzyl chloride, measured bimolecular velocity constants over the early stages of the reaction. Other than benzyl chloride the only other compound used was p-nitrobenzyl chloride. His results are summarised in Table II. He did however extend the range of amines and obtained comparative rates of reaction of these with benzyl chloride. Jones and Preston[57]

Table II

k in l. mole^{-1} min.$^{-1}$

Nucleophile	Benzyl Chloride	k_{35}°	k_{45}°
Aniline	H	0.00157	0.00315
"	p-NO_2	0.000588	0.00125
p-toluidine	H	0.00217	0.00495
"	p-NO_2	0.00137	0.00252

were the first to compare the relative rates of reaction of three isomeric benzyl halides under these conditions. They measured bimolecular velocity constants of the reaction of the three xylyl bromides and p-bromobenzyl bromide with dimethylaniline and triisoamylamine. The general order of activity observed was:

$$p\text{-Me} > o\text{-Me} > m\text{-Me} > p\text{-Br}$$

Norrish and Smith[58] investigated the kinetics of the reaction between m- and p-nitrobenzyl chloride and trimethylamine in benzene at 30° and found that the p-isomer reacted quickest. MacCombie et al.[59], investigating quaternary ammonium salt formation, studied the bimolecular reactions of benzyl chloride and its three isomeric nitro derivatives in a range of solvents with a variety of nucleophiles, including two amines. A summary of the observed results appears in Table III. All rate constants have been related to p-nitrobenzyl chloride, which is taken as unity.

Table III

Nucleophile	Solvent	Benzyl Chloride	o-NO_2	m-NO_2	p-NO_2
Alkali	aq.EtOH	2.6	1.06	1.28	1.00
$Na_2S_2O_3$	"	0.54	0.54	0.64	1.00
NEt_3	"		0.81	0.86	1.00
KI	Acetone	0.14	1.32	0.57	1.00
NMe_3	"	0.98	0.55	0.86	1.00

Reaction rate constants for these halides, were then obtained in a still wider range of organic solvents, for the reaction with trimethylamine. A few of the results are listed in Table IV. Again the rate for p-nitrobenzyl chloride, not listed, is taken as unity.

Table IV

Solvent	Benzyl chloride	o-NO_2	m-NO_2
Ethyl acetate	0.62	0.42	0.79
Acetone	0.97	0.55	0.80
Benzene	1.02	0.68	0.74
Ethyl benzoate	1.08	0.63	0.72
Anisole	1.32	0.70	0.71
Nitrobenzene	1.45	0.67	0.68

At about the same time Mukhin et al.,[60] were investigating solvent effects on the reactions between benzyl bromide and pyridine or triethylamine. Solvents employed included nitrobenzene, ethanol, benzene and mixtures of the last two.

The first extensive investigation of the kinetics of the amine-benzyl halide reactions were conducted by Baker et al.[50,61-63] Initially[61] he measured the reaction rate of benzyl chloride with large excesses of aniline or pyridine in ethanol (90%) and then extended his work to include a variety of mainly p-substituted benzyl bromides, chlorides and iodides. Under these

conditions the reactions were pseudounimolecular. Table V summarises his results.

Table V

$R.C_6H_4.CH_2X$ at 30.5° in 90% EtOH

k is in $min.^{-1} \times 10^3$

R	X = Cl		X = Br		X = I	
	Aniline	Pyridine	Aniline	Pyridine	Aniline	Pyridine
p-MeO	-	14.6[12]	-		-	-
p-Me	-	-	87	9.5	-	-
H	0.70	0.09	35	4.4	61	5.1
m-NO_2	-	-	30.4	1.4	44	1.6
p-NO_2	-	-	22.3	1.56	36.2	1.8

Later[62] using the same pseudounimolecular conditions he investigated other p-substituted benzyl bromides. From these and earlier results the following order of reactivities could be written

p-MeO $\gg$ p-Me $>$ H $>$ p-I $>$ p-Cl $\gtrless$ p-Br $>$ p-NO_2

Using equimolecular amounts of amine and benzyl bromide with ethanol as solvent Baker[50] then obtained good bimolecular rate constants for the initial stages of

reactions between p-nitro and p-methylbenzyl bromide and pyridine at 30°. The order of reactivity was

$$\underline{p}\text{-Me} > H > \underline{p}\text{-}NO_2$$

A series of reactions[63] was then conducted using pyridine, first in dry acetone and then aqueous acetone and ethanol. All the calculated rate constants were in accordance with the order of reactivity shown above for the initial stages of the reaction. Replacement of pyridine by picoline as the nucleophile in reactions conducted in dry acetone did not alter the relative reactivities of the benzyl bromides. Finally Baker made a survey of the effect of nuclear halogen substitution on the benzyl bromide-pyridine reaction in dry acetone at 20°. A summary of these results is included in Table VI.

Pyridine was again used as a nucleophile by Pearson et al.,[64] who compared it with thiourea. On treatment of benzyl bromide in methanol with these two nucleophiles it was found that although pyridine was a stronger base by a factor of 10^5, thiourea was a stronger nucleophile by a factor of thirty due to the polarisability of its carbon-sulphur bonds. Pseudounimolecular aminolyses have been conducted by Swain and Dittmer[65] on benzyl

Table VI

$R.C_6H_4.CH_2Br$

k in l. $mole^{-1}$ $sec.^{-1}$

Substituent R	k	Substituent R	k
H	1.22	p-F	1.48
p-NO_2	1.12	p-Cl	1.27
m-NO_2	0.99	p-Br	1.30
p-Me	2.02	p-I	1.48
m-Me	1.43	m-F	0.95
p-Bu^t	1.65	m-Cl	1.08
m-Bu^t	1.22	m-Br	1.07
		m-I	1.14

chloride alone, with emphasis placed more on the amines than the halide. Recently however, another extensive investigation has been conducted by Mukaiyama and Tanaka[66] on the reaction kinetics of bulkily substituted amines with a series of benzyl chlorides in benzyl alcohol at 105°. The amines used were dimethylaminoethanol, diethylaminoethanol, di-isopropylaminoethanol, di-isobutylaminoethanol, di-n-butylaminoethanol and tri-n-butylamine. In each case the relative reactivities of the substituted benzyl chlorides

could be summarised

$$\underline{p}\text{-Me} > \underline{o}\text{-Me} > H > \underline{p}\text{-Cl} > \underline{o}\text{-Cl} > \underline{p}\text{-CN} > \underline{o}\text{-CN} > \underline{p}\text{-NO}_2 > \underline{o}\text{-NO}_2$$

in agreement with those obtained by earlier workers. The conclusions drawn by the Japanese workers were that, in the single stage nucleophilic substitution processes measured, the polar effects of substituent groups were not clearly shown. Surveying all the benzyl halide kinetic work mentioned here, if it is assumed that the reactions are occurring by an essentially S_N2 process, it appears that the initial electron donation process, under the conditions used, outweighs the electron withdrawal process in determining reactivity.

Amines, although the most extensively investigated group of compounds used in bimolecular reactions, constitute only about half of the literature on the subject. Many other possibly stronger nucleophiles have been used.

Franzen[67,67] measured the kinetics of the reaction between equimolecular amounts of sodium ethoxide and substituted benzyl chlorides in ethanol. For the first half of the reaction he recorded quite good bimolecular rate constants. A summary of his findings appears in Table VII.

Table VII

k is in l. mole^{-1} day^{-1} at 30°

Substituent	k	Substituent	k	Substituent	k
H	6.40				
o-Me	16.20	o-Cl	7.1	o-Br	6.3
m-Me	7.14	m-Cl	9.0	m-Br	9.3
p-Me	10.10	p-Cl	12.5	p-Br	9.5

Ethoxide ion was the nucleophilic reagent chosen by Bernstein and Miller[35] to compare the reactivities of their substituted benzyl fluorides under bimolecular conditions, when they proved so unreactive to potassium iodide in acetone. A summary of their results for reactions between equimolecular amounts of reactants at 76° is given in Table VIII.

The authors chose conditions conducive to an S_N2 mechanism and obtained results in agreement with those predicted by Ingold[69] for the electron attracting powers of substituent groups. Ingold et al.,[70] have investigated this S_N2 process employing tertiary butoxide ion in tertiary butanol as well as the ethoxide system already described. They investigated the influence

Table VIII

k is in l. mole^{-1} hr.$^{-1}$

Substituent	k	Substituent	k	Substituent	k
o-Br	0.055	p-Me	0.012	p-Br	0.143
m-Me	0.090	m-Cl	0.116	p-Cl	0.146
m-Me	0.095	m-Br	0.120	p-I	0.160
m-F	0.097	m-I	0.129	m-NO_2	0.322
o-Cl	0.099	p-F	0.130	p-NO_2	v.fast

of p-methyl and p-tertiary butyl substituents in both benzyl chlorides and bromides on the reaction rate. The order of reactivity with both nucleophilic systems was the same.

$$\text{p-Me} > \text{p-Bu}^{t} > \text{H}$$

Potassium iodide in acetone has been one of the most widely used systems for bimolecular investigations on benzyl halides. The pioneers in this field, Conant and Kirner,[71] studied the reaction between benzyl chloride and this system over a range of different concentrations and temperatures. The mechanism was

not discussed but they realised that the reaction occurring was

$$PhCH_2Cl + I^- \rightarrow PhCH_2I + Cl^-$$

the actual iodide ion concentration being unknown. Later Conant et al.,[72] investigated this bimolecular exchange with a number of substituted benzyl chlorides. A number of anomalous results were obtained due to impure reactants and the work was repeated and amplified by Bennett and Jones[34] who obtained the results summarised in Table IX.

Table IX

k is in l. mole^{-1} hr.$^{-1}$ $R.C_6H_4.CH_2Cl$ 5.13:1 ratio of chloride to iodide

R	$k_{0.10}$	k_{200}	R	$k_{0.10}$	k_{200}
H	0.133	1.32	p-F	0.205	1.90
m-F	0.183	1.84	p-Cl	0.293	2.80
m-Cl	0.235	2.17	p-Br	0.301	3.12
m-Br	0.260	2.47	p-I	0.295	2.98
m-I	0.242	2.34	o-F	0.45	3.89
m-NO_2	0.486	4.83	o-Cl	0.632	5.25
p-NO_2	0.907	8.17	o-Br	0.565	5.27
o-NO_2	1.30	11.40	o-I	0.627	5.51

Fierens et al.,[40] conducted a number of these exchange reactions over a range of temperatures and later[53] compared the reactivities of a range of substituted benzyl chlorides. In general the reactivities were

$$\underline{p}\text{-}NO_2 \rangle \underline{p}\text{-}OMe \rangle \underline{p}\text{-}Me \rangle H$$

Ingold et al.,[70] using the same type of reaction for p-substituted benzyl bromides at 0° found

$$\underline{p}\text{-}Me \rangle \underline{p}\text{-}Bu^t \rangle H$$

Sulphur-containing compounds were first used as nucleophiles in bimolecular reactions with benzyl halides by Slator and Twiss[73] who followed the reaction of sodium thiosulphate and the nitrobenzyl chlorides in aqueous ethanol at 35°. The observed order of reactivity was

$$\underline{p}\text{-}NO_2 \rangle \underline{m}\text{-}NO_2 \rangle \underline{o}\text{-}NO_2 = H$$

More recently Fuchs[74] used sodium thiosulphate as a nucleophile, in solvents of varying dielectric constant, on p-substituted benzyl chlorides. The first two solvents employed were diglyme-water (60/40) and ethanol--water (60/40). All reactions followed second order kinetics even in the latter solvent where a solvolysis

reaction might be expected. These results are summarised in Table X.

Table X

k is in l. $mole^{-1}$ $sec.^{-1}$

Substituent	k_D	k_E
p-NO_2	26	9.67
p-Cl	12	7.31
H	7.1	5.33
p-Me_2CH-	7.95	8.38

Fuchs and Nisbet[75] then extended their kinetic investigations to a large range of aqueous solvents of differing dielectric constant. Although the relative reaction rates remained in the following order

$$\text{p-}NO_2 \rangle \text{ p-Cl} \rangle \text{ p-isopropyl} \rangle \text{ H}$$

the k p-NO_2/k p-Me_2CH- was decreasing with increase in dielectric constant. This was taken as an indication by the authors that they were nearing the experimental limits inside which the S_N2 type of reaction was occurring even though second order kinetics were being

observed.

The other sulphur compound used for bimolecular investigations was sodium sulphite. By using it in aqueous ethanol Sprung[76] investigated a large series of substituted benzyl bromides and chlorides. The reaction was

$$RCH_2X + SO_3^{--} \longrightarrow RCH_2SO_3^- + X^-$$

and he assumed that the activity of the sulphite ion was proportional to its concentration, the ratio remaining constant for all the halides investigated. His results, which are summarised in Table XI, are what would be expected for an essentially S_N2 process.

Silver nitrate has also been employed as a nucleophile but unfortunately the silver halide formed during the reaction becomes photosensitized on exposure to light and exhibits a catalytic effect on the reaction rate. It was however used by Baker[50] to compare the relative rates of reaction of p-methyl and p-nitrobenzyl chloride and by Prevost and Martin[77] who measured the bimolecular rate constant of its reaction with benzyl chloride at 10^o in aqueous acetone.

Apart from a number of bimolecular isotope exchange reactions by Sugden and Willis [78] and de la Mare[79] the

Table XI

k is in l. mole^{-1} min.$^{-1}$

R.C_6H_4.CH_2Cl	$k_{40°}$	R.$C_6H_4CH_2Br$	$k_{30°}$	$k_{40°}$
H	0.392	H	5.86	18.6
Cl p-	0.345	Cl p-	5.17	14.2
Cl o-	0.328	Cl o-	3.84	8.67
Cl m-	0.238	Cl m-	3.00	7.16
Br p-	0.465			
Br o-	0.262			
Br m-	0.238	Br m-	3.40	6.42
NO_2 p-	0.738	NO_2 p-	17.2	
NO_2 o-	0.525	NO_2 o-	10.5	
NO_2 m-	0.487	NO_2 m-	9.55	

only other reaction of interest is that between potassium tertiary butyl peroxide and o-chlorobenzyl chloride conducted by Coppinger and Campbell.[80] In methanol this exhibited bimolecular kinetics in spite of the competing alcoholysis reaction.

$$\text{o-Cl.C}_6\text{H}_4\text{.CH}_2\text{Cl} + {}^{-}\text{OO.C}_4\text{H}_9{}^{t} \longrightarrow \text{o-Cl.C}_6\text{H}_4\text{.CH}_2\text{OO.C}_4\text{H}_9{}^{t} + \text{Cl}^{-}$$

$$\text{C}_4\text{H}_9\text{OH}^{t} + \text{o-Cl.C}_6\text{H}_4\text{.CHO.}$$

THEORETICAL

THEORETICAL

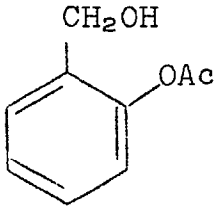
Syntheses of Substituted Benzyl Halides.

The object of the present work was partly to obtain some o-, m-, and p-substituted benzyl halides for use both in kinetic and biological experiments in an attempt to correlate the chemical reactivity of the halide, under approximately physiological conditions, with its actual toxic effect on animals (the latter determined by Professor J.F. Danielli and his associates at King's College, London).

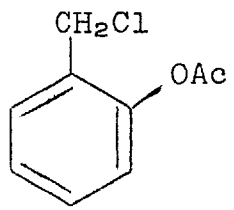
The normal mode of synthesis was based on obtaining the appropriately substituted benzyl alcohol and replacing the hydroxyl group by chlorine or bromine. Initial attempts were directed towards the synthesis of phenolic benzyl halides because of the possible ease with which this grouping could be modified to vary the reactivity of the side chain halogen atom. Although all the chloromethyl anisoles have been made previously, no free chloromethyl phenol has been described and only one acetyl derivative is known.

Early attempts by Gray[81] to convert saligenin to o-hydroxybenzyl chloride by treating the diol with thionyl chloride in an excess of diethylaniline gave extensive amounts of tar and no halide. In the present attempts, saligenin was suspended in chloroform or benzene containing a trace of pyridine, and thionyl chloride was added. Much sulphur dioxide and hydrogen chloride were evolved but the isolated viscous oil rapidly decomposed with the evolution of hydrogen chloride. Attempts to isolate an S-alkylthiouronium picrate were unsuccessful. p-Hydroxybenzyl alcohol gave a similar result.

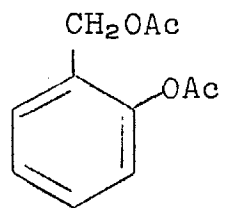
o-Acetoxybenzyl alcohol[81,82] (I) and o-acetoxybenzyl chloride[81] (II) have been described by earlier workers. The former compound was said to be obtained



(I)



(II)



(III)

by refluxing potassium saligenate with excess acetic anhydride or by adding acetyl chloride to the salt in

ether. Efforts to reproduce these experiments failed. The reaction between potassium saligenate and acetic anhydride under reflux gave, as would be expected, saligenin diacetate, whilst the acetyl chloride process yielded viscous oils which decomposed on attempted distillation. Less drastic treatment of the potassium salt with acetic anhydride again gave undistillable viscous products. The free diol in an equimolecular amount of aqueous potassium hydroxide when treated with a slight excess of acetic anhydride (a process devised for obtaining the other isomers, see below) gave polymer. Vigorous treatment of saligenin diacetate (III) with thionyl chloride under reflux gave no benzyl halide but prolonged refluxing with hydrogen chloride in benzene did result in preferential replacement of the primary acetate and formation of small amounts of o-acetoxybenzyl chloride, which was characterised as its S-alkylthiouronium picrate. The corresponding o-acetoxybenzyl bromide was obtained in good yield by adding saligenin diacetate to a large excess of hydrogen bromide in dry acetic acid. This yielded the same S-alkylthiouronium picrate as was obtained from o-acetoxybenzyl chloride.

m-Hydroxybenzyl alcohol was obtained by reducing either m-hydroxybenzaldehyde or methyl m-hydroxybenzoate with lithium aluminium hydride, the latter rather than the former process comparing well in yield with the reduction of m-hydroxybenzaldehyde using sodium borohydride conducted by Chaikin and Brown.[83] The reaction of the diol (1 equiv.) in aqueous potassium hydroxide solution (1 equiv.) with acetic anhydride (1.1 equiv.) was performed many times but in each case the stable colourless oil obtained could not be purified by fractional distillation; the presence of the desired monoacetate was however confirmed by characterisation as a naphthylurethane. The marked reduction in boiling point, when any benzyl alcohol is converted to its chloride, made it possible to treat this crude m-acetoxybenzyl alcohol with thionyl chloride and obtain a good yield of pure m-acetoxybenzyl chloride. Selective replacement reactions conducted with m-acetoxybenzyl acetate, similar to those tried with saligenin diacetate, using hydrogen bromide in dry acetic acid gave no pure product, but an S-alkylthiouronium picrate prepared from the crude material was identical with that obtained from

m-acetoxybenzyl chloride, thus showing that the bromide was in fact formed.

p-Hydroxybenzyl alcohol was obtained in a similar way to the m-isomer. Reduction of methyl p-hydroxybenzoate with lithium aluminium hydride gave the required diol in good yield. Reese[84] mentions this reduction but quotes no yields. Catalytic hydrogenation of p-hydroxybenzaldehyde under pressure using Adams' catalyst was slow and incomplete and gave only half of the quantitative yield obtained by Kelecsenyi-Dumesnil[85] who used Raney nickel as catalyst. The diol however, could be easily separated from unchanged aldehyde due to the latter's high solubility in ethyl acetate, a solvent from which p-hydroxybenzyl alcohol could be crystallised. When dissolved in aqueous potassium hydroxide (1 equiv.) and treated with acetic anhydride (1 equiv.) the diol readily gave pure p-acetoxybenzyl alcohol. Treatment of this with thionyl chloride in benzene containing a trace of pyridine gave pure p-acetoxybenzyl chloride as a colourless liquid; this decomposed on storage to give first a pink resin and eventually a brittle pink solid of high melting point, with the evolution of hydrogen chloride.

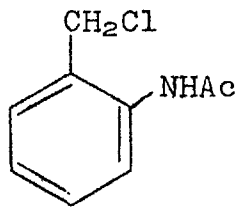
Similar treatment of p-acetoxybenzyl alcohol with thionyl bromide gave crystalline p-acetoxybenzyl bromide; this also was unstable and darkened on storage with the evolution of hydrogen bromide. Neither the above chloride nor bromide could be obtained by selective reaction of hydrogen chloride or hydrogen bromide on p-acetoxybenzyl acetate, by the methods described above in the isomeric series.

o- and m-Methoxybenzyl alcohol were prepared in excellent yield by reducing the corresponding methoxybenzaldehyde with lithium aluminium hydride, a process used by Tadros et al.,[86] for obtaining a number of alkoxybenzyl alcohols. These alcohols, and also the commercially available p-isomer, were smoothly converted into their benzyl chlorides by treatment in benzene or chloroform solution with thionyl chloride. m-Methoxybenzyl bromide was synthesised by the method of Lapworth and Shoesmith,[87] which involved passage of hydrogen bromide through a solution of m-methoxybenzyl alcohol in benzene.

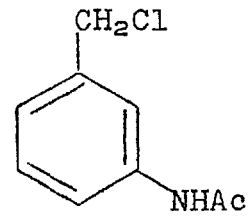
Amino-substituted benzyl halides were of particular interest, as were the above oxygenated compounds, because of the possibility of modification of the

amino-group, and because the presence of the amine or hydroxy functions, groups often occurring in living tissue, would lend 'carrier' properties to the molecules and render them more easily assimilated by the host.

