A thesis entitled

'STUDIES ON SOME POTENTIALLY CYTOTOXIC NITROGEN MUSTARDS AND RELATED COMPOUNDS'

submitted by

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ABSTRACT

In the introduction, the chemistry of compounds of the nitrogen mustard type has been reviewed with particular reference to their use in the chemotherapy of cancer.

The first part of the work described in this thesis concerns the preparation of some potentially cytotoxic nitrogen mustard carbamates obtained i) from the reaction of p-(bis-2-chloroethylamino)phenol with some substituted phenyl isocyanates and ii) from the reaction of a range of substituted phenyl chloroformates with NN-bis-(2-chloroethyl)-p-phenylene-diamine (and, in one case, its m-isomer). A new method of preparation of NN-bis-(2-chloroethyl)-p-phenylenediamine is described and the new secondary mustard amine, NN-bis-(2-chloro-ethyl)-N'-methyl-p-phenylenediamine, is reported.

Biological results (provided by Dr. P. Hebborn) are tabulated and briefly discussed. Some of the carbamate compounds have remarkably high chemotherapeutic indices.

In Part 2, the preparations of the dimethanesulphonates of 2-N-methylanilinopropane-1,3-diol and 3-N-methylanilino-propane-1,2-diol are described. The mechanism of the alkylating reactions of these dimethanesulphonates was investigated by a study of their reactions with various nucleophiles. The results prove that all of these reactions involve an intermediate

aziridinium ion, although in the reactions with sodium thiophenate some direct displacement of methanesulphonyloxy was observed, without participation by nitrogen. With methanol the aziridinium ion reacts only at the secondary position giving rise exclusively to 1,2-dimethoxy-3-N-methylanilinopropane irrespective of which dimethanesulphonate is used in the reaction; with sodium methoxide and with potassium acetate mixtures of products are obtained, resulting from attack both at the secondary and the primary positions of the aziridinium ion. The course of the alkylating reaction is therefore influenced by the nature of the nucleophile.

ACKNOWLEDGEMENTS

I would like to express my gratitude to Professor L.N. Owen for his advice and encouragement throughout the course of this work.

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CONTENTS

Page

THE CHEMOTHERAPY OF CANCER 7

THE CHEMISTRY OF NITROGEN MUSTARDS 10

DRUG DESIGN 29

DISCUSSION AND RESULTS :-

Part 1: Some Carbamates Derived from Aromatic Nitrogen Mustards.

p-(Bis-2-chloroethylamino)phenol 43

NN-Bis-(2-chloroethyl)-p-phenylenediamine

and its m-isomer 47

NN-Bis-(2-chloroethyl)-N'-methyl-p-phenylenediamine . . 61

Biological Results 67

Part 2 : Studies on the Mechanism of the Alkylation Reactions of Compounds of the Nitrogen Mustard Type.

The Dimethanesulphonates of 2-N-methylanilinopropane-1,3-diol

and 3-N-methylanilinopropane-1,2-diol 73

Reactions of the above Dimethanesulphonates 84

EXPERIMENTAL :-

Some carbamates derived from

p-(bis-2-chloroethylamino)phenol 97

CONTENTS

Page

Substituted phenyl chloroformates 108

Some carbamates derived from NN-bis-(2-chloroethyl)-p-phenylenediamine and its m-isomer 124

NN-Bis-(2-chloroethyl)-N'-methyl-p-phenylenediamine . . 140

The Dimethanesulphonates of 2-N-methylanilinopropane-1,3-diol and 3-N-methylanilinopropane-1,2-diol 146

REFERENCES 162

THE CHEMOTHERAPY OF CANCER

The past two decades have seen much scientific research directed to the examination of the causes and treatment of the group of diseases known collectively as cancer. As an adjunct to surgical and radiation treatments, a search has been made for chemicals which will selectively destroy cancerous tissue while causing as little damage as possible to normal cells. Unfortunately, cancer cells are very similar to those of normal tissue and selectivity of action is difficult to achieve.