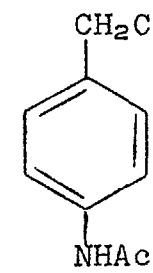
No free aminobenzyl chlorides or bromides have yet been prepared, probably because of their unstability; the amine group would render the halogen in the side chain very labile, and self-condensation to give polymeric products would be expected. When the electron donating properties of the amine group are arrested, stable benzyl halides are obtained, and both o-aminobenzyl chloride and bromide have earlier been prepared as their hydrochloride and hydrobromide respectively. This was accomplished by Gabriel and Posner[88] who heated o-aminobenzyl alcohol with hydrogen chloride or hydrogen bromide in a sealed tube at 100°. All three isomeric N-acetylaminobenzyl chlorides (IV), (V) and (VI) were obtained by Kühn[89] whilst investigating the chemical properties of phosgene. He treated the three isomeric N-acetylaminobenzylpiperidines (VII), (VIII) and (IX) in chloroform with phosgene in toluene but he recorded no yields; the corresponding



(IV)

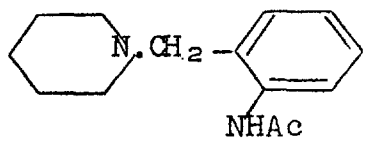


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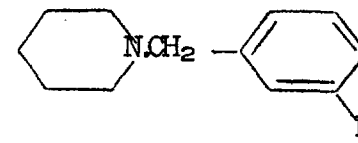


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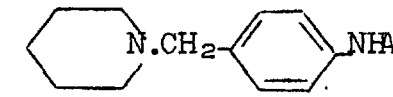
bromides have not been described.



(VII)

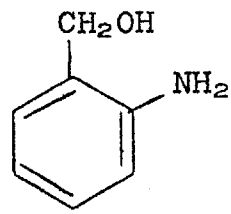


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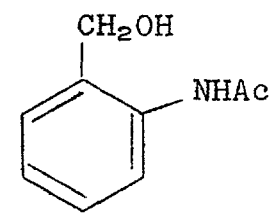


(IX)

In the present work more direct methods of synthesis were attempted, the essential intermediate in each case being the aminobenzyl alcohol. o-Nitrobenzyl alcohol was quickly and quantitatively hydrogenated in the presence of Adams' catalyst to o-aminobenzyl alcohol (X), a much more efficient method than the



(X)



(XI)

sodium hydrosulphide reduction of Reissert and Cramer[90] or the normal metal-acid reduction. The amine, which darkened on exposure to air, could be selectively N-acetylated by treating it with one equivalent of thiolacetic acid; a more efficient process was to treat the amine suspension in ethyl acetate with one equivalent of acetic anhydride. The amine gradually dissolved as the reaction mixture became warm and cooling of the clear solution effected deposition of pure o-N-acetylaminobenzyl alcohol (XI) in very good yield. The conversion of this material to o-N-acetylaminobenzyl chloride (IV) was difficult and the yield poor. The reaction conducted with thionyl chloride, using a catalytic trace of pyridine, occurred only at elevated temperatures with much decomposition. The failure of this reaction to proceed smoothly was attributed to the hydrolysis of the amide group under acid conditions. Attempts to prevent this occurring by using an excess of pyridine gave no halide at all. The corresponding o-N-acetylaminobenzyl bromide was prepared by the use of phosphorus tribromide in benzene. This reaction in either dioxane or benzene gave a pale yellow granular product

which analysed well but could not be recrystallised.

m-Nitrobenzyl alcohol was hydrogenated in the presence of Adams' catalyst at atmospheric pressure and temperature to give a quantitative yield of m--aminobenzyl alcohol. These results are in accordance with those of Phillips and Maggiolo[91] who carried out the same hydrogenation at slightly elevated pressures. The amine was converted in excellent yield to m-N--acetylaminobenzyl alcohol by treating its suspension in ethyl acetate with acetic anhydride. The reaction of this alcohol with thionyl chloride in dry benzene gave a slightly better yield of the required benzyl chloride than was obtained of the o-isomer. The corresponding bromide, which was synthesised by heating the alcohol in benzene with thionyl bromide, fortunately crystallised from the reaction mixture in an analytically pure state; it was extremely unstable in solution and recrystallisation was impossible.

Phillips and Maggiolo[91] stated that, on reduction in ethanol using Adams' catalyst at 2-3 atmospheres, p-nitrobenzyl alcohol gave a polymer of high melting point. They attributed this to traces of acid and showed that polymerisation occurred when p-aminobenzyl

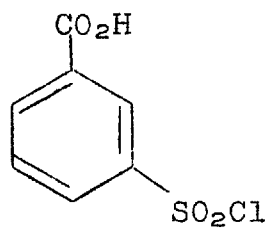
alcohol was treated with acetic acid. In the present work a similar reduction using the same catalyst, but at atmospheric pressure, gave p-amino-benzyl alcohol quantitatively. A more direct attempt to prepare p-aminobenzyl alcohol involved the lithium aluminium hydride reduction of methyl p-aminobenzoate. Nystrom and Brown[92] reduced anthranilic acid to o--aminobenzyl alcohol in excellent yield and Phillips and Maggiolo[91] reduced the p-isomer in good yield. Conover and Tarbell[93] however, noted that reduction of both o- and p-aminobenzoic acids with lithium aluminium hydride gave varying amounts of o- and p-toluidines which increased in proportion with reaction time; this observation has been confirmed in the present case, both p-toluidine and p-aminobenzyl alcohol being obtained.

The free amine on treatment with thiolacetic acid or with acetic anhydride in ethyl acetate in the manner previously described gave p-N-acetylaminobenzyl alcohol. The thionyl chloride reaction was again accompanied by polymerisation and the yield of p-N--acetylaminobenzyl chloride was rather poor. The reaction with thionyl bromide occurred more smoothly and p-N-acetylaminobenzyl bromide was obtained in

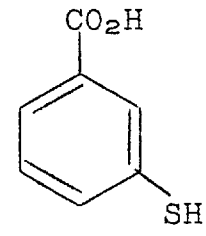
much better yield.

Although much work has been directed towards the synthesis and investigation of the properties of oxygenated benzyl halides, particularly the halomethylanisoles, analogous sulphur derivatives have been relatively neglected. Only one methylmercaptobenzyl chloride and its parent methylmercaptobenzyl alcohol have hitherto been synthesised, while no work has been reported on free mercaptobenzyl alcohols or mercaptobenzyl halides.

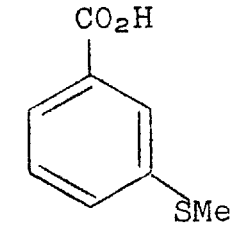
Two routes were studied for the preparation of the various thiol-substituted intermediates. The first involved reduction (zinc and hydrochloric acid) of the appropriate carboxybenzenesulphonyl chloride, e.g.



(XII)

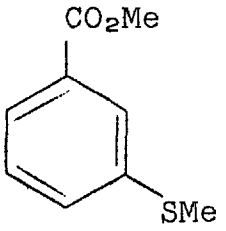


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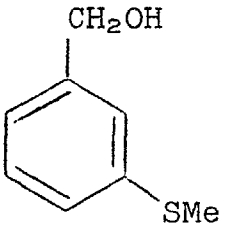


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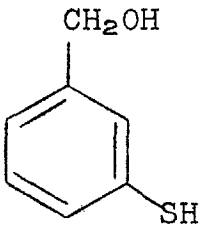
(XII), to give the free thiol (XIII), conversion to its S-methyl derivative (XIV) where required, esterification and reduction of this ester (XV) with lithium



(XV)

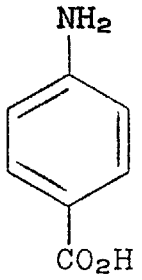


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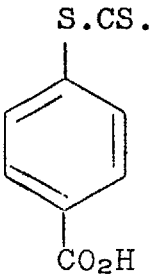


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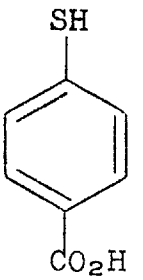
aluminium hydride to the alcohol (XVI). Strating and Backer[94] showed that aromatic sulphonyl chlorides could be reduced by lithium aluminium hydride in very good yields to give the free thiol and theoretically the carboxybenzenesulphonyl chloride (XII) could have been reduced directly by this means to the required mercapto-benzyl alcohol (XVII), but experience of other attempted reductions of two groupings attached to the benzene nucleus (to be described later) had not been encouraging, and this possibility was not examined. The second method employed Leuckart's[95] alkaline cleavage of a xanthate (XIX) to generate a thiol (XX), the starting material being an aminobenzoic acid (XVIII). This xanthate cleavage has also been achieved by Djerassi et al.,[96] with lithium aluminium hydride. The alkaline cleavage procedure was preferred in the present work because direct methylation could be



(XVIII)



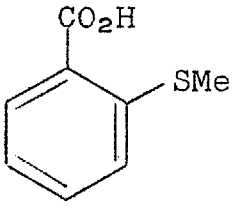
(XIX)



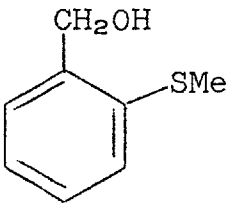
(XX)

carried out, where required, without isolation of the intermediate free thiol.

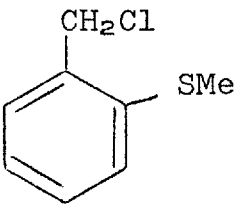
The synthesis of the o-series required neither of these processes because of the availability of thiosalicylic acid. For S-methylated compounds this was treated with methyl sulphate under alkaline conditions giving o-methylmercaptobenzoic acid (XXI). Esterification with methanolic hydrogen chloride



(XXI)



(XXII)

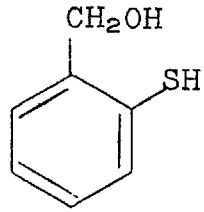


(XXIII)

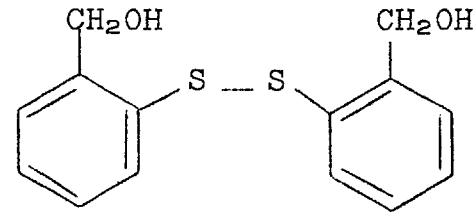
followed by reduction with lithium aluminium hydride yielded o-methylmercaptobenzyl alcohol (XXII) as a colourless liquid. Treatment with thionyl chloride

in benzene converted this in good yield to o-methylmercaptobenzyl chloride (XXIII). Treatment of the alcohol (XXII) in benzene with thionyl bromide yielded a liquid which analysed fairly well for the benzyl bromide, but a later preparation gave mainly a dibrominated material with one bromine atom in the aromatic nucleus, proved by its conversion to an S-alkylthiouronium picrate which still contained bromine. Nuclear bromination probably arose because of the presence of free bromine in the thionyl bromide used. The desired product, o-methylmercaptobenzyl bromide, was eventually prepared in the pure state as a low-melting solid by treating a benzene solution of the alcohol (XXII) with gaseous hydrogen bromide.

Attempts were now made to prepare free o-mercaptobenzyl chloride to see if it was more stable than the analogous phenol. The parent o-mercaptobenzyl alcohol (XXIV) had not been prepared as such. Reissert and Cramer[90] had obtained it as its lead salt and characterised it by oxidation to the disulphide(XXV). In their process o-aminobenzyl alcohol was diazotised and treated with potassium ethyl xanthate, giving a xanthate which was decomposed



(XXIV)



(XXV)

with potassium hydroxide to give the free thiol in solution, from which a pure product could not be isolated. In the present work thiosalicylic acid was esterified with methanolic hydrogen chloride and the ester was reduced with lithium aluminium hydride to give o-mercaptobenzyl alcohol (XXIV) as a low-melting solid. Oxidation with aqueous iodine gave the disulphide (XXV) described by Reissert and Cramer.[90] Treatment of this alcohol (XXIV) with thionyl chloride in chloroform gave a liquid which could not be distilled and from which neither a naphthyl ether or an S-alkylthiouronium picrate could be obtained.

In the m-series initial studies were begun with m-carboxybenzenesulphonyl chloride (for reaction scheme see p. 45), obtained by Stewart and Smiles[97] in the chlorosulphonation of benzoic acid. This

was reduced in acid solution with zinc and the resulting thiol isolated by oxidation to the disulphide with ferric chloride. Cleavage of the disulphide with alkali again regenerated the thiol which was methylated with methyl sulphate to give m-methylmercaptobenzoic acid. Later, intermediates were prepared from m-amino benzoic acid by diazotising, adding potassium ethyl xanthate and forming the thiol by cleaving the xanthate with alkali; methylation was effected as before. Refluxing the acid with methanolic hydrogen chloride gave methyl m-methylmercaptobenzoate which was reduced with lithium aluminium hydride in ether to give m-methylmercaptobenzyl alcohol in very good yield. Treatment of this material with thionyl chloride in chloroform or benzene gave m-methylmercaptobenzyl chloride in almost quantitative yield. As in the case of the o-isomer, m-methylmercaptobenzyl bromide was obtained by reaction of hydrogen bromide with a solution of the alcohol in benzene.

Methyl m-mercaptobenzoate, the parent compound for investigations on m-mercaptobenzyl halides, was first prepared by Schwarzenbach and Rudin[98] in a

Leuckart type reaction. In the present case the 3,3'-dicarboxydiphenyl disulphide obtained by Stewart and Smiles[97] was converted to the free m-mercapto-benzoic acid which was esterified and then reduced with lithium aluminium hydride to m-mercaptobenzyl alcohol. It has been noted by Arnold et al.,[99] that disulphides can be reduced with lithium aluminium hydride to thiols and that excellent yields may be obtained; this principle was therefore used to give a more direct route to m-mercaptobenzyl alcohol. The disulphide of Stewart and Smiles[97] was esterified with methanolic hydrogen chloride giving 3,3'-bis-methoxycarbonyldiphenyl disulphide which was reduced directly to the mercapto-alcohol with a large excess of lithium aluminium hydride. On reaction of the alcohol with thionyl chloride in benzene a resinous product was obtained which could not be distilled.

Initial attempts to synthesise p-substituted sulphur derivatives of benzyl halides were based on p-carboxybenzenesulphonyl chloride (compare scheme for m-series, p. 45) but reduction of this with zinc and hydrochloric acid gave not the free p-mercapto-benzoic acid but a high melting solid. This was

probably the corresponding disulphide since on esterification and subsequent reduction with lithium aluminium hydride it gave a low-melting solid which was later shown to be mainly p-mercaptobenzyl alcohol.

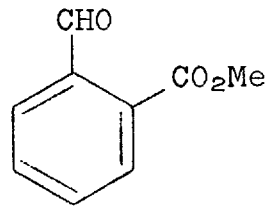
The alternative synthesis using a Leuckart reaction (cf. p. 47) was also investigated. p-Aminobenzoic acid was diazotised, treated with potassium ethyl xanthate and the resulting xanthate decomposed and methylated to give p-methylmercaptobenzoic acid. This was esterified with methanolic hydrogen chloride, and this ester when reduced with lithium aluminium hydride gave p-methylmercaptobenzyl alcohol as a low-melting solid identical with that described by Goldberg and Jampolsky[100], who obtained it by reduction of p-methylmercaptobenzoic acid. Treatment of this alcohol with thionyl chloride gave p-methylmercaptobenzyl chloride, previously obtained by Goldberg and Jampolsky[100]. The corresponding bromo-compound, p-methylmercaptobenzyl bromide, a crystalline solid, was obtained by treating the alcohol in benzene solution with gaseous hydrogen bromide. Compounds with the free thiol group were obtained by the above xanthate procedure but with omission of the methylation stage, the solution being

acidified in the presence of zinc dust to prevent oxidation. By this method p-mercaptobenzoic acid was obtained in good yield and esterification with methanolic hydrogen chloride gave methyl p-mercaptobenzoate as mentioned by Schwarzenbach and Rudin.[98] This was reduced with lithium aluminium hydride to give crystalline p-mercaptobenzyl alcohol, identical with that obtained in the reduction of the supposed 4,4'-bismethoxycarbonyldiphenyl disulphide.

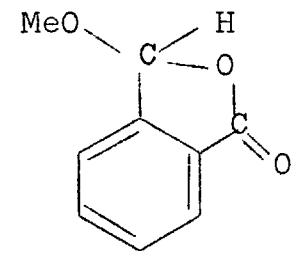
Although Reissert and Cramer[90] were unable to isolate o-mercaptobenzyl alcohol from their xanthate cleavage product an attempt was made to obtain p-mercaptobenzyl alcohol from the readily available p-aminobenzyl alcohol by a similar reaction. The intermediate xanthate was isolated either as a pale yellow oil or low-melting solid, but in very poor yield. When it was treated with alkali, free thiol quickly appeared but attempts to isolate any product either by direct acidification or oxidation to the disulphide were unsuccessful. As with the other isomers, direct treatment of free p-mercaptobenzyl alcohol with thionyl chloride gave a resinous material. It therefore appears that the free mercaptobenzyl halides are as inaccessible as their phenolic analogues.

All the benzyl halides described above have been derivatives of hydroxy-, amino-, or mercapto-benzyl halides, none of the parent compounds being available. Thus although, for example, acetoxy- and methoxybenzyl halides were obtained, no direct comparison of activity could be made between these and the inaccessible hydroxybenzyl halides. Investigations were now begun on aldehydo-benzyl halides, since these should be stable as such, and also allow the preparation of derivatives of the aldehyde group.

It has been noted by a number of workers[101,102,103] that phthalaldehydic acid in esterification reactions can give either methyl phthalaldehydate (XXVI) or



(XXVI)



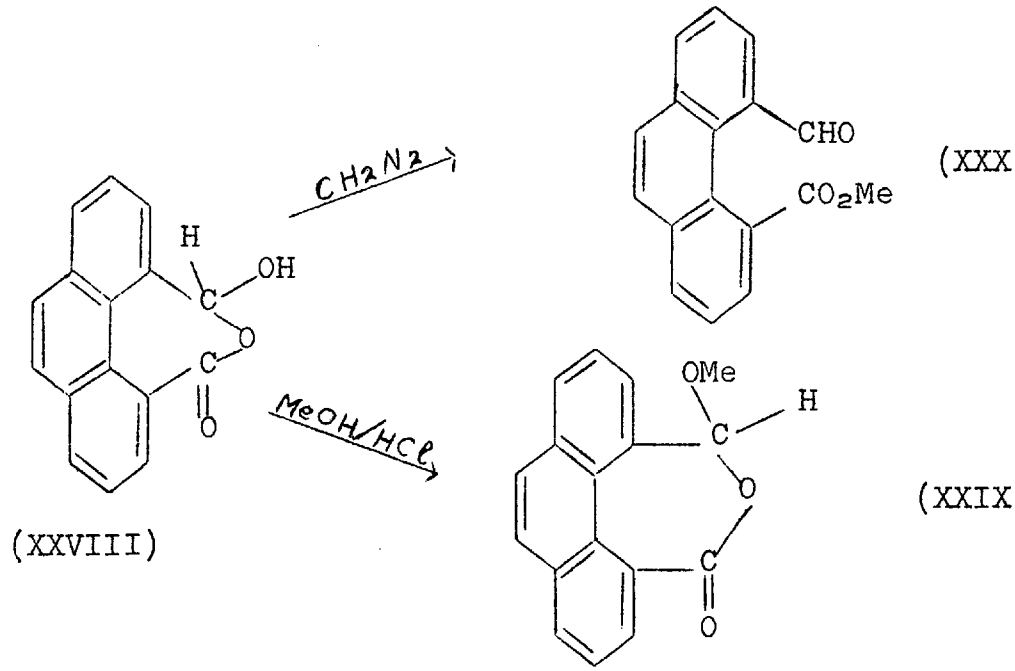
(XXVII)

phthalaldehydic acid pseudo methyl ester (XXVII). Thus by heating the acid with methanol and sulphuric acid Meyer[101] obtained the true ester as an oil.

In similar reactions however Gabriel,[102] and v. Auwers and Heinze,[103] obtained the pseudo methyl ester. It is mentioned that the true methyl ester can be synthesised by heating the silver salt of the acid with methyl iodide but that it then spontaneously reverts to the pseudo form. In the present work o-aldehydobenzoic acid on refluxing with methanolic hydrogen chloride gave the pseudo methyl ester, a compound, as noted in the earlier work which gave no 2,4 - dinitrophenylhydrazone.

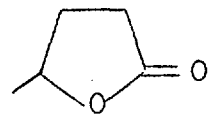
It has been shown by a number of workers including Prins,[104] Swoboda,[105] and Marvel and Hill[106] that acetals are not reduced by lithium aluminium hydride and provided the reaction is worked up in alkaline conditions these groupings remain untouched. Coupled with this, the acetal grouping would provide a good derivative for comparison with the free aldehyde as well as being a protective grouping which could be easily hydrolysed, perhaps by an enzymic process. By conversion of phthalaldehydic acid to an acetal derivative it was hoped to avoid this isomerisation to the pseudo ester; the acid entity could then be reduced directly with lithium aluminium hydride.

Care was taken to employ a mild process in the acetal formation. The aldehyde was refluxed with either methyl or ethyl orthoformate in the corresponding dry alcohol as solvent with a little ammonium chloride as catalyst according to the method of Claisen[107]. In both cases only the pseudo esters were obtained. Theoretically it was possible that reduction of these pseudo esters with a restricted amount of lithium aluminium hydride might give o-aldehydobenzyl alcohol. Thus Newman et al.,[108] and Badger et al.,[109] reported that 4-formylphenanthrene--5-carboxylic acid possessed no free carbonyl group and should be allocated structure (XXVIII); furthermore, treatment with methanolic hydrogen chloride gave

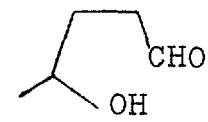


(XXVIII) (XXX) (XXIX)

the pseudo methyl ester (XXIX) whilst diazomethane gave the true methyl ester (XXX). Reduction of both true and pseudo methyl ester with lithium aluminium hydride gave the diol. On the other hand Arth[110] obtained γ- and δ-hydroxyaldehydes e.g. (XXXI) by reduction of lactones e.g. (XXXII) with the calculated quantity of lithium aluminium hydride.

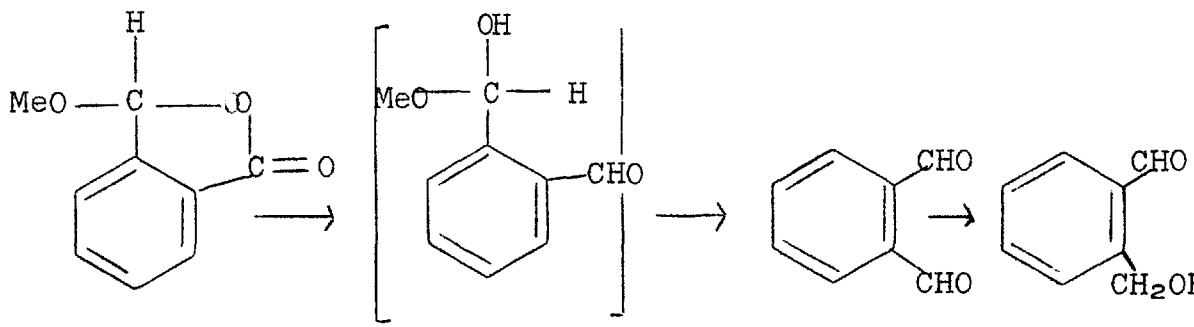


(XXXII)



(XXXI)

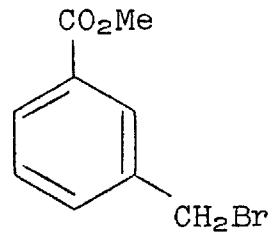
With this as an analogy the reduction of phthalaldehydic acid pseudo methyl ester could be expected to proceed through the following stages, yielding phthalaldehyde (XXXIII) or o-aldehydobenzyl alcohol (XXXIV).



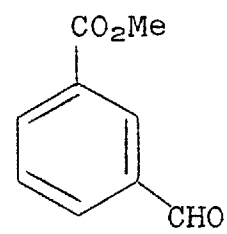
(XXVII) (XXXIII) (XXXIV)

Contrary to this expectation, the pseudo methyl ester on reduction with one quarter of a mole of lithium aluminium hydride gave only a very poor yield of phthalide. This product has been noted as a product of lithium aluminium hydride reductions of phthalic anhydride and half esters of phthalic acid by Parinni[111] when the reductions have been conducted in tetrahydrofuran, but its formation from such sources is easily understandable. In the present reactions it appears, however, that the methoxy grouping has undergone hydrogenolysis in preference to the lactone ring.

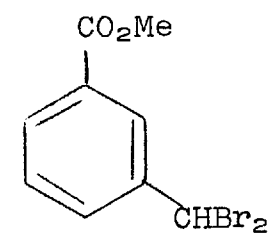
In the m-series the aldehydobenzoic acid was not available. Toluic acid was esterified and photobrominated yielding mainly m-methoxycarbonylbenzyl bromide (XXXV) and a smaller amount of dibromo-compound.



(XXXV)



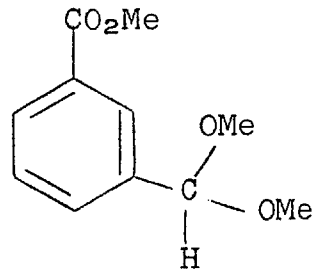
(XXXVI)



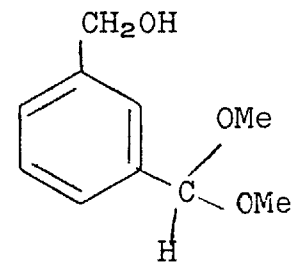
(XXXVII)

This latter substance gave no S-alkylthiouronium picrate and on treatment with acetic acid and potassium acetate

under reflux gave m-methoxycarbonylbenzaldehyde (XXXVI) establishing the structure of the parent material as m-methoxycarbonylbenzylidene bromide (XXXVII). A Sommelet reaction using hexamethylenetetramine converted m-methoxycarbonylbenzyl bromide to m-methoxycarbonylbenzaldehyde (XXXVI) in larger quantities than were obtained from the benzylidene bromide. The aldehyde on treatment with methyl orthoformate by Claisen's[107] method gave m-methoxycarbonylbenzaldehyde dimethyl acetal (XXXVIII), which on reduction with lithium aluminium hydride gave



(XXXVIII)



(XXXIX)

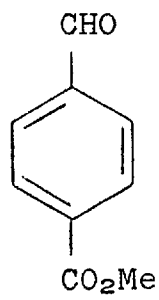
(after working up under alkaline conditions) a moderate yield of m-hydroxymethylbenzaldehyde dimethyl acetal (XXXIX) as a colourless liquid. When this was treated with thionyl chloride in an excess of pyridine a product was obtained which contained

halogen and gave a delayed test when treated with 2,4 dinitrophenylhydrazine in acid solution, but which could not be purified.

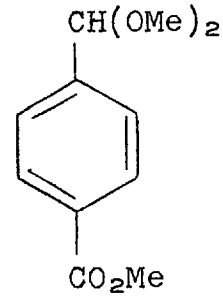
The reason for the failure of this series of reactions was appreciated when investigations were conducted with the p-series of compounds. These afforded a range of solids, and thus the uncertainty as to the purity of intermediates (which had been experienced when these were liquids) could be eliminated.

Methyl p-toluate was photobrominated to give p--methoxycarbonylbenzyl bromide, which was treated with the sodium salt of 2-nitropropane in ethanol in a known reaction devised by Hass and Bender[112] for synthesising substituted benzaldehydes. For this particular reaction they obtained a conversion of 72%, the product being isolated by distillation. It was found in the present work that purification was best effected by conversion of the crude product into its semicarbazone, which was then decomposed by the method of Goldschmidt and Veer[113] involving treatment in hot acetic acid with sodium nitrite, but the overall yield was very poor. The required aldehyde (XL) was prepared eventually by a process devised by Stotta and

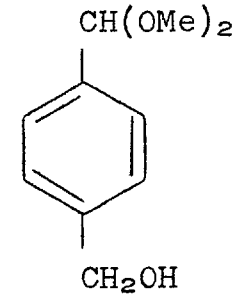
Kethur,[114] who converted methyl p-aminobenzoate



(XL)



(XLI)

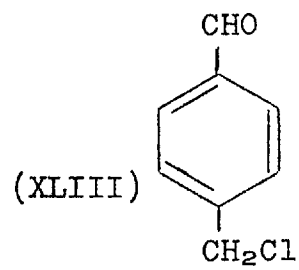


(XLII)

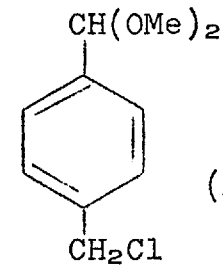
to methyl p-cyanobenzoate by a Sandmeyer reaction and reduced this by Stephen's method. Whereas they isolated the intermediate nitrile by steam distillation, in the present case extraction with light petroleum was preferred.

Initial attempts to block the aldehyde group were conducted with ethyl orthoformate by Claisen's method. There was however, the possibility of ester exchange, methoxy and ethoxy groups being interchangeable. This was not realised until lithium aluminium hydride reduction gave a product possessing the alcohol and acetal bands in the infrared spectrum, and with no carbonyl band, but which showed a low carbon content on analysis. Attention was therefore turned to the dimethyl acetal derivatives where the possibility of

ester exchange did not exist. p-Methoxycarbonylbenzaldehyde dimethyl acetal (XLI) had been prepared by Wegscheider and Suida[115] by heating the aldehyde with methanolic hydrogen chloride in a sealed tube. An identical product was obtained, in the present case, by refluxing the aldehyde with methyl orthoformate. This compound when reduced with lithium aluminium hydride gave an almost quantitative yield of p-aldehydobenzyl alcohol dimethyl acetal (XLII) as a crystalline solid. On treatment with thionyl chloride in excess pyridine a very poor yield of p-aldehydobenzyl chloride (XLIII) was isolated, the acetal groupings



(XLIII)



(XLIV)

being apparently broken down even in the presence of pyridine. This explained the lack of success with the corresponding reaction in the m-series. p-Aldehydobenzyl chloride was obtained in good yield by hydrolysing the dimethyl acetal (XLII) with hydrochloric acid and treatment of the product with thionyl chloride.

This, when treated with methyl orthoformate, gave p-aldehydobenzyl chloride dimethyl acetal (XLIV). p-Aldehydobenzyl chloride has only recently been synthesised by Baker et al.,[116] by a Stephen's reduction of p-cyanobenzyl chloride.

Studies in the Substituted Xylylene Dihalide series

Whereas many monosubstituted benzyl halides are known, relatively few monosubstituted xylylene dihalides have been prepared. No amine, amide, phenolic hydroxy or acetoxy derivatives are known. The sole oxygenated compound, 4-methoxy-m-xylylene dichloride was prepared[117] by treating anisole at 0° with hydrochloric acid and formaldehyde, a synthesis since emulated by other workers.[118,119,120] The only carboxylic acid derivative was prepared by Perkin and Stone[121] who brominated 4-chlorocarbonyl-m-xylene to obtain 4-bromocarbonyl-m-xylylene dibromide which on treatment with anhydrous formic acid gave 4-carboxy--m-xylylene dibromide. Addition of the acid bromide to methanol at 0° gave the corresponding methyl ester. Nitration of p-xylylene dichloride by Grimaux[122] gave 2-nitro-p-xylylene dichloride, and more recently Reich, Rose and Wilson[123] photobrominated 5-nitro-m--xylylene in ethylene dibromide to give 5-nitro-m--xylylene dibromide (19%).

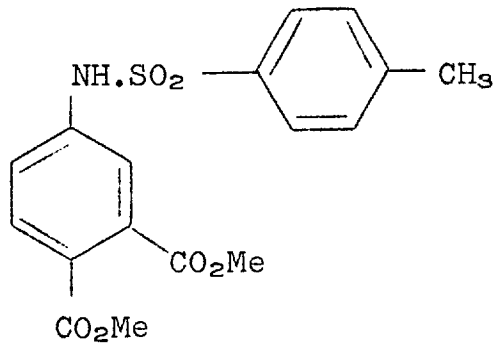
From the biological aspect it would be interesting to compare the toxic effects of substituted

xylylene dihalides with those of similarly substituted benzyl halides, in view of the fact that nitrogen mustards are much more effective than their monofunctional analogues. Consequently some exploratory investigations were carried out on the synthesis of aminophthalyl alcohols and their derivatives. Two routes were studied,

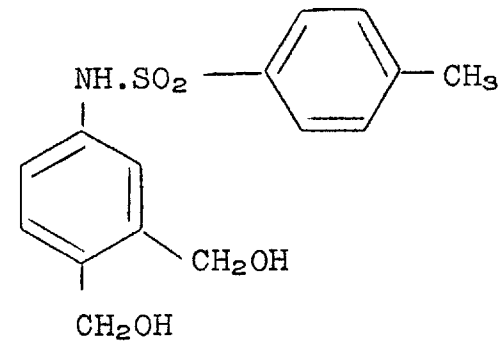
(i) involving the hydride reduction of dimethyl 4-aminophthalate;

(ii) involving the use of various mono-nitroxylenes.

It was hoped to reduce dimethyl 4-aminophthalate with lithium aluminium hydride to give 4-aminophthalyl alcohol; the only solid product isolated, however, was identified as 4-aminophthalaldehyde. This inadequate reduction was possibly due to the insolubility of the initial complex formed by reaction of the free amino group with the lithium aluminium hydride. To establish if this reduction could be effected if the complicating factors associated with the amino group were modified, the latter was protected as its toluene-p-sulphonyl derivative. Reduction of dimethyl 4-toluene-p-sulphonamidophthalate (I) with lithium



(I)



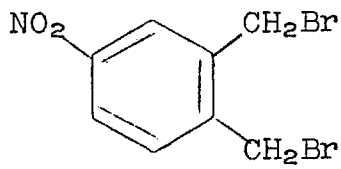
(II)

aluminium hydride gave a poor yield of product from which 4-toluene-p-sulphonamidophthalyl alcohol (II) was isolated, after acetylation, as its diacetate.

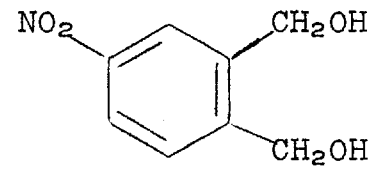
Attempted selective reduction of the diester groupings in dimethyl 4-N-acetylaminophthalate with potassium borohydride was unsuccessful; the starting material was recovered unchanged. When reduced with potassium borohydride and lithium chloride in tetrahydrofuran or with sodium borohydride and aluminium chloride in diglyme solution preferential attack occurred on the amide linkage with the regeneration of the free amine.

More successful were the syntheses based on the nitroxylenes. 4-Nitro-o-xylene was photobrominated

(under conditions perfected whilst brominating the three isomeric xylenes - see later), to give 4-nitro--o-xylylene dibromide (III) which when refluxed with

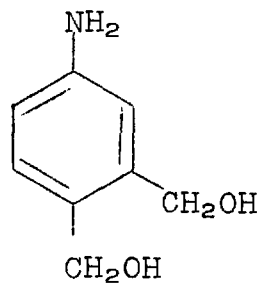


(III)

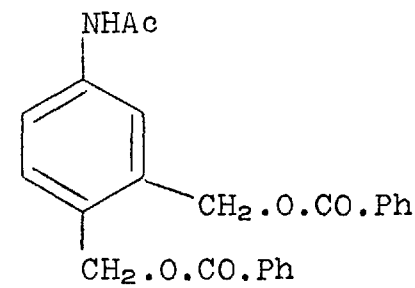


(IV)

potassium acetate in acetic acid gave 4-nitrophthalyl diacetate. This was deacetylated with sodium ethoxide in ethanol to give the corresponding diol (IV), a compound previously prepared in very poor yield by Tirouflet,[124] who reduced diethyl 4-nitrophthalate with lithium aluminium hydride. Catalytic hydrogenation using Adams' catalyst gave a quantitative yield of crystalline 4-aminophthalyl alcohol (V). This compound was unstable and decomposed on storage. Attempted



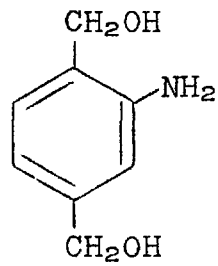
(V)



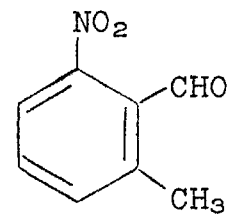
(VI)

N-acetylation by treating one mole of the pure amine with one mole of either acetic anhydride or thiol-acetic acid gave only oils, though complete acetylation gave a crystalline triacetyl derivative. Proof that the oils contained 4-N-acetylaminophthalyl alcohol was obtained by conversion to crystalline 4-N-acetylaminophthalyl dibenzoate (VI). Attempts to prepare a purer 4-N-acetyldiol by selective O--deacetylation of the triacetyl compound were unsuccessful.

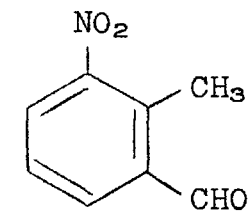
Bromination of 2-nitro-p-xylene was much slower than with 4-nitro-o-xylene and a lower yield of solid dibromide was obtained. A similar series of reactions on this dibromide as in the previous case gave crystalline 2-aminoterephthalyl alcohol (VII); like the isomer described above, this also was unstable



(VII)



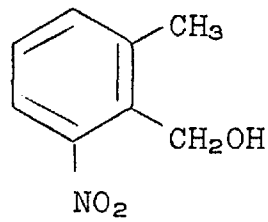
(VIII)



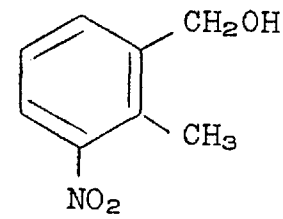
(IX)

and decomposed on storage. Here again no pure N-acetyl derivative could be isolated.

Bromination of 3-nitro-o-xylene failed to give a solid dibromide, and the crude product was therefore used for reaction with potassium acetate in acetic acid. This gave an oil possessing both acetate and aldehyde bands in the infrared. The aldehyde, characterised as a 2,4-dinitrophenylhydrazone, must be either 3-(VIII) or 6-(IX) nitro-o-tolualdehyde. Deacetylation of the crude material gave a fraction which was 2-methyl-6-nitrobenzyl alcohol (X) and/or 2-methyl-3-nitrobenzyl alcohol (XI).

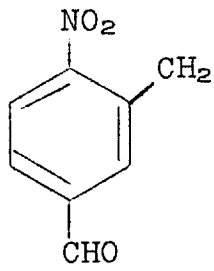


(X)

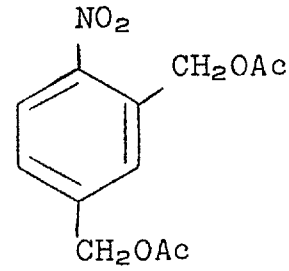


(XI)

The crude bromination product of 4-nitro-m-xylene on reaction with potassium acetate in acetic acid gave several products. One was unidentified, but the others were shown to be 6-nitro-m-tolualdehyde (XII) (prepared initially by Suida[125]) and the required 4-nitroisophthalyl diacetate (XIII).



(XII)



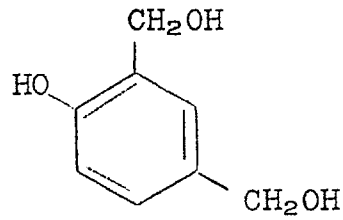
(XIII)

Thus it appears that dibromination occurs to some extent in the w,w-position as well as in the w,w'--position, and from the experiments on 4-nitro-m-xylene it is the least hindered methyl group which is preferentially attacked. The aldehyde itself is probably produced in a two step reaction, the initial stage being the formation of a w,w-diacetate which then decomposes under acid conditions.

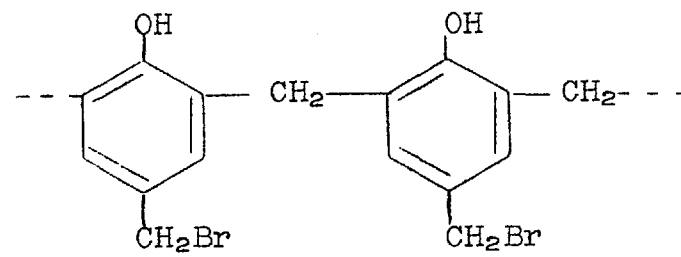
These investigations on the nitroxylenes have thus been successful in so far as they have given several new nitroxylylene dibromides and new aminophthalyl alcohols but much further work will be necessary to exploit the potentialities of the latter class of compounds.

Reactions of 4-hydroxyisophthalyl alcohol.

One interesting intermediate for the production of oxygenated dihalides 4-hydroxyisophthalyl alcohol (XIV), was already known, but attempted reactions



(XIV)



(XV)

of the primary hydroxyl groups using hydrobromic acid, hydrochloric acid, hydrogen chloride gas, or thionyl chloride, gave high melting pink or brown polymers possessing similar infrared spectra. Analyses of the products of the bromination reactions established that the polymers were probably of the type (XV).

Sulphonic acid derivatives of the phthalyl alcohols.

Attempts were made to prepare a series of di-sulphonic esters of the three phthalyl alcohols analogous to the xylylene dibromides. These compounds would fall into the category exemplified by disulphonic

esters of the " Myleran" type, and being sterically more rigid than " Myleran" would perhaps provide information on the steric requirements for activity.

The parent phthalyl alcohols were prepared from the corresponding xylylene dibromides by an improved route, via the diacetates followed by deacetylation. Previous workers[126,127] refluxed the dibromide with aqueous carbonate, a method which was found in the present case to give poor yields. An extensive series of reactions, including toluene-p-sulphonation and methanesulphonation in pyridine, conducted with the phthalyl alcohols gave none of the desired products. In the case of the methanesulphonation of terephthalyl alcohol, p-xylylene dichloride was the only product isolated. This type of chlorination has been reviewed by Tipson.[128] The difficulty in isolating these sulphonic acid esters was not unexpected, in view of the known instability even of simple benzyl esters of sulphonic acids. Such compounds often cannot be made by normal methods, and in preparing a number of substituted benzyl toluene-p-sulphonates Kochi and Hammond[129] treated the sodium salt of the alcohol, in completely anhydrous conditions, with toluene-p-sulphonyl chloride.

Application of this method to the phthalyl alcohols was, however, unsuccessful and it is possible that the phthalyl esters are too unstable even under these conditions of preparation, as was p-methoxybenzyl toluene-p-sulphonate in the work of Kochi and Hammond.[129]

Kinetic Investigations

The object of the kinetic work was to determine the relative reactivities of the benzyl halides under approximately physiological conditions of pH, and to try to correlate these values with their biological toxicities.

Drawing an analogy with the lachrymators tested by Mackworth, the most likely way in which these benzyl halides would attack living tissue would be at points where free thiol groups occurred, consequently the thiol entity was chosen as the nucleophilic standard for the kinetic determinations. At the outset 2-mercaptoethanol was selected as the most desirable thiol because of its ease of purification, estimation by iodine titration and its solubility in both water and organic solvents. It did however, deteriorate by aerial oxidation to the extent of 16.5% in 3 hours as determined in a blank experiment; this however could easily be prevented by conducting all runs in an atmosphere of nitrogen.

(A second possible nucleophile, thiourea, was considered but titration with iodine gave results corresponding to only 70% of the theoretical thiol value).

As the nucleophilic power of 2-mercaptoethanol in solution would depend on the proportion available as the mercaptide ion it was necessary to buffer the reaction mixture so that the acid produced did not

$$CH_2OH.CH_2SH + RX \longrightarrow CH_2OH.CH_2SR + X^- + H^+$$

suppress the ionisation of the thiol. Furthermore the pH of the reaction had to be of such a value that a measurable reaction rate between the thiol and benzyl halide was obtained. Fortunately the value obtained approximated quite well to a physiological pH.

Investigations were begun employing ammonium acetate as buffer. This gave an acceptable pH 7, but in certain ratios of acetone-water separation into two liquid layers occurred. More important still, in blank experiments omitting the thiol and using benzyl bromide as the halide, it was found that the acetate ion was a moderately strong nucleophile. Thus at 30° with a five fold excess of acetate after 3 hours 26.7% of the bromide had been attacked, after 5 hours 41.7% and 93.65% after 21 hours; the bromide ion was estimated by Volhard's method.

Later lithium acetate was tried as a buffer but in dioxan-water at 30° in eight-fold excess it too attacked benzyl bromide to the extent of 12.1% in 2 hours and 26.9% in 5 hours.

In an attempt to dispense with buffers a number of runs were tried with completely ionised thiol. This was achieved by adding sodium hydroxide (1 equiv.) to the 2-mercaptoethanol (1 equiv.). The reactions conducted in tetrahydrofuran-water mixtures at 30° with both benzyl chloride and benzyl bromide were too fast to follow by titration. A similar run conducted with the less reactive benzyl chloride at 2° was complete within a minute and kinetic investigations under these conditions were obviously unpracticable.

Amines would have been ideal buffers from the point of view of solubility but like the acetates (mentioned above) they too were considered too strong as competing nucleophiles. Triethylamine when tested against benzyl bromide in tetrahydrofuran-water at 30° showed an 85% reaction in $4\frac{1}{3}$ hours.

Weak nucleophilic buffers of the carbonate-bicarbonate type were now investigated. These, unlike the inorganic acetates which had given two liquid layers, were partially precipitated in high organic solvent-water

ratios. Their relatively weak competitive nucleophilic power was confirmed by blank experiments, potassium bicarbonate for example causing only 5.4% hydrolysis of benzyl bromide in 3 hours at 30° in acetone-water. The buffer chosen for the complete series of runs was sodium carbonate. This gave an acceptable pH 8 at which a reasonable reaction rate occurred. Initially the anhydrous material was employed, but erratic results suggested that it was removing water from the reaction solution and thereby affecting the concentrations of the reactants. When the hydrated form was used many of the discrepancies were eliminated.

Finding a suitable organic solvent to use in conjunction with water for the kinetic runs was of particular importance because the ratio of organic solvent-water was very critical as regards the solubility of the various organic and inorganic materials present. Acetone required the lowest proportion of water to throw some of the benzyl halide out of solution. Furthermore it needed the highest proportion of water to give adequate buffer solutions. This latter disadvantage also occurred when tetrahydrofuran was

employed instead of acetone. Dioxan, the third solvent tested, tolerated a higher proportion of water and showed less tendency so separate into two liquid layers, and this was therefore used throughout.

In the actual kinetic runs investigations were largely concerned with those benzyl halides which could be obtained in a high state of purity. This necessitated the omission of some of the benzyl bromides, but as in any case the reaction of the bromides with 2-mercaptoethanol was too fast to follow at 30°, a few runs were conducted with some of the more stable members at ca. 0°.

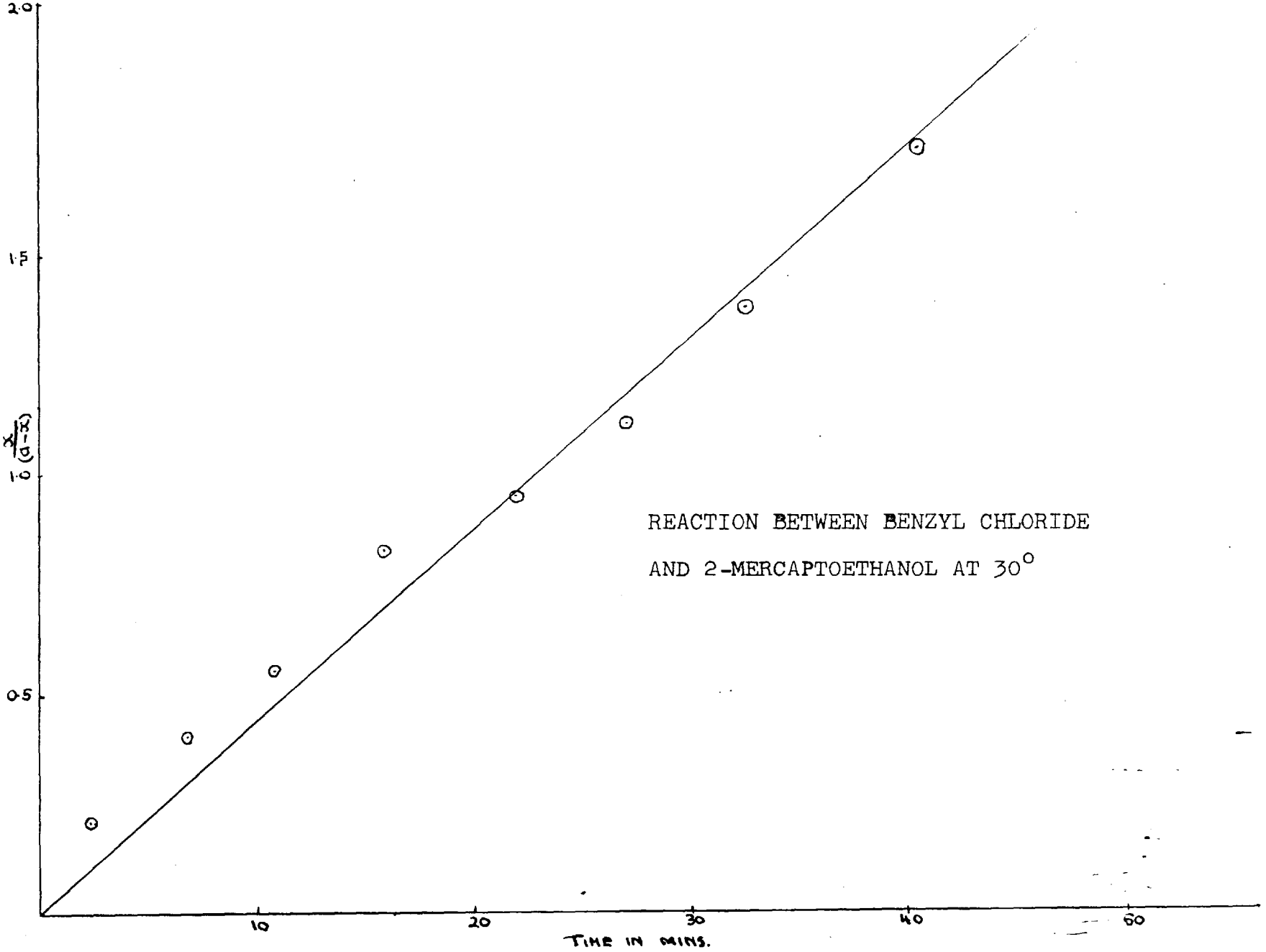
Emphasis was placed mainly on the correlation between the methoxy- and the methylmercapto-benzyl chlorides because these were the most stable and easily purified, because all the members of the series were available and mainly because no comparison has yet been made between the relative effects of the sulphur and oxygen atoms in such a system. The other main point of interest was the comparison between the reaction rates of p-aldehydobenzyl chloride and its dimethyl acetal, especially when taken in conjunction with their relative toxicities. From the rest of the

compounds synthesised a few representative members were selected to assess their order of reactivity.

The kinetic measurements were carried out using equimolecular proportions of halide and of 2-mercaptoethanol. Using the second-order equation

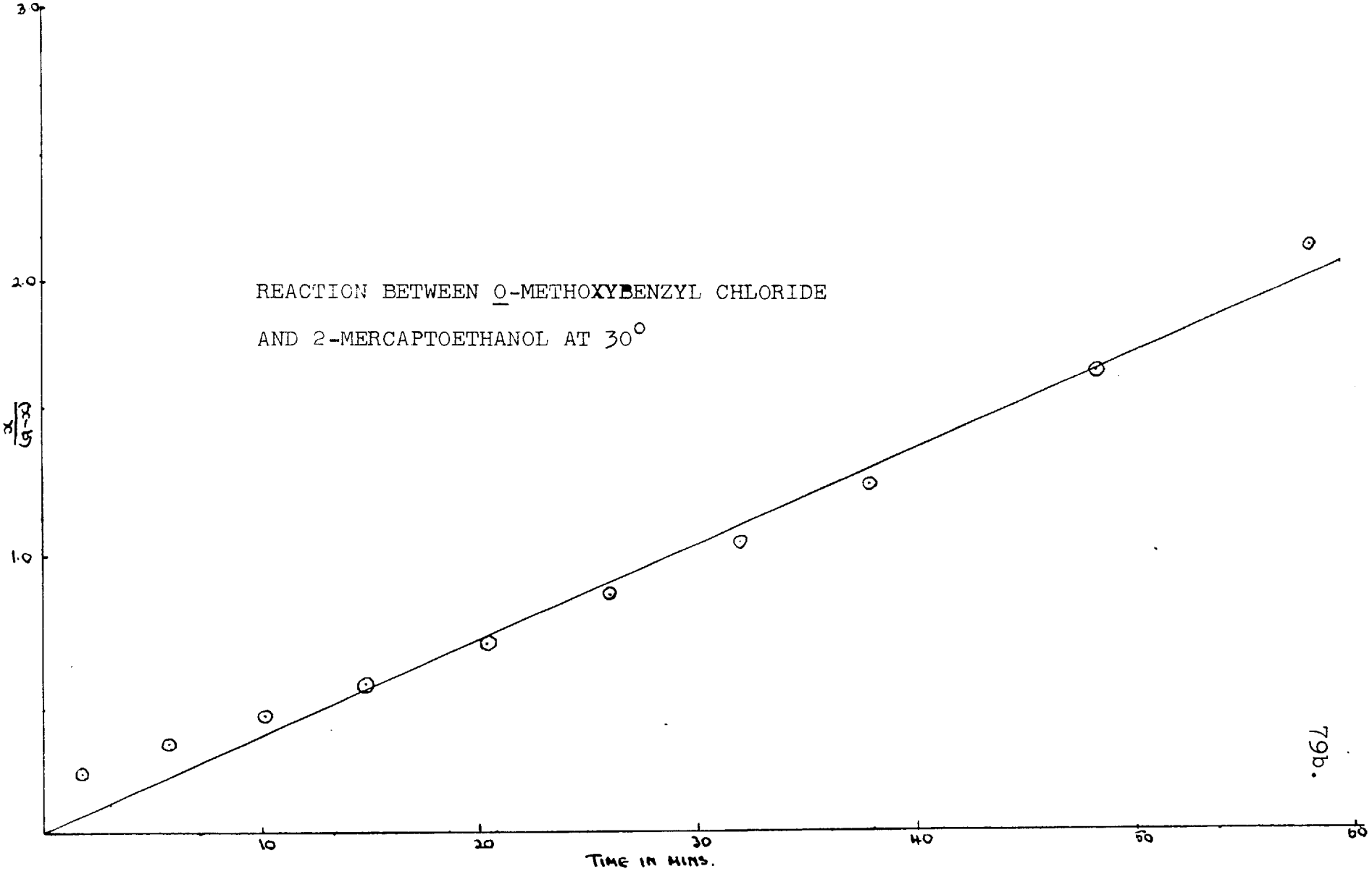
$$k = \frac{1}{t} \cdot \frac{x}{a(a-x)}$$

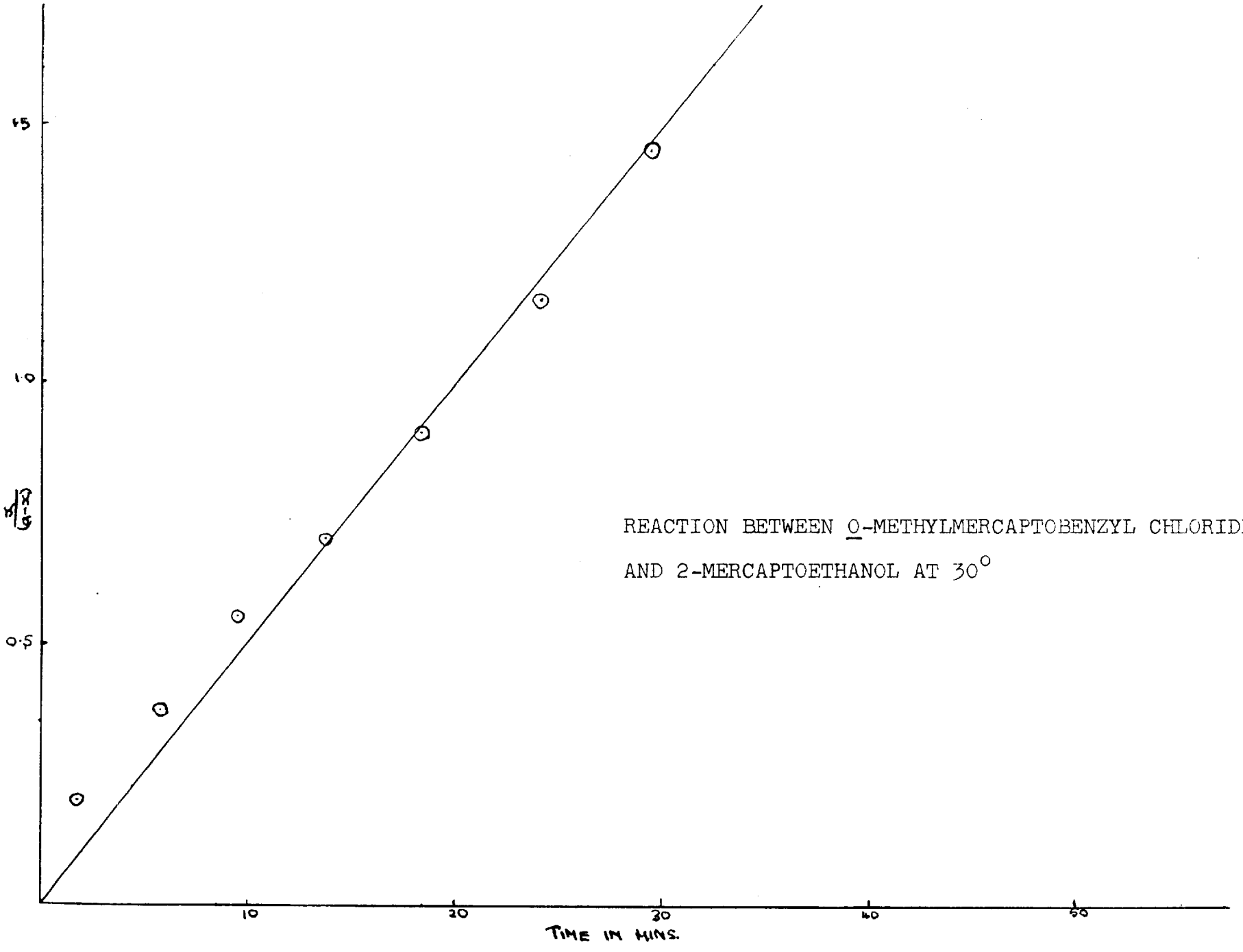
values of $\frac{x}{(a-x)}$ were plotted against t and gave approximately straight lines for about 70% of the total reaction, thus showing that essentially an S_N2 process was involved. In all cases, however, a relatively greater rate constant was observed for the first few minutes of the reaction (see typical graphs on pp.79a-c). This could be attributed to a number of causes. An assessment of these is difficult because of the unknown surface and other effects exerted by the sodium carbonate in suspension. Dealing with just the liquid phase, it is possible that the addition of benzyl halide is accompanied by a high local heat of mixing resulting in a higher initial rate; no significant temperature rise could be detected however. A more probable explanation is that the reaction rate is controlled by the equilibrium process for the supply of mercaptide ion represented by the



REACTION BETWEEN BENZYL CHLORIDE

AND 2-MERCAPTOETHANOL AT 30°


REACTION BETWEEN O-METHOXYBENZYL CHLORIDE
AND 2-MERCAPTOETHANOL AT 30°
3.0
2.0
1.0
$\frac{x}{(a-x)}$
10
20
30
40
50
60
TIME IN MINS.



REACTION BETWEEN O-METHYLMERCAPTOBENZYL CHLORIDE AND 2-MERCAPTOETHANOL AT 30°

equation

$$CO_3^{--} + SHCH_2.CH_2OH \rightleftharpoons SCH_2.CH_2OH + HCO_3^-$$

At the outset of the reaction the demand for the mercaptide ion by the benzyl halide is high and perhaps in excess of the rate at which is is being supplied by the above equilibrium process. A higher initial rate would thus be expected, settling down to a more steady rate as the equilibrium is re-established. Coupled with this is the fact that the solubility of sodium carbonate in the aqueous dioxan medium is rather small, and the rate transfer of the solid into solution (i.e. rate of formation of the CO_3^{--} ion) may not equal the rate at which it is being destroyed in solution by its buffering action. This lag in the restoration of equilibrium would affect the activity of the mercaptide ion with a resultant slackening in rate. A similar effect may also have been produced as a result of the mode of mixing of reactants. The halide was added in pure dioxan, and this addition (though only 5% of the total volume) may have suppressed the solubility of the sodium carbonate over a period of time, gradually reducing the activity of the mercaptide ion to a lower

constant value. Addition of the halide in its pure form, instead of in solution, effected a partial suppression of the high initial rate, but this was obviously only one of the contributing factors.

High accuracy, therefore, cannot be claimed for the absolute values of k listed in Table I, but they nevertheless provide an indication of the relative

Table I

Reaction of $R.C_6H_4.CH_2Cl$ with $CH_2OH.CH_2SH$ in dioxan-water at $30^{\circ}c$ in the presence of Na_2CO_3, 10 H_2O.

k in l. mole. $min.^{-1}$

R	k_{30}	R	k_{30}
H	0.044	m-NHAc	0.092
o-MeO	0.034	o-MeS	0.050
m-MeO	0.028	m-MeS	0.041
p-MeO	0.159	p-MeS	0.188
$p-NO_2$	0.082	p-CHO	0.149
m-AcO	0.075	$p-CH(OMe)_2$	0.070

reactivities of the halides. (From the purely chemical point of view it would be more satisfactory to carry out the kinetic measurements in homogeneous solution, using some other nucleophile, such as an amine; choice of the above conditions, as already indicated, was dictated by biological considerations). The four benzyl bromides studied also showed second order kinetics in their reaction with 2-mercaptoethanol and the results are summarised in Table II, but as the temperatures at which they were conducted ranged over

Table II

Reaction of $R.C_6H_4.CH_2Br$ with $CH_2OH.CH_2SH$ in dioxan-water in the presence of Na_2CO_3, $10H_2O$

k in l. mole. $min.^{-1}$

R	t^o	k
H	2	0.052
p-MeS	2-3	0.0425
p-NO_2	2-3	0.139
m-MeO	3	0.048

one degree the only tentative deduction that can be made is that the rates for the benzyl bromides at about 0° are similar to those for the benzyl chlorides at 30°. With regard to the chlorides, the rate constants are all of the same order of magnitude and there is only a factor of five between the least and the most reactive. For the two complete series of methylmercapto- and methoxy-benzyl chlorides the order of reactivity is

$$\underline{p} > \underline{o} > \underline{m}$$

with the sulphur compounds possessing an enhanced activity over their oxygenated analogues. In comparing the reaction rate values it is noticeable that o-methoxy-benzyl chloride is slightly less reactive, while the comparable sulphur compound is slightly more reactive than benzyl chloride; in both cases however the values for the p-isomers are three to four times higher than the unsubstituted compound. The effects exerted by these groupings seem to be unusual for a measured S_N2 process when considering the known electron donating properties of the methoxy group and the similar predictable effect of the methylmercapto entity, especially

in the p-position. It appears as if electron accession to the side chain, rather than withdrawal, is increasing the reaction rate, an effect which would normally be associated with an S_N1 process. Similarly in the m--positions the low rates, near to those of benzyl chloride itself may be attributed to the small electron attracting inductive effect in the absence of any mesomeric effect. Of the o-isomers little can be deduced because of the unknown steric hindrance factor. Again theoretically, p-nitrobenzyl chloride might be expected to have an even higher reaction rate due to the large electron-withdrawing inductive and mesomeric effects of the nitro group facilitating attack by mercaptide ion on the side chain. In fact its reaction rate is only twice that of benzyl chloride.

Similar unusual relationships in reaction rates have been noted in the earlier kinetic work on the benzyl halides (see pages23 etc)and investigated more recently by Swain and Langsdorf[130]. The latter measured the second order rate constants for the reaction between some substituted benzyl halides and a number of amines in benzene solution. They found

$$\text{p- MeO} > \text{p-NO}_2 \simeq \text{H}$$

and suggested from these and other results that strict classification of such displacement reactions into discreet mechanistic categories was not valid.

The other compounds whose reaction rates were determined in the present work behaved in a predictable manner. With m-acetoxy- and m-acetylaminobenzyl chloride a higher reaction rate than that of benzyl chloride was noted, indicating that the rate was governed by the electron withdrawing inductive effect. In the case of p-aldehydobenzyl chloride a high reaction rate, four to five times that of benzyl chloride, was obtained which dropped to a factor of less than two in its dimethyl acetal, in which the electron attracting properties of the carbonyl group were absent.

The overall figures seem to substantiate the comments of Swain and Langsdorf, the rates of reaction being increased by both electron accession and removal from the side chain. It is possible that expulsion of the halogen atom (which would be facilitated by the presence of methoxy and methylmercapto groupings) and nucleophilic attack (aided by electron withdrawing groups) are both important contributing factors in raising the reaction rate.

Biological Results and Their Discussion

I am indebted to a team of workers at King's College, London, directed by Professor J.F. Danielli, F.R.S., for much of the biological information summarised below.

Test conditions.

Wistar albino rats, in which the Walker 256 carcinoma was growing, were used to determine the antitumour action of the various compounds, which were administered in arachis oil. Similar rats, but free from the tumour, were used for determination of the toxicities, the effects becoming apparent in weight loss and a general decline in the physical condition of the animal. No quantitative assignments could be given of the effects on the rat (as has been made in the case of the nitrogen mustards) and the following is only a comparative order:

$$+++ \rangle ++ \rangle + \rangle - \text{ (no effect)}$$

Similarly the effects on the tumour were assigned only comparative values and the highest value, that for p-aldehydobenzyl chloride (++) bears no relationship

to the same symbol, meaning partial regression, given to the nitrogen mustards. Thus the order is

++ > + > - (no effect).

The results of the compounds tested are summarised in Table I.

Table I

Summary of Biological Results

I.C.L. No.	COMPOUND	M.L.D. mg./100g	EFFECT ON RAT	EFFECT ON TUMOUR	NO.OF RATS TESTED
1	Xylylene dibromide	40	++	-	11
2	1 ethyl α,α'-dibromoadipate	40	+	-	9
3	Xylylene diiodide	40	+++	-	6
4	Ethyl α,α'diiodoadipate	40	++	-	6
5	p-Xylylene dibromide	40	+	-	6
6	m-Xylylene dibromide	40	+++	-	5
7	4-Nitro-o-xylylene dibromide	3	++	-	2
8	2-Nitro-p-xylylene dibromide	3	+	-	2

Table I (cont.)

I.C.L. No.	COMPOUND	M.L.D. mg./100g	EFFECT ON RAT	EFFECT ON TUMOUR	NO.OF RATS TESTED
9	p-N-acetylamino-benzyl chloride	2	++	+	16
10	p-Acetoxybenzyl chloride	2	+++	+	7
11	p-Nitrobenzyl bromide	3	+	-	2
12	p-Nitrobenzyl chloride	6	+	-	1
13	Benzyl chloride	25	+	+	2
14	Benzyl bromide	3	++	-	1
15	m-N-Acetylamino-benzyl chloride	20	++	-	6
16	m-Methoxycarbonyl-benzyl bromide	20	+++	+	3
17	p-N-Acetylamino-benzyl bromide	25	++	+	4
18	o-Methylmercapto-benzyl chloride	18	++	+	8
19	m-Methylmercapto-benzyl chloride	35	+	-	4
20	p-Methoxycarbonyl-benzyl bromide	4	++	+	2
25	p-Aldehydobenzyl chloride dimethyl acetal	25+	+	+	4
27	p-Aldehydobenzyl chloride	10+	+	++	5

A brief summary of the scope and biological results of some of the compounds listed has been published,[141,144] and it is intended here to give a more detailed assessment of these and other findings.

The earlier compounds of the bifunctional type I.C.L. 1-6 are all characterised by a high Median Lethal Dose (M.L.D.), an ineffectiveness towards the tumour and a variable effect on the rat. The last two in this group I.C.L. 7 and 8 again have no effect on the tumour but their M.L.D. has decreased ten fold. It might be deduced therefore that the first six, which all contain quite reactive halogen atoms are controlled in their action by lack of solubility in the biological system and perhaps in the case of the xylylene dihalides by added steric factors; the low M.L.D. of the two nitro xylylene dibromides may be due to a contributing effect of the nitro groups towards the toxicity.

This indiscriminate attack on the host, far exceeding any tumour attack, is again manifest in all but one of the benzyl halides. The attempt to correlate the toxicites of some of this latter group with chemical reactivity under approximately physiological conditions (see preceeding kinetic section) is summarised in

Table 2 where $^{1}/M.L.D.$ is shown against k_{30}.

Table II

I.C.L. No.	COMPOUND	$^{1}/M.L.D.$	k_{30}
12	p-Nitrobenzyl chloride	0.167	0.082
13	Benzyl chloride	0.040	0.044
15	m-N-Acetylaminobenzyl chloride	0.050	0.092
18	o-Methylmercaptobenzyl chloride	0.056	0.050
19	m-Methylmercaptobenzyl chloride	0.029	0.041
25	p-Aldehydobenzyl chloride dimethyl acetal	0.040	0.070
27	p-Aldehydobenzyl chloride	0.100	0.149

Overall a rough parallel exists, the toxicity increasing with reaction rate. The only anomaly is the p-nitrobenzyl chloride where a toxicity out of all proportion to its reaction rate can only be explained by some contribution to its toxic effect from the nitro group as was proposed for the nitro-xylylene dibromides. As

was expected, chemical deactivation of p-aldehydobenzyl chloride by conversion to its dimethyl acetal was paralleled by a similar drop in toxicity substantiating the theory that the biological mechanism of reaction was similar to that measured chemically.

The one benzyl halide in which preferred attack on the tumour occurred was p-aldehydobenzyl chloride, and as this differed from the general pattern exhibited by the other benzyl halides it seems that this compound might well be acting bifunctionally, the aldehyde group condensing, for example, with a free amino group.

EXPERIMENTAL

References to Original Notebooks

Numerals in brackets following sub-headings refer to page numbers in the original laboratory notebooks.

The Preparation of Substituted Benzyl Halides

Phenolic substituted benzyl halides

Reaction of Saligenin with thionyl chloride (316)

Saligenin (2.0 g.), suspended in dry chloroform (8 c.c.), was treated at 0° with thionyl chloride (2.1 g.) in dry chloroform (7 c.c.) over 10 minutes with vigorous stirring. Nitrogen was bubbled through the now clear solution while it was kept at 0° for 2 hours and allowed to warm up to room temperature over a further 1 hour. Evaporation of the solution gave a brown mobile liquid which on exposure to air evolved hydrogen chloride. Attempts to isolate an S-alkylthiouronium picrate were unsuccessful.

Acetylation of potassium saligenate (379, 380, 395, 400, 402, 405, 416, 512).

(i) Potassium saligenate was prepared quantitatively by adding ethanolic potassium hydroxide (50 c.c. of 3.571N) to saligenin (20 g.) in acetone (300 c.c.) according to the method of Hart and Hirschfelder[82].

Treatment of the potassium salt (25 g.) with acetic anhydride (50 c.c.) under their conditions gave only saligenin diacetate (15.8 g., 49%) n_D^{22} 1.4955, b.p. $104^\circ/10^{-3}$ mm. $\nu_{max.}$ (liquid film) 1770 and 1745 $cm.^{-1}$ (diacetate) (Found: equiv. by saponification, 102. Calc. for $C_{11}H_{12}O_4$, equiv. 104. Calc. for monoacetate, $C_9H_{10}O_3$, equiv. 166).

(ii) Potassium saligenate (10 g.), suspended in ethyl acetate (50 c.c.), was stirred and slowly treated with acetyl chloride (7 g.). After 30 minutes the solution was filtered and the solvent removed under reduced pressure to give a viscous oil which resinified on attempted distillation.

o-Acetoxybenzyl bromide (435, 451).

Saligenin diacetate (4.0 g.) was added to acetic anhydride (4.0 g.) in 50% (w/w) hydrogen bromide in acetic acid (20 g.) and the solution was kept at 0° for 4 days. Evaporation under reduced pressure followed by distillation gave o-acetoxybenzyl bromide (3.2 g., 73%), b.p. $94^\circ/2 \times 10^{-4}$ mm., $n_D^{19.5}$ 1.5519 (Found: C, 47.42; H, 4.43. $C_9H_9BrO_2$ requires C, 47.19; H, 3.96%). This gave an S-alkylthiouronium picrate,

m.p. 172-174°, yellow needles from ethanol (Found: C, 42.39, H, 3.21; N, 15.01. $C_{16}H_{15}N_5O_9S$ requires C, 42.38; H, 3.33; N, 15.45%).

o-Acetoxybenzyl chloride (460).

Saligenin diacetate (4 g.) in acetic acid (50 c.c.) containing acetic anhydride (10 c.c.) was treated with dry hydrogen chloride gas for two 4 hour periods with intermittent refluxing for one hour. After it had stood at room temperature for 2 weeks the solution was evaporated to give a brown oil containing o-acetoxybenzyl chloride,[81] b.p. $91°/10^{-4}$ mm., which could not be obtained pure and was characterised as its yellow S-alkylthiouronium picrate m.p. 176-178°, mixed m.p. 176-179° with that obtained from o-acetoxybenzyl bromide.

m-Hydroxybenzyl alcohol (247, 256, 439).

(i) m-Hydroxybenzaldehyde (25 g.), in dry ether (350 c.c.), was added dropwise to a slurry of lithium aluminium hydride (10 g.) in dry ether (200 c.c.) with vigorous stirring. After the mixture had been stirred under gentle reflux for five hours the flask was cooled in ice, ice-water (25 c.c.) added carefully to destroy

excess lithium aluminium hydride and the complex decomposed with 6N-sulphuric acid (170 c.c.). The aqueous portion was extracted with fresh ether (2 x 150 c.c.), and the ether extract was washed with saturated sodium bicarbonate solution (300 c.c.), water (200 c.c.) and then dried ($MgSO_4$). Evaporation gave m-hydroxybenzyl alcohol (13 g., 51%) m.p. 70-71°, white rhombs from benzene.

(ii) Methyl-m-hydroxybenzoate (23 g.) was reduced with lithium aluminium hydride (see above) to give m-hydroxybenzyl alcohol (17 g., 91%), m.p. 68-70°.

m-Acetoxybenzyl alcohol. (251, 252, 254, 262, 265, 442).

m-Hydroxybenzyl alcohol (8.4 g.) was dissolved in aqueous potassium hydroxide solution (5.447 N., 11.1 c.c.). To this well stirred pale green solution was added acetic anhydride (7 g.) dropwise over ten minutes with external cooling. The oil which separated was extracted with ether (2 x 10 c.c.); the ether extracts were washed with saturated sodium bicarbonate solution (10 c.c.), water (15 c.c.) and then dried ($MgSO_4$). Evaporation and distillation yielded crude m-acetoxybenzyl alcohol, b.p. 97°/2 x 10^{-3} mm. n_D^{19} 1.5240.

This was characterised as its α-naphthylurethane, white needles from methanol, m.p. 102-103° (Found: C, 71.76; H, 5.28. $C_{20}H_{17}NO_3$ requires C, 71.62; H, 5.11%).

m-Acetoxybenzyl chloride (266, 444).

(i) Crude m-acetoxybenzyl alcohol (3.5 g.) was diluted with dry benzene (8 c.c.) containing a drop of pyridine. Thionyl chloride (4 g.) in dry benzene (8 c.c.) was added dropwise over 5 minutes to the stirred solution which was then left at room temperature for 2 hours. The benzene was removed under reduced pressure and the residual brown oil was dissolved in ether (20 c.c.), washed with water (10 c.c.) and dried ($MgSO_4$). Evaporation and distillation gave m-acetoxybenzyl chloride (2.7 g., 69%), b.p. 95-98°/ 2 x 10^{-3} mm., $n_D^{21.5°}$ 1.5272 (Found: C, 58.38; H, 5.02. $C_9H_9ClO_2$ requires C, 58.54; H, 4.91%). The S-alkylthiouronium picrate formed yellow rhombs from methanol, m.p. 184-187° (decomp.) (Found: C, 42.72; H, 3.79; N, 15.10. $C_{16}H_{15}N_5O_9S$ requires C, 42.38; H, 3.33; N, 15.45%).

(ii) m-Hydroxybenzyl alcohol (5 g.) was refluxed with acetic anhydride (15 g.) in pyridine (25 c.c.) for an hour. Evaporation followed by treatment with water (50 c.c.) gave an oil which was isolated by ether extraction and distilled to give m-acetoxybenzyl acetate (6 g., 72%), b.p. $97^{\circ}/3 \times 10^{-3}$ mm., n_D^{23} 1.5011. Treatment of this diacetate (1 g.) in acetic acid - acetic anhydride with gaseous hydrogen chloride as for saligenin diacetate gave no m-acetoxybenzyl chloride; the diacetate was recovered unchanged.

m-Acetoxybenzyl bromide (458).

(i) m-Acetoxybenzyl acetate (4 g.) was added to 50% (w/w) hydrogen bromide in acetic acid (20 g.) containing acetic anhydride (4 g.). After eight days the reaction mixture was evaporated and the oil distilled (with much polymerisation) to give, in poor yield, m-acetoxybenzyl bromide b.p. $90\text{-}93^{\circ}/3 \times 10^{-2}$ mm., $n_D^{22^{\circ}}$ 1.5538 (Found: C, 46.65; H, 4.39. $C_9H_9BrO_2$ requires C, 47.19; H, 4.39%). This material gave an S-alkylthiouronium picrate m.p. 185-188°, yellow rhombs from methanol. Mixed with the S-alkylthiouronium picrate derived from

m-acetoxybenzyl chloride the m.p. was 188° (decomp.).

p-Hydroxybenzyl alcohol (218, 223).

(i) Methyl p-hydroxybenzoate (19 g.) in dry ether (300 c.c.) was added to lithium aluminium hydride (6 g.) in dry ether (250 c.c.) in the normal way to give p-hydroxybenzyl alcohol (12 g., 77%), m.p. 105°.

(ii) Hydrogenation of p-hydroxybenzaldehyde (25 g.) under pressure using Adams' catalyst gave p-hydroxybenzyl alcohol (12 g., 47%), isolated by extraction of unchanged aldehyde with ethyl acetate.

p-Acetoxybenzyl alcohol (225, 227, 231).

The diol (5.1 g.) was dissolved in water (10 c.c.) containing potassium hydroxide (2.4 g.) to give a pale blue solution which when treated with acetic anhydride (4.4 g.) formed a yellow turbidity. The oil was extracted with ether (2 x 10 c.c.) and distilled to give p-acetoxybenzyl alcohol (2.0 g., 29%), b.p. 110°/ 2×10^{-3} mm., n_D^{21} 1.5289 (Found: C, 65.19; H, 5.89. $C_9H_{10}O_3$ requires C, 65.05; H, 6.02%). The α-naphthylurethane, white needles from benzene, had m.p. 134° (Found: C, 71.24; H, 5.23. $C_{20}H_{17}NO_4$ requires C, 71.62; H, 5.11%).

p-Acetoxybenzyl chloride (232, 246, 248)

p-Acetoxybenzyl alcohol (4.2 g.), in dry benzene (15 c.c.), was added to thionyl chloride (5 g.) in dry benzene (10 c.c.) containing a drop of pyridine. This solution was heated at 90° for an hour, cooled, extracted with water (10 c.c.) and dried ($MgSO_4$). The oil obtained on evaporation was distilled to give p-acetoxybenzyl chloride (3.5 g., 75%), b.p. 82°/3 x 10^{-2} mm., $n_D^{21.5°}$ 1.5315 (Found: Cl, 19.19. $C_9H_9ClO_2$ requires Cl, 19.21%). It formed an S-alkylthiouronium picrate, yellow plates from ethanol, m.p. 194-195° (Found: C, 42.45; H, 3.24. $C_{16}H_{15}N_5O_9S$ requires C, 42.38; H, 3.34%). The chloride soon decomposed on storage.

p-Acetoxybenzyl bromide (206, 212, 220, 269, 270).

(i) The above alcohol (2 g.), in dry benzene (2 c.c.), was added slowly to redistilled thionyl bromide (4 g.) in dry benzene (7 c.c.) containing a trace of pyridine. The mixture was refluxed for 3 hours, then evaporated under reduced pressure to a brown oil which was dissolved in ether (10 c.c.), washed with water (5 c.c.), dried ($MgSO_4$) and evaporated to a brown solid. This was recrystallised from light petroleum (b.p. 60-80°) to

give white rhombs of p-acetoxybenzyl bromide (1 g., 37%), m.p. 54-55°, which evolved hydrogen bromide when stored (Found: C, 46.77; H, 4.31. $C_9H_9BrO_2$ requires C, 47.17; H, 3.96%). Its yellow S-alkylthiouronium picrate, m.p. 194°, had a mixed m.p. 196° with the same derivative derived from p-acetoxybenzyl chloride.

(ii) Crude p-hydroxybenzyl alcohol (7 g.) when refluxed with pyridine (30 c.c.) and acetic anhydride (30 c.c.) for half an hour gave p-acetoxybenzyl acetate (3.2 g., 29%) m.p. 75-76°, white rhombs from aqueous methanol, b.p. 120-130°/2 mm. This diacetate (0.3 g.) was dissolved in 50% (w/w) hydrogen bromide in acetic acid (5 c.c.) containing acetic anhydride (1.5 c.c.) and the resulting clear orange solution was kept at room temperature for 2 weeks. Evaporation at 40° gave a brown glass m.p. 205-210°, soluble in ethyl acetate but non-crystalline.

A similar attempted displacement reaction using hydrogen chloride gas in acetic acid (6 c.c.) and acetic anhydride (1 c.c.) on p-acetoxybenzyl acetate (0.2 g.) at 60° for 30 hours gave back unchanged starting material.

o-Methoxybenzyl alcohol (445).

o-Methoxybenzaldehyde (30.0 g.) in anhydrous ether (200 c.c.) was added dropwise over 2 hours to a slurry of lithium aluminium hydride (8.5 g.) in dry ether (200 c.c.) with vigorous stirring. After being refluxed for six hours and standing overnight the mixture was treated with ice-water to destroy excess reagent and 6N-sulphuric acid (140 c.c.) to decompose the complex. The aqueous layer was extracted with ether (2 x 200 c.c.), which was washed with saturated sodium bicarbonate (200 c.c.), water (200 c.c.) and dried ($MgSO_4$). Evaporation and distillation of the residual oil gave o-methoxybenzyl alcohol (25.7 g., 85%), b.p. 80-82°/10^{-2} mm., n_D^{21} 1.5470.

o-Methoxybenzyl chloride (494).

This was obtained by treating o-methoxybenzyl alcohol (10 g.) with thionyl chloride (15 g.) in dry benzene in the normal way. Distillation of the crude oil obtained gave o-methoxybenzyl chloride (7.5 g., 68%), b.p. 52-54°/8 x 10^{-2} mm., n_D^{23} 1.5478. Cragoe and Pietruszkiewicz[131] quote b.p. 110-114°/14 mm.

m-Methoxybenzyl alcohol (446).

m-Methoxybenzaldehyde (25 g.) in ether (150 c.c.) when reduced with lithium aluminium hydride (9 g.) in ether (300 c.c.) by the same process used for the o-isomer gave m-methoxybenzyl alcohol (23 g., 90%), b.p. 86-87°/2 x 10^{-3} mm., n_D^{25} 1.5418.

m-Methoxybenzyl chloride (498).

The alcohol (10 g.) in benzene (30 c.c.) when treated with thionyl chloride (15 g.) containing a trace of pyridine gave m-methoxybenzyl chloride (7.7 g., 68%), b.p. 58°/8 x 10^{-2} mm., n_D^{21} 1.5445. Tsukamoto et al.[133] give b.p. 92.5-95°/5 mm.

p-Methoxybenzyl chloride (496, 504).

p-Methoxybenzyl alcohol (6 g.) in dry benzene (20 c.c.) on treatment with thionyl chloride (12 g.) in dry benzene (10 c.c.) gave p-methoxybenzyl chloride (14.5 g., 66%) b.p. 59-60°/4 x 10^{-2} mm., n_D^{19} 1.5492 (Found: Cl, 22.39; Calc. for C_8H_9Cl: Cl, 22.65%). Shriner and Hull[132] state b.p. 101-103°/8-10 mm.

Amino-substituted benzyl halides.

o-Aminobenzyl alcohol (396).

o-Nitrobenzyl alcohol (20 g.) was hydrogenated in ethanol at atmospheric temperature and pressure using Adams' catalyst giving o-aminobenzyl alcohol (16 g., 100%), m.p. 83-84°, rhombs from benzene (observed uptake of hydrogen 8.4 litres. Calculated 8.8 litres).

o-N-Acetylaminobenzyl alcohol (397, 443).

The amine above (5.0 g.) was suspended in ethyl acetate (25 c.c.) and vigorously stirred whilst treated with acetic anhydride (5 g.) over 30 minutes. The now clear solution was quickly cooled to give o-N--acetylaminobenzyl alcohol (5.2 g., 78%), m.p. 116°, pale yellow needles from benzene.

o-N-Acetylaminobenzyl chloride (406).

The alcohol (2.0 g.) suspended in dry benzene (10 c.c.) containing a trace of pyridine, was treated with thionyl chloride (1.6 g.) in dry benzene (5 c.c.) over 15 minutes. The mixture was heated at 80-90° for 3 hours during which time an oil separated.

Evaporation of the mixture gave an oily solid which when triturated with benzene gave o-N-acetylaminobenzyl chloride (0.3 g., 13%), white needles from benzene-light petroleum (b.p. 60-80°), m.p. 116-119°. Kühn [89] quotes m.p. 114°.

o-N-Acetylaminobenzyl bromide (471, 473).

The alcohol (1.5 g.) suspended in dry benzene (10 c.c.) on treatment with phosphorus tribromide (1.0 g.) gave an oil which solidified. This crude o-N-acetylaminobenzyl bromide (1.8 g., 87%) had m.p. 165° (decomp.), but attempts to recrystallise it were unsuccessful due to extensive decomposition.

m-Aminobenzyl alcohol (249).

m-Nitrobenzyl alcohol (28 g.) on hydrogenation at room temperature in ethanol using Adams' catalyst gave m-aminobenzyl alcohol quantitatively, m.p. 89-91° (calculated hydrogen uptake 12.0 litres. Observed uptake 12.5 litres).

m-N-Acetylaminobenzyl alcohol (250, 276).

A suspension of the amine (5 g.) in ethyl acetate (15 c.c.) when treated with acetic anhydride (5 g.) by the method already described gave m-N-acetylaminobenzyl alcohol (6.6 g., 98%), yellow rhombs from nitromethane, m.p. 106-108°.

m-N-Acetylaminobenzyl chloride (253)

Addition of thionyl chloride (3.5 g.), in dry benzene (15 c.c.), to m-N-acetylaminobenzyl alcohol (5 g.) in dry benzene (80 c.c.) gave m-N-acetylaminobenzyl chloride (1.3 g., 23%), needles from benzene--light petroleum (60-80°), m.p. 86-88°. Kühn[89] quotes m.p. 89°.

m-N-Acetylaminobenzyl bromide (260, 275, 277).

Thionyl bromide (4 g.) in dry benzene (10 c.c.) was added to the alcohol (1.1 g.) in dry benzene (50 c.c.) to give m-N-acetylaminobenzyl bromide, which was washed with ethyl acetate and had m.p. ca. 120°. (Found: C, 47.37; H, 4.47. $C_9H_{10}BrNO$ requires C, 47.41; H, 4.42%). It was not possible to recrystallise it owing to its instability.

p-Aminobenzyl alcohol (233-237).

(i) p-Nitrobenzyl alcohol (20 g.), prepared according to the method of Hartmann and Rahrs[134] was hydrogenated in the way already described to give p-aminobenzyl alcohol (16 g., 100%), m.p. 58-61° (observed hydrogen uptake, 9.5 litres. Calculated uptake 9.0 litres).

(ii) Methyl p-aminobenzoate (12 g.) in dry ether (400 c.c.) was added to lithium aluminium hydride (6.5 g.) in dry ether (150 c.c.) over 2 hours. The mixture was refluxed with vigorous stirring for 3 hours, cooled, and the excess hydride destroyed by the addition of ice-water. The complex was decomposed by adding excess 6N-sulphuric acid and the ethereal layer and extracts dried ($MgSO_4$) and evaporated to give a small amount of p-toluidine, m.p. 40-42°, mixed m.p. 42-44° with an authentic specimen. The acid layer was made strongly alkaline with sodium hydroxide solution and extracted with ether to give p-aminobenzyl alcohol (0.6 g., 16%), plates from benzene, m.p. 61-62°.

p-N-Acetylaminobenzyl alcohol (238, 239, 241).

(i) The amine (0.7 g.) in ethyl acetate (7 c.c.) was treated with acetic anhydride (0.7 g.) in ethyl acetate (5 c.c.) in the usual way to give p-N-acetyl-

aminobenzyl alcohol (0.7 g., 75%), rhombs from the reaction mixture, yellow prisms from nitromethane, m.p. 120-121° (Found: C, 65.30; H, 6.83. $C_9H_{11}NO_2$ requires C, 65.35; H, 6.71%).

(ii) Thiolacetic acid (0.5 g.) was added directly to the amine (0.5 g.). Violent effervescence occurred with the deposition of crude p-N-acetylaminobenzyl alcohol (0.6 g., 89%), m.p. 115-119°.

p-N-Acetylaminobenzyl chloride (240, 242, 244).

p-N-Acetylaminobenzyl alcohol (0.8 g.), in dry benzene (8 c.c.) was treated with thionyl chloride (0.8 g.) in dry benzene (5 c.c.) and the mixture was heated at 80-90° for ten minutes. Extensive decomposition occurred, but working up in the normal way gave p-N-acetylaminobenzyl chloride (0.2 g., 23%), brown needles from benzene, m.p. 151-154°. Kühn[89] quotes m.p. 155°.

p-N-Acetylaminobenzyl bromide (261, 272, 331).

Thionyl bromide (3 g.) in dry benzene (7 c.c.) was added to p-N-acetylaminobenzyl alcohol (1 g.) in dry benzene (5 c.c.) to give p-N-acetylaminobenzyl

bromide (0.8 g., 58%), m.p. 162°, plates from ethyl acetate (Found: C, 47.77; H, 4.33. $C_9H_{10}BrNO$ requires C, 47.41; H, 4.42%).

Sulphur-containing benzyl halides

Methyl o-methylmercaptobenzoate (301, 340)

Thiosalicylic acid (o-mercaptobenzoic acid) (15.4 g.) in N-sodium hydroxide (250 c.c.) was warmed and slowly treated with methyl sulphate (15 g.). The resulting mixture was shaken for 4 hours and then acidified with concentrated hydrochloric acid to give o-methylmercaptobenzoic acid (15 g., 89%), m.p. 168°, needles from water (changing to plates at 140°). This acid (15 g.) was refluxed for 7 hours in methanol saturated with hydrogen chloride (130 c.c.) to give methyl o-methylmercaptobenzoate (14.4 g., 87%), m.p. 66-67°, rhombs from methanol.

o-Methylmercaptobenzyl alcohol (306, 328, 341, 359, 507).

To a well stirred slurry of lithium aluminium hydride (4 g.) in dry ether (200 c.c.) was added

methyl o-methylmercaptobenzoate (10 g.) in dry ether (250 c.c.). The mixture was refluxed for six hours, cooled, water added to destroy excess hydride and the complex dissolved by adding 6N-sulphuric acid. The ethereal layer, after drying ($MgSO_4$), was evaporated to give o-methylmercaptobenzyl alcohol (6.4 g., 76%), b.p. $88^{\circ}/5 \times 10^{-3}$ mm., n_D^{20} 1.6060 (Found: C, 61.97; H, 6.44. $C_8H_{10}OS$ requires C, 62.30; H, 6.53%).

o-Methylmercaptobenzyl chloride (308, 344, 508)

o-Methylmercaptobenzyl alcohol (1 g.) was added to thionyl chloride (1.4 g.) in benzene (7 c.c.) containing one drop of pyridine. The mixture was heated at 100° for an hour, cooled, washed with water (2 x 5 c.c.) and dried ($MgSO_4$). Evaporation gave o-methylmercaptobenzyl chloride (0.8 g., 72%), b.p. $75\text{-}76^{\circ}/4 \times 10^{-2}$ mm., n_D^{21} 1.6045 (Found: C, 55.29; H, 5.50. C_8H_9ClS requires C, 55.64; H, 5.25%).

o-Methylmercaptobenzyl bromide (312, 343, 470).

(i) Thionyl bromide (2 g.) in dry benzene (8 c.c.) was treated with o-methylmercaptobenzyl alcohol (1 g.) in dry benzene (10 c.c.) containing a trace of pyridine.

Evaporation, after heating for an hour at 80°, gave crude o-methylmercaptobenzyl bromide (ca. 1 g., 71%), b.p. 85°/2 x 10^{13} mm. (Found: C, 43.54; H, 4.16. C_8H_9BrS requires C, 44.25; H, 4.18%).

(ii) A similar reaction conducted with the alcohol (2.5 g.) and thionyl bromide (4.2 g.) gave a product which crystallised in needles from light petroleum (60-80°), had m.p. 79-82° and appeared to be mainly a dibromo-compound (Found: Br; 50.76. Calculated for $C_8H_8Br_2S$: Br, 53.99%).

(iii) The alcohol (2.6 g.) in dry benzene (10 c.c.), cooled in ice, was treated with dry hydrogen bromide for an hour. The lower aqueous layer was removed and the organic layer was dried ($CaCl_2$) and evaporated to give a dark brown oil which was distilled to give o-methylmercaptobenzyl bromide (2.0 g., 54%), b.p. 89°/6 x 10^{-4} mm., n_D^{20} 1.6350, needles from light petroleum (b.p. 30-40°), m.p. 43-44° (Found: C, 44.40; H, 4.24. C_8H_9BrS requires C, 44.25; H, 4.18%).

Methyl o-mercaptobenzoate (304, 311, 313, 323).

Thiosalicylic acid (19 g.) was refluxed overnight in methanol (120 c.c.) saturated with hydrogen chloride

gas to give methyl o-mercaptobenzoate (17.5 g., 84%), b.p. $83^{\circ}/10^{-1}$ mm., n_D^{21} 1.5919.

o-Mercaptobenzyl alcohol (305, 314, 324).

Methyl o-mercaptobenzoate (18.3 g.) in dry ether (150 c.c.) was reduced with lithium aluminium hydride (6.8 g.) in dry ether (200 c.c.) to give o-mercaptobenzyl alcohol (13.6 g., 89%), b.p. $85^{\circ}/2 \times 10^{-3}$ mm., n_D^{22} 1.6080, m.p. 30-31° (Found:, C, 59.78; H, 5.93. C_7H_8OS requires C, 59.97; H, 5.75%). Oxidation with aqueous iodine gave the disulphide m.p. 141-142°, Reissert and Cramer[90] quote m.p. 141-142°.

Reaction of o-mercaptobenzyl alcohol with thionyl chloride (321, 322).

Thionyl chloride (1.1 g.) in chloroform (8 c.c.) was treated with o-mercaptobenzyl alcohol (0.8 g.) in chloroform (5 c.c.) at 0°. The reaction mixture was allowed to attain room temperature overnight when it was evaporated to give an oil which decomposed on distillation. Attempts to obtain an S-alkylthiouronium picrate, from another preparation, were unsuccessful.

m-Methylmercaptobenzoic acid (300, 472).

(i) This was obtained by the method of Stewart and Smiles[97] from benzoic acid m.p. 127-129° (32.5%). They quote m.p. 126-127° (31%).

(ii) m-Aminobenzoic acid (48 g.) suspended in 2N-hydrochloric acid (360 c.c.) was diazotised by cooling to 0° and adding sodium nitrite (25 g.) in cold water (100 c.c.). This mixture was treated with potassium ethyl xanthate (60 g.) in water (200 c.c.) to give the corresponding xanthate (59 g., 70%). The xanthate (33 g.) was cleaved by heating at 100° for an hour in water (250 c.c.) containing potassium hydroxide (35 g.). Methyl sulphate (20 g.) was added and the solution shaken for 3 hours; acidification gave m-methylmercaptobenzoic acid (12 g., 57%), m.p. 128°.

Methyl m-methylmercaptobenzoate (307, 472).

m-Methylmercaptobenzoic acid (14.7 g.) was refluxed for 6 hours in methanol (120 c.c.) saturated with hydrogen chloride to give methyl m-methylmercaptobenzoate (13 g., 82%), b.p. 83°/4 x 10^{-3} mm., n_D^{20} 1.5767.

m-Methylmercaptobenzyl alcohol (309,346,510).

Reduction of methyl m-methylmercaptobenzoate (10.6 g.) with lithium aluminium hydride (2.6 g.), both in ether, gave m-methylmercaptobenzyl alcohol (7.0 g., 83%), b.p. $98^{\circ}/10^{-4}$ mm., n_D^{24} 1.5987 (Found: C, 62.32; H, 6.64. $C_8H_{10}OS$ requires C, 62.30; H, 6.53%).

m-Methylmercaptobenzyl chloride (315, 349, 511).

m-Methylmercaptobenzyl alcohol (4.6 g.) in chloroform (20 c.c.) was added to thionyl chloride (5 g.) in chloroform (20 c.c.) to give m-methylmercaptobenzyl chloride (4.9 g., 96%), b.p. $78^{\circ}/3 \times 10^{-3}$ mm., n_D^{24} 1.5987 (Found: C, 55.62; H, 5.22. C_8H_9ClS requires C, 55.64; H, 5.25%).

m-Methylmercaptobenzyl bromide (318, 330, 469).

(i) Reaction of m-methylmercaptobenzyl alcohol (1.9 g.) in dry benzene (8 c.c.) with thionyl bromide (3.8 g.) in dry benzene (5 c.c.) at 80° gave, in very poor yield, a solid, m.p. 76°, needles from light petroleum (b.p. $80\text{-}100^{\circ}$) identified as a dibromo--compound (Found: C, 32.94; H, 2.93; S, 11.17.

$C_8H_8Br_2S$ requires C, 32.46; H, 2.72; S, 10.82%). The structure was established as a nuclear substituted benzyl bromide by converting it to its S--alkylthiouronium picrate, m.p. ca.220° (decomp.), needles from ethanol (Found: C, 35.55; H, 2.93. $C_{15}H_{14}BrN_5O_7S$ requires C, 34.62; H, 2.71%).

(ii) m-Methylmercaptobenzyl alcohol (3.8 g.) in dry benzene (15 c.c.) was treated with dry hydrogen bromide gas for an hour. The lower aqueous layer was removed and the benzene solution dried ($CaCl_2$) and evaporated to give a brown oil which on distillation yielded m-methylmercaptobenzyl bromide (2.9 g., 54%), b.p. $89°/10^{-4}$ mm., $n_D^{20°}$ 1.6298 (Found: C, 44.21; H, 4.03. C_8H_9BrS requires C, 44.25; H, 4.18%).

3,3'-Bismethoxycarbonyldiphenyl disulphide (427).

3,3'-Diphenyl disulphide dicarboxylic acid (4 g.), prepared according to the method of Stewart and Smiles[97], was refluxed in methanol (70 c.c.) saturated with hydrogen chloride gas overnight. Evaporating and extraction with ether gave 3,3'-bismethoxycarbonyldiphenyl disulphide (2.5 g., 63%), b.p. 185-190°

/2 x 10^{-3} mm., plates from aqueous methanol, m.p. 45-47° (Found: C, 57.59; H, 4.47. $C_{16}H_{14}O_4S_2$ requires C, 57.47; H, 4.22%).

m-Mercaptobenzyl alcohol (338, 429, 431).

(i) Methyl m-mercaptobenzoate (6.5 g.) in ether (100 c.c.) was reduced with lithium aluminium hydride (4 g.) in ether (150 c.c.) to give m-methylmercaptobenzyl alcohol (2.4 g., 44%), as a colourless oil, b.p. 88°/10^{-4} mm., n_D^{22} 1.6044 (Found: C, 59.54; H, 5.60. C_7H_8OS requires C, 59.97; H, 5.75%).

(ii) 3,3'-Bismethoxycarbonyl diphenyl disulphide (11 g.) in ether (100 c.c.) was reduced with lithium aluminium hydride (6 g.) in ether (100 c.c.) to give m-methylmercaptobenzyl alcohol (3.8 g., 43%), b.p. 92°/5 x 10^{-3} mm., (Found: thiol-S, 22.3. C_7H_8OS requires S, 22.9%). Oxidation of a sample with aqueous iodine gave 3,3'-bishydroxymethyldiphenyl disulphide, m.p. 75-76°, rhombs from ether-light petroleum (b.p. 40-60°) (Found: C, 60.53; H, 5.36. $C_{14}H_{14}O_2S_2$ requires C, 60.40; H, 5.07%).

Methyl p-Methylmercaptobenzoate (412, 415).

p-Aminobenzoic acid (10 g.) in 2N-hydrochloric acid (75 c.c.) at 0° was diazotised by adding sodium nitrite (5 g.) in water (20 c.c.). This mixture was treated with potassium ethyl xanthate (12 g.) in water (15 c.c.) to give a crude yellow solid (16.5 g., quantitative). This xanthate (3 g.) in water (20 c.c.) containing potassium hydroxide (4 g.) was heated at 100° for an hour. The solution was cooled, diluted with water (10 c.c.) and shaken for 3 hours with methyl sulphate (2 g.). Acidification with concentrated hydrochloric acid gave p-methylmercaptobenzoic acid (1.5 g., 72%), m.p. 187-190°. This acid (1.5 g.) was refluxed overnight in methanol (20 c.c.) saturated with hydrogen chloride yielding methyl p-methylmercaptobenzoate (1.5 g., 92%), which after crystallisation from aqueous methanol had m.p. 78-80°, (with change of crystal form at 60-70°). Brack and Stall[135] quote m.p. 82°.

p-Methylmercaptobenzyl alcohol (421).

Methyl p-methylmercaptobenzoate (8.2 g.) in ether (100 c.c.) was reduced with lithium aluminium hydride

(4.5 g.) in ether (150 c.c.) in the normal way to give p-methylmercaptobenzyl alcohol (4.1 g., 59%), b.p. $100^{\circ}/2 \times 10^{-3}$ mm., m.p. 37-39°. Goldberg and Jampolsky[100] quote b.p. 108-109°/0.4 mm., m.p. 41-42°.

p-Methylmercaptobenzyl chloride (500).

p-Methylmercaptobenzyl alcohol (5 g.) in benzene was treated with thionyl chloride (10 g.) in benzene (15 c.c.) in essentially the same manner as that described by Goldberg and Jampolsky.[100] Distillation of the product gave p-methylmercaptobenzyl chloride (4.1 g., 82%), b.p. $77-78^{\circ}/3 \times 10^{-2}$ mm., n_D^{19} 1.6075. They quote b.p. 83°/0.3 mm., n_D^{27} 1.6034.

p-Methylmercaptobenzyl bromide (468).

Dry hydrogen bromide was bubbled through a solution of p-methylmercaptobenzyl alcohol (2.6 g.) in dry benzene (15 c.c.) for an hour. After removing the lower aqueous phase the benzene solution was dried ($CaCl_2$) and evaporated to give p-methylmercaptobenzyl bromide (2.2 g., 60%), plates from light petroleum (b.p. 60-80°), m.p. 44° (Found: C, 44.32; H, 4.24. C_8H_9BrS requires C, 44.25; H, 4.18%).

Methyl p-mercaptobenzoate (437).

The xanthate from p-aminobenzoic acid (10 g.) was cleaved with potassium hydroxide (13 g.) in ethanol (200 c.c.). The bulk of the ethanol was distilled off and the residue acidified in the presence of zinc dust to give p-mercaptobenzoic acid (5.2 g., 82%), m.p. 220° (decomposition). Esterification of this solid in methanol (60 c.c.) saturated with hydrogen chloride gas gave methyl p-mercaptobenzoate (5.6 g., 98%), m.p. 49-50°. Schwarzenbach and Rudin,[98] quote m.p. 50°. This was oxidised quantitatively with aqueous iodine to give 4,4'-bismethoxycarbonyldiphenyl disulphide, m.p. 127-128°, rhombs from methanol (Found: C, 57.44; H, 4.28. $C_{16}H_{14}O_4S_2$ requires C, 57.47; H, 4.22%).

p-Mercaptobenzyl alcohol (339, 411, 418, 422, 423, 440).

(i) Pure methyl p-mercaptobenzoate (7 g.) in dry ether (40 c.c.) on reduction with lithium aluminium hydride (2.5 g.) in ether (30 c.c.) gave p-mercaptobenzyl alcohol (2.8 g., 43%), an obnoxious smelling compound, m.p. 52-54°, plates from carbon tetrachloride--light petroleum (b.p. 60-80°) (Found: C, 60.24;

H, 5.98. C_7H_8OS requires C, 59.97; H, 5.75%).

4,4'-Bishydroxymethyldiphenyl disulphide (440).

Oxidation of p-mercaptobenzyl alcohol with aqueous iodine gave a quantitative yield of 4,4'-bis-hydroxymethyldiphenyl disulphide, m.p. 130-132°, white needles from aqueous acetone (Found: C, 60.06; H, 5.22. $C_{14}H_{14}O_2S_2$ requires C, 60.40; H, 5.07%).

Treatment of the diol (1.5 g.) in dry benzene (5 c.c.) with thionyl chloride (3 g.) in dry benzene (5 c.c.), with a trace of pyridine as catalyst, gave after 3 hours stirring a white solid, m.p. 74-78° containing halogen (Beilstein), but also free hydroxyl functions ($\nu_{max.}$ 3401 cm.$^{-1}$).

Aldehyde-substituted benzyl halides

Phthalaldehydic acid pseudo-methyl ester (369, 376).

Phthalaldehydic acid (4 g.) was refluxed in methanol (50 c.c.) saturated with dry hydrogen chloride for 20 hours to give a yellow oil which slowly crystallised to give phthalaldehydic acid pseudo-methyl ester (3.8 g.,

87%), rhombs from light petroleum (b.p. 40-60°), m.p. 44° (Found: C, 65.94; H, 4.91. Calc. for $C_9H_8O_3$: C, 65.85; H, 4.91%), $\nu_{max.}$ (carbon tetrachloride) 1786 cm.$^{-1}$ (lactone). Gabriel[102] quotes m.p. 44°.

Phthalaldehydic acid pseudo-ethyl ester (390).

Phthalaldehydic acid (3.0 g.) was refluxed in dry ethanol (5 c.c.) containing ethyl orthoformate (3.5 g.) and ammonium chloride (0.1 g.) for 15 minutes. The excess solvent and reagent were removed under reduced pressure to give a partially crystalline solid; this was dissolved in ether (20 c.c.), washed with water (10 c.c.) and dried (Na_2SO_4). Evaporation gave phthalaldehydic acid pseudo-ethyl ester (2.8 g., 78%), plates from light petroleum (b.p. 60-80°), m.p. 68° (Found: C, 67.64; H, 5.75. $C_{10}H_{10}O_3$ requires C, 67.39; H, 5.66%).

Reduction of phthalaldehydic pseudo-methyl ester (432).

Lithium aluminium hydride in ether was standardised according to the method of Felkin.[136] The pseudo-methyl ester (4.0 g., 0.0244 moles) in dry

ether (40 c.c.) was treated with standard lithium aluminium hydride solution (14.0 c.c., 0.0136 moles) over 30 minutes. The mixture was stirred for an hour, left overnight and worked up by acid decomposition to give a very poor yield of material (b.p. $120^{\circ}/6 \times 10^{-4}$ mm., m.p. 62-73°, plates from light petroleum (b.p. 60-80°). This was identified as phthalide, with which it had an identical infrared spectrum in carbon tetrachloride.

m-Methoxycarbonylbenzyl bromide (350).

Methyl m-toluate (40 g.) in carbon tetrachloride (100 c.c.), irradiated by light from a 1000 watt bulb, was treated with bromine (45 g.) in carbon tetrachloride (100 c.c.) over 20 minutes. The oil obtained after removal of the solvent was distilled to give mainly m-methoxycarbonylbenzyl bromide (31 g., 51%), b.p. $90^{\circ}/10^{-1}$ mm. From the higher boiling fractions was isolated m-methoxycarbonyl benzylidene bromide (3.5 g.), rhombs from light petroleum (b.p. 30-50°), m.p. 41° (Found: C, 35.52; H, 2.74. $C_9H_8Br_2O_2$ requires C, 35.09; H, 2.62%). This compound gave no S-alkylthiouronium picrate, and when it (1.0 g.)

was refluxed in acetic acid (12 c.c.) with sodium acetate (3.0 g.) an oily solid (0.4 g., 75%) was obtained which gave a 2,4-dinitrophenylhydrazone and a semicarbazone; the latter was the derivative of m-methoxycarbonylbenzaldehyde and formed white needles from methanol, m.p. 231-233° (Found: C, 54.30; H, 5.16. $C_{10}H_{11}N_3O_3$ requires C, 54.29; H, 5.01%).

m-Methoxycarbonylbenzaldehyde (381).

(i) This was prepared by the method of Mayer and Sieglitz[137] adapted by Reynolds and Fuson[138] for p-methoxycarbonylbenzaldehyde.

Hexamethylenetetramine (20 g.) in water (200 c.c.) was refluxed with m-methoxycarbonylbenzyl bromide (31 g.) in methanol (350 c.c.) for 7 hours. The methanol was distilled off under reduced pressure and the aqueous residue extracted with ether to give m-methoxycarbonylbenzaldehyde (8 g., 36%), b.p. 90°/10^{-4} mm.

(ii) A small amount was prepared from m-methoxycarbonyl benzylidene bromide by the method already described.

m-Methoxycarbonylbenzaldehyde dimethyl acetal (398, 404).

The aldehyde (3.0 g.) was refluxed in dry methanol (5 c.c.) with methyl orthoformate (2.5 g.) and ammonium chloride (0.1 g.) for 20 minutes. The excess reactant and solvent were removed under reduced pressure and the residue diluted with ether (10 c.c.). The ethereal solution was extracted with water (5 c.c.), dried ($MgSO_4$) and evaporated to give m-methoxycarbonylbenzaldehyde dimethyl acetal (3.1 g., 83%), b.p. $82^{\circ}/6 \times 10^{-4}$ mm., n_D^{18} 1.5063 (Found: C, 62.87; H, 7.02. $C_{11}H_{14}O_4$ requires C, 62.84; H, 6.71%).

m-Hydroxymethylbenzaldehyde dimethyl acetal (407, 413, 414).

The ester (7.0 g.) in dry ether (20 c.c.) was added to lithium aluminium hydride (1.2 g.) in dry ether (20 c.c.) fast enough to maintain gentle reflux. The mixture was stirred at room temperature for 2 hours, the excess reagent then destroyed with water (10 c.c.) and the complex decomposed with 2N sodium hydroxide solution (10 c.c.). The mixture was filtered and after the alumina had been washed with

fresh ether the organic layer was separated, dried ($MgSO_4$ - K_2CO_3) and evaporated to give m-hydroxymethylbenzaldehyde dimethyl acetal (3.4 g., 56%), b.p. 114-115°/2 x 10^{-3} mm., $n_D^{21°}$ 1.5182. (Found: C, 66.55; H, 7.72. $C_{10}H_{14}O_3$ requires C, 65.91; H, 7.74%). $\nu_{max.}$ (liquid film) 3401, 2933 and 2825 cm.$^{-1}$

Reaction of the acetal with thionyl chloride (417, 420).

m-Hydroxymethylbenzaldehyde dimethyl acetal (1.9 g.) was diluted with dry benzene (5 c.c.) and pyridine (2 c.c.). This solution was treated with thionyl chloride (1.5 g.) in dry benzene (5 c.c.) over 3 minutes followed by heating at 90° for 3 hours. The mixture was allowed to stand overnight, washed with water, dried ($MgSO_4$) and evaporated to give in poor yield a liquid b.p. 98°/4 x 10^{-2} mm. This compound contained halogen and gave a delayed test with 2,4-dinitrophenylhydrazine. An S-alkylthiouronium picrate, m.p. ca. 180° was isolated but this decomposed on attempted recrystallisation.

p-Methoxycarbonylbenzyl bromide (347).

Methyl p-toluate (42 g.), in carbon tetrachloride (200 c.c.) was treated with bromine (46 g.) in

carbon tetrachloride over 30 minutes in the light of a 1000 watt bulb to give p-methoxycarbonylbenzyl bromide (35 g., 55%), b.p. $100^{\circ}/5 \times 10^{-2}$ mm., m.p. $48\text{-}51^{\circ}$. Codington and Mosetta[139] quote m.p. $52\text{-}53^{\circ}$.

p-Methoxycarbonylbenzaldehyde (352, 365, 373, 377, 449).

(i) The reaction of p-methoxycarbonylbenzyl bromide with the sodium salt of 2-nitropropane according to the method of Hass and Bender[112] gave an impure aldehyde which was converted directly to its semicarbazone. This semicarbazone (2.2 g.), suspended in hot acetic acid (35 c.c.) was treated with solid sodium nitrite (4 g.) over 20 minutes. A clear solution was obtained from which the acetic acid was vacuum distilled. Addition of water to the residue gave p-methoxycarbonylbenzaldehyde (1.3 g., 80%), m.p. $59\text{-}60^{\circ}$, plates from light petroleum (b.p. $80\text{-}100^{\circ}$) changing to needles on heating.

(ii) p-Methoxycarbonylbenzaldehyde was also prepared by essentially the method of Stotta and Kethur[114], except that the intermediate methyl p--cyanobenzoate was isolated by extraction with light petroleum (b.p. $60\text{-}80^{\circ}$) and not steam distillation.

The aldehyde (60%) had m.p. 59-61°; they quote m.p. 60° (90%).

p-Methoxycarbonylbenzaldehyde diethyl acetal (387).

p-Methoxycarbonylbenzaldehyde (3.0 g.), ammonium chloride (0.1 g.), and ethyl orthoformate (3 g.) in absolute ethanol (3 g.) were refluxed for 15 minutes. Evaporation of the mixture gave an oil which was diluted with ether (30 c.c.), washed with water (7 c.c.), dried (K_2CO_3) and distilled to give what was considered to be p-methoxycarbonylbenzaldehyde diethy acetal (4.1 g., 95%), b.p. 97°/10^{-5} mm., $n_D^{18°}$ 1.4951 (Found: C, 66.00; H, 7.70. $C_{13}H_{18}O_4$ requires C, 65.52; H, 7.61%), but in which some methyl-ethyl interchange might have occurred (see Theoretical section, p.61).

p-Aldehydobenzyl alcohol diethyl acetal (392).

The above diethyl acetal (2.5 g.), in dry ether (10 c.c.) was reduced with lithium aluminium hydride (0.5 g.) in dry ether (10 c.c.) by stirring for 5 hours at room temperature. Water (5 c.c.) followed by 2N-sodium hydroxide solution (5 c.c.) was used to decompose the complex. The ethereal layer was

separated, dried (K_2CO_3) and evaporated to give impure p-aldehydobenzyl alcohol diethyl acetal (1.6 g., 72%), b.p. 115°/0.07 mm., n_D^{24} 1.5020 (Found: C, 66.76; H, 8.50. $C_{12}H_{18}O_3$ requires C, 68.55; H, 8.50%). It showed $\nu_{max.}$ (liquid film) 3401, 2967 and 2833 cm.$^{-1}$ It probably contained some methyl acetal (see Theoretical section, p.61).

p-Methoxycarbonylbenzaldehyde dimethyl acetal (408).

p-Methoxycarbonylbenzaldehyde (9.6 g.) in dry methanol was refluxed with methyl orthoformate (10 g.) and ammonium chloride (0.1 g.) for an hour to give on evaporation and distillation p-methoxycarbonylbenzaldehyde dimethyl acetal (10.1 g., 82%), b.p. 90°/ 4 x 10^{-2} mm., m.p. 32-33°, $\nu_{max.}$ (carbon tetrachloride) 2933, 2825 (acetal) and 1724 cm.$^{-1}$ (ester). Wegscheider and Suida[115] quote m.p. 30°.

p-Aldehydobenzyl alcohol dimethyl acetal (428).

The ester (10.1 g.) in dry ether (50 c.c.) was reduced with lithium aluminium hydride (4 g.) in dry ether (50 c.c.) by stirring at room temperature for 5 hours and allowing to stand overnight. Water

(25 c.c.) and 2N-sodium hydroxide solution (30 c.c.) was used to decompose the complex. The solution was filtered, the alumina washed with ether and the organic portion dried ($MgSO_4$) and evaporated to give p-aldehydobenzyl alcohol dimethyl acetal (8.6 g., 98%), m.p. 42-43°, rhombs from carbon tetrachloride--light petroleum (b.p. 60-80°) (Found: C, 65.80; H, 7.71. $C_{10}H_{14}O_3$ requires C, 65.91; H, 7.74%).

p-Aldehydobenzyl chloride (462, 515).

The dimethyl acetal (5.2 g.) in ether (30 c.c.) was saturated with dry hydrogen chloride gas for an hour and left at 0° overnight. The solution was evaporated and the residue dissolved in benzene (30 c.c.) which was treated with thionyl chloride (8 g.) in benzene (10 c.c.) over 2 hours at room temperature. Evaporation and distillation of the residual oil gave p-aldehydobenzyl chloride (2.2 g., 58%), m.p. 74°, needles from light petroleum (b.p. 60-80°) (Found: C, 62.16; H, 4.57. Calc. for C_8H_7ClO: C, 62.15; H, 4.57%), $\nu_{max.}$ (carbon tetrachloride) 1704 cm.$^{-1}$ (CHO). Baker et al.[116] quote m.p. 74°.

p-Aldehydobenzyl chloride dimethyl acetal (465).

p-Aldehydobenzyl chloride (1 g.) mixed with ammonium chloride (0.5 g.) was refluxed with methanol (12 c.c.) containing methyl orthoformate (0.8 g.) for 45 minutes. The solvent was removed under reduced pressure, the remaining oil diluted with ether (10 c.c.), washed with water (10 c.c.), dried ($MgSO_4$) and evaporated to give p-aldehydobenzyl chloride dimethyl acetal (1.0 g., 77%), b.p. 78-80°/ 10^{-4} mm., n_D^{21} 1.5189 (Found: C, 59.54; H, 6.49. $C_{10}H_{13}ClO_2$ requires C, 59.86; H, 6.53%), $\nu_{max.}$ (liquid film) 2907 and 2801 cm.$^{-1}$ (acetal).

Preliminary Synthetic Work on Substituted Xylylene Dihalides.

4-Aminophthalaldehyde (16).

Dimethyl 4-aminophthalate (10 g.), in dry tetrahydrofuran (50 c.c.) was added slowly to a well stirred slurry of lithium aluminium hydride (3.2 g.) in dry ether (100 c.c.). The addition being complete, the mixture was refluxed for two hours. After cooling, the excess hydride was destroyed with ice-water (10 c.c.) and the complex decomposed with 6N-hydrochloric acid (25 c.c.). The organic layer was separated, dried ($MgSO_4$), and evaporated to give a yellow oil which crystallised. Recrystallisation from methanol gave yellow plates of 4-aminophthalaldehyde (0.53 g., 7%), m.p. 195-196° (Found: C, 64.01; H, 4.98; N, 9.32. $C_8H_7NO_2$ requires C, 64.42; H, 4.72; N, 9.39%). The infrared spectrum $\nu_{max.}$ 3379, 3270, 3157 (NH_2), 1718 (C=O), was similar to that of phthalaldehyde but contained the additional amine bands.

Dimethyl 4-N-acetylaminophthalate (135, 136, 137, 140, 175).

This was prepared essentially by the method of Bogert,[142] and possessed a m.p. 110-111° from benzene and m.p. 137-138° from benzene-light petroleum (b.p. 60-80°); he quotes m.p. 137-138°.

Attempted conversion of dimethyl 4-N-acetylaminophthalate to 4-N-acetylaminophthalyl alcohol (139, 143, 181, 185).

(i) The above diester (1 g.) in tetrahydrofuran (25 c.c.) was added to potassium borohydride (0.23 g.) in tetrahydrofuran (15 c.c.). After being stirred under reflux for 9 hours the mixture was worked up in the normal way yielding dimethyl 4-N-acetylaminophthalate (0.8 g., 80% recovery) m.p. 134-136°, mixed m.p. with authentic specimen, 136-140°.

(ii) To the above dimethyl ester (1 g.) in tetrahydrofuran (30 c.c.) was added, in one lot, potassium borohydride (0.5 g.) followed by powdered lithium chloride (0.4 g.). After stirring under reflux for fifteen hours more potassium borohydride (0.25 g.) and lithium chloride (0.2 g.) were added.

Working up in the normal way after a further 4 hours yielded an orange oil $\nu_{max.}$ (chloroform) 3460, 3365 (NH_2), 1724 (ester), which after diazotisation coupled with alkaline β-naphthol to give a red dye.

(iii) Diglyme (10 c.c.) was used to dissolve the diester (1.25 g.) and sodium borohydride (0.4 g.). To this well stirred solution was added anhydrous aluminium chloride (0.46 g.) in diglyme (1.5 c.c.). After five hours at room temperature, working up gave a glass. This gave a red dye when diazotised and coupled with alkaline β-naphthol. Attempted acetylation by refluxing with acetic anhydride (3 c.c.) in pyridine (5 c.c.) for half an hour gave a red oil which gave no solid on seeding with 4-N-acetylamino-phthalyl diacetate (described p..138).

Dimethyl 4-(toluene-p-sulphonamido)phthalate (149, 150, 155, 196).

Dimethyl 4-aminophthalate (0.5 g.) was heated at 100° with toluene-p-sulphonyl chloride (0.5 g.) to give an orange oil. Treatment with potassium bicarbonate (excess) followed by extraction with ethanol

gave an orange solution which when diluted with water gave white needles, m.p. 135-136° from benzene-light petroleum (b.p. 60-80°) of dimethyl 4-(toluene-p-sulphonamido)phthalate (0.3 g., 29%) (Found: C, 55.58; H, 4.84; N, 3.69. $C_{17}H_{17}NO_6S$ requires C, 56.18; H, 4.72; N, 3.86%).

4-(Toluene-p-sulphonamido)phthalyl diacetate (151, 156, 158, 178, 198).

The above diester (2.2 g.) was extracted from a soxhlet thimble onto well stirred lithium aluminium hydride (2.2 g.) in dry ether (150 c.c.). After eight hours the excess hydride was destroyed by adding ethyl acetate (20 c.c.). Decomposition of the complex with 6N-sulphuric acid (50 c.c.) followed by neutralisation of the acid layer with solid sodium bicarbonate and subsequent evaporation to dryness of both layers gave a white solid. This was extracted to give a glassy solid (0.2 g.) which on acetylation with acetic anhydride (3 c.c.) in pyridine (5 c.c.) gave 4-(toluene-p-sulphonamido)phthalyl diacetate as a granular powder from benzene-light petroleum (b.p. 80-100°), m.p. 123-124° (Found: C, 58.22; H, 5.19.

$C_{17}H_{21}NO_6S$ requires C, 58.29; H, 5.41%).

Bromination Reactions.

Brominations were conducted in a deep rectangular box lined with aluminium foil in which the reaction flask and a 300 or 1000 watt bulb, used for irradiation, were contained.

3-Nitro- and 4-nitro-xylene.

o-Xylene was nitrated by the method of Emerson and Smith[143] to give 3-nitro-o-xylene, b.p. 120°/10 mm., and 4-nitro-o-xylene, b.p. 134°/11 mm., m.p. 29-30°.

4-Nitro-o-xylylene dibromide (50, 67, 86).

4-Nitro-o-xylene (33 g.), in carbon tetrachloride (100 c.c.), was irradiated with light from a 300 watt bulb and vigorously stirred while bromine (70 g.) in carbon tetrachloride (100 c.c.) was added over 8 hours. Evaporation of the solution gave a brown oily liquid which deposited crystals of 4-nitro-o--xylylene dibromide (15.0 g., 22%), m.p. 82°, rhombs from ethanol (Found: C, 31.59; H, 2.24; Br, 51.48. $C_8H_7Br_2NO_2$ requires C, 31.10; H, 2.27; Br, 51.71%).

4-Nitrophthalyl diacetate (58, 68, 87).

4-Nitro-o-xylylene dibromide (1.5 g.) was stirred under reflux for two hours with potassium acetate (1.6 g.) in acetic acid (10 c.c.). The cooled reaction mixture was poured into water from which a brown solid separated. Recrystallisation from methanol gave white needles of 4-nitrophthalyl diacetate (1.1 g., 84%), m.p. 80-81° (Found: C, 54.26; H, 5.02. $C_{12}H_{13}NO_6$ requires C, 53.94; H, 4.91%).

4-Nitrophthalyl alcohol (59, 69, 89).

4-Nitrophthalyl diacetate (0.7 g.), suspended in absolute ethanol (5 c.c.) containing a trace of sodium, was allowed to stand at 0° for two days. During this time the diacetate slowly dissolved. Evaporation of the solution gave a pale yellow oil which on addition of benzene gave crystals of 4-nitrophthalyl alcohol (0.4 g., 86%), m.p. 88° from acetone-benzene (Found: C, 52.42; H, 4.62; N, 7.59. Calc. for $C_8H_9NO_4$: C, 52.44; H, 4.96; N, 7.65%). Tirouflet[124] gives m.p. 87-88°.

4-Aminophthalyl alcohol (76, 90).

4-Nitrophthalyl alcohol (4.5 g.) was dissolved in ethanol (20 c.c.) containing Raney nickel (1 g.) and allowed to stand for one hour. The mixture was filtered and Adams' catalyst (0.17 g.) added to the filtrate, which was hydrogenated at room temperature and pressure (uptake: 1.70 litres of hydrogen. Calc.: 1.65 Litres). Evaporation of the filtered solution gave 4-aminophthalyl alcohol, rhombs from benzene-ethanol (3.7 g., 95%), m.p. 96° (Found: C, 62.73; H, 7.24. $C_8H_{11}NO_2$ requires C, 62.72; H, 7.24%). This compound gave a red dye on diazotisation and coupling with β-naphthol. On storage it decomposed to give a solid, m.p. $> 300°$.

4-N-Acetylaminophthalyl alcohol (77, 93, 110, 128).

Acetic anhydride (1.33 g.) was added to 4-aminophthalyl alcohol (2.0 g.). A viscous brown solution was formed which after one hour was diluted with water (10 c.c.), the acetic acid produced then being neutralised with saturated sodium bicarbonate (15 c.c.). The solution was saturated with salt and extracted continuously with ether for 30 hours to give a brown

oil; this was extracted with ethanol, and evaporation of the extract gave, in poor yield 4-N-acetylaminophthalyl alcohol, which crystallised from ethanol;light petroleum (b.p. 60-80°) and had m.p. 104-106° (Found: C, 59.32; H, 6.55; N, 7.10. $C_{10}H_{13}NO_3$ requires C, 61.53; H, 6.65; N, 7.18%). Subsequent attempts to prepare this compound failed to give any crystalline product.

4-N-Acetylaminophthalyl dibenzoate (98).

A non-crystalline product (0.7 g.) from a later attempt to prepare 4-N-acetylphthalyl alcohol (see above) was dissolved in pyridine (20 c.c.) and treated at 0° with benzoyl chloride (2.5 g.) in pyridine (20 c.c.) to give 4-N-acetylaminophthalyl dibenzoate, needles (0.3 g., 21%) from aqueous methanol, m.p. 140--142° (Found: C, 72.10; H, 6.02; N, 3.34. $C_{24}H_{21}NO_5$ requires C, 71.45; H, 5.25; N, 3.47%).

4-N-Acetylaminophthalyl diacetate (94).

Crude 4-N-acetylaminophthalyl alcohol (1.5 g.) in pyridine (8 g.) was treated with acetic anhydride (4 g.) added dropwise with shaking. After two days the

solution was diluted with water and evaporated to an oil, which on trituration with water gave 4-N-acetylaminophthalyl diacetate (2.2 g., 76%), rhombs from benzene, m.p. 105-106° (Found: C, 59.88; H, 6.04; N, 4.98. $C_{14}H_{17}NO_5$ requires C, 60.18; H, 6.14; N, 5.02%).

2-Nitro-p-xylylene dibromide (57, 79, 107).

2-Nitro-p-xylene (75 g.) in carbon tetrachloride (500 c.c.), irradiated by a 1000 watt bulb, was stirred and treated with bromine (180 g.) in carbon tetrachloride (250 c.c.) over eight hours. Evaporation of the solvent gave an oily solid which crystallised from ethyl acetate to give rhombs of 2-nitro-p-xylylene dibromide (20 g., 13%), m.p. 91° (Found: C, 31.51; H, 2.59; Br, 51.16. $C_8H_7Br_2NO_2$ requires C, 31.10; H, 2.27; Br, 51.71%).

2-Nitroterephthalyl diacetate (64, 85, 134).

Pure 2-nitro-p-xylylene dibromide (20 g.) was stirred under reflux for three hours with potassium acetate (30 g.) and glacial acetic acid (70 c.c.). The cooled mixture was poured into water (100 c.c.).

and the deposited solid crystallised from methanol (charcoal) to give 2-nitroterephthalyl diacetate (7.5 g., 44%), m.p. 47° (Found: C, 53.84; H, 4.76; N, 5.27. $C_{12}H_{13}NO_6$ requires C, 53.94; H, 4.91; N, 5.25%).

2-Nitroterephthalyl alcohol (88).

2-Nitroterephthalyl diacetate (7.5 g.) was added to dry ethanol containing a trace of sodium and left at 0° for a day. During this time the solid dissolved and was replaced by needles of 2-nitroterephthalyl alcohol (4.0 g., 60%), m.p. 95° from ethyl acetate (Found: C, 52.20; H, 4.69; N, 7.52. $C_8H_9NO_4$ requires C, 52.44; H, 4.96; N, 7.65%).

2-Aminoterephthalyl alcohol (92).

2-Nitroterephthalyl alcohol (4 g.) was hydrogenated in the same way as 4-nitrophthalyl alcohol using Adams' catalyst in ethanol to give 2-aminoterephthalyl alcohol (8 g., 90%), m.p. 131-132°, plates from ethyl acetate (Found: C, 63.06; H, 7.28. $C_8H_{11}NO_2$ requires C, 62.72; H, 7.24%). This compound quickly decomposed on exposure to air.

3-Nitro-o-xylylene dibromide (25, 26, 32, 60, 65).

3-Nitro-o-xylene (20 g.), in dry carbon tetrachloride (80 c.c.) was brominated in essentially the same way as the 4-isomer by the addition of bromine (46 g.) in carbon tetrachloride (120 c.c.) which irradiated by light from a 1000 watt bulb. The working up process gave a dark brown oil from which no solid separated. Distillation under high vacuum gave no uniform fraction but analyses of samples b.p. $130\text{-}140^{\circ}/10^{-4}$ mm., n_D^{20} 1.6227 and $140\text{-}142^{\circ}/10^{-4}$ mm., n_D^{20} 1.6316 (Found: Br, 51.25 and Br, 50.56. $C_8H_7Br_2NO_2$ requires Br, 51.71%) indicated dibromination.

3-Nitrophthalyl diacetate and 3-nitrophthalyl alcohol (37, 38, 65, 66, 82, 83).

The crude dibrominated compound from above (160 g.) was refluxed with potassium acetate (200 g.) in glacial acetic acid (500 c.c.) for 30 hours with vigorous stirring. The acetic acid was distilled off, the brown residue poured into water (500 c.c.) and extracted with ether (3 x 500 c.c.) to give an oil, which was distilled at $120^{\circ}/10^{14}$ mm., n_D^{21} 1.5415. The infrared spectrum, $\nu_{max.}$ 1740, 1702 cm.$^{-1}$, indicated the

presence of both acetate and aldehyde groupings. Fractional distillation of this material gave an impure product, a portion of which gave a precipitate with 2,4-dinitrophenylhydrazine; purification by chromatography on bentonite-Kieselguhr, and elution with chloroform, gave the 2,4-dinitrophenylhydrazone, m.p. 267° (Found: C, 48.72; H, 3.19; N, 20.19. $C_{14}H_{11}N_5O_6$ requires C, 48.70; H, 3.21; N, 20.29%), of either 3- or 6-nitro-o-tolualdehyde.

Another portion (5 g.) of the oil was diluted with ethanol (20 c.c.) containing a trace of sodium and left at 0° for three days. Addition of water (1 c.c.) followed by evaporation yielded an orange oil, b.p. $100°/10^{-4}$ mm., n_D^{20} 1.5730, (Found: C, 57.85; H, 4.99; N, 8.66. $C_8H_9NO_3$ requires C, 57.47; H, 5.43; N, 8.38%) which was probably 2-methyl-6-nitrobenzyl alcohol and/or 2-methyl-3-nitrobenzyl alcohol.

4-Nitro-m-xylylene dibromide (70, 71).

4-Nitro-m-xylene (75 g.) in carbon tetrachloride (200 c.c.) was treated with bromine (160 g.) in carbon tetrachloride (300 c.c.) while irradiated with light from a 1000 watt bulb in the same manner as 2-nitro-

-p-xylene. Evaporation of the solvent yielded an orange oil (125 g.), used crude in the next stage.

4-Nitroisophthalyl diacetate (72, 73, 74, 75).

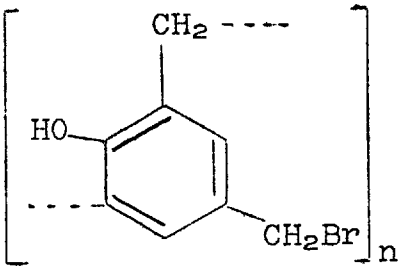
The orange oil (125 g.) was treated with potassium acetate (200 g.) in glacial acetic acid (500 c.c.) by the method already described. Working up in the normal way gave a thick orange oil which on distillation yielded 6-nitro-m-toluic aldehyde as pale yellow needles b.p. $120^{\circ}/10^{-2}$ mm., m.p. 65-66°, previously described by Suida[125] (Found: C, 57.55; H, 4.04; N, 8.39. Calc. for $C_8H_7NO_3$: C, 58.15; H, 4.22; N, 8.48%), $\nu_{max.}$ in carbon tetrachloride 1701 $cm.^{-1}$ A fraction, b.p. $140\text{-}160^{\circ}/10^{-2}$ mm., crystallised from ethanol to give 4-nitroisophthalyl diacetate, m.p. 53-54° (Found: C, 54.33; H, 4.93; N, 5.31. $C_{12}H_{13}NO_6$ requires C, 53.92; H, 4.90; N, 5.27%).

4-Hydroxyisophthalyl alcohol (153).

This was obtained by reducing dimethyl 4-acetoxy-isophthalate with lithium aluminium hydride according to the method of Freeman[145] and had m.p. 89-90° (yield 62%); he quotes m.p. 91.7-92.5° (yield 79%).

Reactions of 4-hydroxyisophthalyl alcohol with hydrogen bromide, etc. (170, 174, 176, 187, 189, 191).

(i) The triol (100 mg.) was added to 47% aqueous hydrobromic acid (3 c.c.). Reaction occurred to give an oil which solidified to a pink brittle solid, m.p. >300°, insoluble in all the normal organic solvents $\nu_{max.}$ (KBr disc) 3571 and 1261 cm.$^{-1}$ (Found: Br, 36.74. Calc. for $C_8H_8Br_2O$: Br, 57.20%; Calc. for a polymer of the type (I), $(C_8H_7BrO)_n$, Br, 40.02%).



(I)

(ii) The above triol (400 mg.) was treated with 47% aqueous hydrobromic acid (10 c.c.) as before. Filtration and evaporation of the resulting solution gave a glass which was soluble in ethyl acetate. Extraction with this solvent gave a red glass m.p. $>300^{\circ}$ (Found: Br, 35.18%).

(iii) Addition of concentrated hydrochloric acid (3 c.c.), with stirring, to the triol (50 mg.) gave a pink oil which solidified in half an hour to give a pink glass, m.p. $>300^{\circ}$, similar to those above.

(iv) A suspension of the triol (200 mg.) in chloroform (8 c.c.) treated with dry hydrogen chloride gas at room temperature dissolved, with the deposition of oily droplets. After ten minutes at room temperature the mixture was evaporated at $<20^{\circ}$ to give a brown glass of indeterminate melting point which could be precipitated from benzene by light petroleum (b.p. 60-80°). The infrared spectrum (in nujol) was essentially the same as obtained in (i) above.

(v) A solution of the triol (200 mg.) in pyridine (1 c.c.) was treated with thionyl chloride (400 mg.) in pyridine (1 c.c.). When the initial reaction had subsided the mixture was heated at 100° for two hours.

After evaporation and extraction with water there remained a brown brittle glass, m.p. $>280^{\circ}$. A direct treatment of the triol (100 mg.) with thionyl chloride (400 mg.) was accompanied by a vigorous reaction to give a brown oil. Stored over potassium hydroxide, under vacuum, the oil solidified to a brittle brown solid, m.p. $>300^{\circ}$.

Improved preparation of the phthalyl alcohols and attempted syntheses of their ditoluene-p-sulphonyl and dimethanesulphonyl derivatives.

Terephthalyl alcohol (111, 113)

p-Xylylene dibromide (25 g.) was stirred under reflux with potassium acetate (50 g.) in glacial acetic acid (100 c.c.) for 4 hours. The cooled mixture was poured onto crushed ice and the precipitated yellow solid was recrystallised from aqueous methanol to give terephthalyl diacetate (18 g., 86%), m.p. 49° (Found: C, 64.92; H, 6.57. $C_{12}H_{14}O_4$ requires C, 64.85; H, 6.35%). This diacetate (18 g.) was catalytically

deacetylated by a trace of sodium in dry ethanol (50 c.c.) for two days at 0° to give terephthalyl alcohol (9 g., 80%) m.p. 114-116°.

Attempted toluene-p-sulphonation of terephthalyl alcohol (115, 118).

(i) Method of Kochi and Hammond.[129]

Terephthalyl alcohol (5 g.) was refluxed with sodium hydride (3.6 g.) in dry ether (150 c.c.) for twenty hours. After having been cooled to -30° the milky reaction mixture was treated with toluene-p-sulphonyl chloride (13.6 g.) in dry ether (80 c.c.) over an hour. The mixture was quickly filtered and cooled to -30° yielding a crystalline material (0.4 g.), m.p. 65-70° identified as unreacted toluene-p-sulphonyl chloride.

(ii) Method of Sekera and Marvel.[146]

Terephthalyl alcohol (0.5 g.) in dry pyridine (10 c.c.) was added to toluene-p-sulphonyl chloride (1.5 g.) in pyridine (10 c.c.) at -10°. The resulting pale yellow solution was allowed to stand at 0°C for three hours, then diluted with water (10 c.c.). No solid product could be isolated.

Attempted methanesulphonylation of terephthalyl alcohol (116, 120).

(i) Substituting methanesulphonyl chloride for toluene-p-sulphonyl chloride in the method of Sekera and Marvel[146] in the reaction with terephthalyl alcohol (0.5 g.) an unidentified product, m.p. ca. 240°, needles from ethanol, was obtained (Found: C, 63.57; H, 6.07; N, 7.96%). This compound contained halogen but no sulphur. A similar reaction conducted with the diol (0.5 g.) and methanesulphonyl chloride (0.9 g.) in pyridine (8 c.c.) gave in very poor yield p-xylylene dichloride, m.p. 100-101°, rhombs from light petroleum (b.p. 40-60°).

Isophthalyl alcohol (112, 114).

Treatment of m-xylylene dibromide (20 g.) with potassium acetate (50 g.) in glacial acetic acid (100 c.c.) under reflux for three hours gave on cooling and treatment with cold water (500 c.c.) an oil, isolated by ether extraction. Distillation yielded isophthalyl diacetate (6 g., 36%), b.p. 118°/10^{-2} mm. (Found: C, 64.77; H, 6.34. $C_{12}H_{14}O_4$ requires C, 64.85; H, 6.35%). This diacetate (6 g.) was deacetylated, in

dry ethanol (20 c.c.) containing a trace of sodium, for one day. Evaporation of the solvent yielded an oil which crystallised on addition of benzene to give isophthalyl alcohol (1.9 g., 51%) m.p. 49-51°.

In a series of methanesulphonylation reactions conducted on isophthalyl alcohol, no solid product could be isolated.

Phthalyl alcohol (122, 123).

o-Xylylene dibromide (200 g.) was converted, by the method described for terephthalyl alcohol, to phthalyl diacetate (80 g., 48%), m.p. 51°. Deacetylation of this product (80 g.) gave phthalyl alcohol (33 g., 77%), m.p. 62-63°, rhombs from ethyl-acetate-light petroleum (b.p. 60-80°).

Attempted methanesulphonylations and toluene-p--sulphonylations were unsuccessful.

Diethyl αα'-dibromoadipate (1)

This compound, m.p. 66°, was prepared according to the method of Guha and Sankaran,[149] the oily product being recrystallised from light petroleum (60-80°). Le Sueur[150] gives m.p. 67°.

Diethyl αα'-diodoadipate (2)

The method quoted by Ingold[151] starting with the dibromo compound, was employed and yielded a product m.p. 92°. He quotes m.p. 92°.

o-Xylylene dibromide (41, 42, 46).

This compound, m.p. 92°, was prepared first by the method of Stephensen[140] who quotes m.p. 89-93°, and later utilising carbon tetrachloride as solvent (see bromination of the nitroxylenes).

o-Xylylene di-iodide (44).

This compound, m.p. 109°-110°, was obtained by the method of Leser[147] who quotes m.p. 109-110°.

p-Xylylene dibromide (45).

A sample of this compound, m.p. 146°, was available.

m-Xylylene dibromide (52).

This compound, m.p. 77°, was obtained by the same method as was used for brominating the nitro xylenes. Radziszewski et al.[148], quote m.p. 77°.

Kinetic Experiments

Reaction of benzyl chlorides with 2-mercaptoethanol (279-293, 474 et seq.).

These kinetic experiments were conducted in one of two ways depending upon the amount of benzyl chloride available:

(i) A solution of sodium carbonate decahydrate (15.0 g.) in distilled water (60.0 c.c.) was placed in a flask equipped with an efficient stirrer, accurate thermometer and nitrogen lead. The flask was three quarters immersed in a trough of water thermostatically controlled at 30° and to the well stirred solution was added pure dioxan (120.0 c.c.) which caused partial precipitation of the sodium carbonate. The stream of oxygen-free nitrogen, saturated with aqueous dioxan, was started and the reaction vessel left for 30 minutes to attain the bath temperature. 2-Mercaptoethanol was added with dioxan washings (15.0 c.c.) bringing the total volume of the solution to 195.0 c.c. The amount of 2-mercaptoethanol used was such that the solution (195.0 c.c.) was ca. 0.1053 N with respect to the thiol. The suspension was stirred for 15 minutes and then a

portion (5.0 c.c.) was withdrawn, acidified with 2N hydrochloric acid (10 c.c.) and the thiol concentration estimated by titration with standard aqueous iodine using a starch indicator. There remained behind in the reaction vessel a suspension (190.0 c.c.), ca. 0.1053N). The benzyl chloride (0.02 moles) was poured into the flask with dioxan washings (10.0 c.c.) and a stop clock started. At intervals, portions (10.0 c.c.) of the reaction mixture were withdrawn, acidified with 2N hydrochloric acid (20 c.c.) and titrated with standard aqueous iodine using a starch indicator.

Using the equation

$$k = \frac{1}{t} \frac{x}{a(a - x)}$$

graphs were plotted of t in minutes against $\left(\frac{x}{a - x}\right)$. The initial concentration, a, of each reactant was taken as 0.1000 g. mole. $litre^{-1}$.

The value x, was determined by calculating the thiol titration for t=0 for 10.0 c.c. of solution, allowing for the dilution of the original 190.0 c.c. to 200.0 c.c. assuming no halide had been added. The equation used was

$$x_1 = \frac{\text{titration}_{(t=0)} - \text{titration}_{(t=t)}}{\text{titration}_{(t=0)}}$$

The value of k was determined by taking the slope of the best straight line through the origin and extending over the initial 60-70% of the reaction.

(ii) Sodium carbonate decahydrate (7.5 g.) in distilled water (30.0 c.c.) was placed in a suitable flask, equipped with an efficient stirrer, thermometer and nitrogen lead, immersed in a thermostat at 30°. Pure dioxan (50.0 c.c.) was added to the well stirred solution causing partial precipitation of the sodium carbonate. At this point the solution registered pH. 8-9. A flow of nitrogen (saturated with aqueous dioxan) was started and the flask allowed to maintain 30° over 30 minutes. 2-Mercaptoethanol (0.01 moles.) was added with dioxan washings (7.0 c.c.) followed after an interval of ten minutes by the benzyl halide (0.01 moles.) with dioxan washings (13.0 c.c.). There resulted a solution (100.0 c.c.), 0.1000 N with respect to both thiol and benzyl chloride. As the chloride was added a stop-clock started and portions (5.0 c.c.) of the reaction mixture were periodically withdrawn, acidified with 2N hydrochloric acid (10 c.c.) and titrated with standard aqueous iodine using a starch indicator. The same equation

$$k = \frac{1}{t} \frac{x}{a\,(a - x)}$$

was employed.

The titration value for t=0 for 5 c.c. of solution was calculated theoretically from the amount of 2-mercaptoethanol taken and the same equation as before was used to evaluate x. The value of k was determined graphically.

Reaction of benzyl bromides with 2-mercaptoethanol

Sodium carbonate decahydrate (7.5 g.) in distilled water (30.0 c.c.) was cooled in a reaction vessel similar to that used for chloride work by immersion in ice-water. Pure dioxan (50.0 c.c.) was added to the stirred solution and the nitrogen flow started; precipitation of the sodium carbonate occurred. The stirred mixture was left for one hour during which time the internal temperature fell and became constant at 2-3°. 2-Mercaptoethanol (0.01 moles.) in dioxan (7.0 c.c.) was added followed after a 10 minute interval by the bromide (0.01 moles.) in dioxan (13.0 c.c.). A stop-clock was started and portions (5.0 c.c.) of the mixture were periodically withdrawn, acidified with 2N-hydrochloric

acid (10 c.c.) and titrated with standard aqueous iodine using a starch indicator. Graphs were constructed as for the benzyl chloride and the values of k determined from their slopes.

Kinetic Results for Representative Compounds

Reaction between benzyl chloride and 2-mercaptoethanol (492).

$$T = 30^{\circ}$$

The reaction mixture was N/10 with respect to both benzyl chloride and 2-mercaptoethanol.

10 c.c. of the initial thiol solution was equivalent to 14.40 c.c. of standard iodine solution.

The value a in the subsequent tables is 0.1000 and x is obtained by the equation

$$\frac{14.40 - \text{titration value}}{14.40}$$

Time min.	Time sec.	Titration value in c.c.	x	$\frac{x}{a(a-x)}$	k
2	15	11.92	0.1723	0.2082	0.09253
6	40	10.26	0.2875	0.4035	0.06049
10	50	9.24	0.3583	0.5584	0.05156
15	45	8.36	0.4195	0.8382	0.05349
21	55	7.39	0.4868	0.9486	0.04346
27	5	6.62	0.5403	1.175	0.04339
32	35	6.05	0.5799	1.380	0.04236
40	35	5.26	0.6347	1.737	0.04281
52	5	4.31	0.7006	2.340	0.04493
69	40	3.28	0.7722	3.390	0.04866
91	37	2.22	0.8458	5.485	0.05986

k (estimated graphically)= 0.044 1.mole.min.$^{-1}$ (see p.79a).

Reaction between o-methoxy chloride and 2-mercaptoethanol.

(495)

$T = 30^{o}$

The reaction mixture was N/10 with respect to both o-methoxybenzyl chloride and 2-mercaptoethanol.

10 c.c. of the initial thiol solution were equivalent to 14.36 c.c. of the standard iodine solution.

$$x = \frac{14.36 - \text{titration value}}{14.36}$$

Time min.	sec.	Titration value in c.c.	x	$\frac{x}{a(a-x)}$	k
2	5	11.86	0.1741	0.2108	0.1013
5	42	10.89	0.2419	0.3187	0.05591
10	6	10.06	0.2994	0.4274	0.04231
14	45	9.38	0.3468	0.5309	0.03600
20	15	8.56	0.4039	0.6776	0.03346
25	58	7.75	0.4603	0.8529	0.03284
31	55	7.09	0.5062	1.039	0.03212
37	58	6.38	0.5557	1.251	0.03294
48	13	5.40	0.6239	1.659	0.03440
58	0	4.61	0.6790	2.115	0.03647
69	28	3.79	0.7360	2.788	0.04013
84	20	2.95	0.7945	3.866	0.07150

k (estimated graphically= 0.034 l.mole.min.$^{-1}$ (see p. 79b).

Reaction between o-methylmercaptobenzyl chloride and 2-mercaptoethanol (509).

$T = 30^{\circ}$

The reaction mixture was N/10 with respect to both o-methylmercaptobenzyl chloride and 2-mercaptoethanol.

10 c.c. of the thiol solution were equivalent to 14.26 c.c. of the standard iodine solution.

$$x = \frac{14.26 - \text{Titration result}}{14.26}$$

Time min.	Time sec.	Titration value in c.c.	x	$\frac{x}{a(a-x)}$	k
1	43	11.85	0.1690	0.2034	0.116
5	40	10.41	0.2700	0.3699	0.063
9	33	9.21	0.3542	0.5491	0.058
13	40	8.40	0.4110	0.6977	0.051
18	23	7.52	0.4727	0.8961	0.049
24	12	6.60	0.5372	1.161	0.048
29	25	5.82	0.5919	1.450	0.049
36	13	5.10	0.6424	1.797	0.0495
42	45	4.31	0.6978	2.309	0.054
49	30	3.72	0.7393	2.835	0.055
61	0	2.88	0.7993	3.982	0.066

k (estimated graphically)= 0.050 $l.mole.min.^{-1}$ see p.79c).

The results of these and of the other kinetic experiments are summarised in the Tables on pp. 81 and 82.

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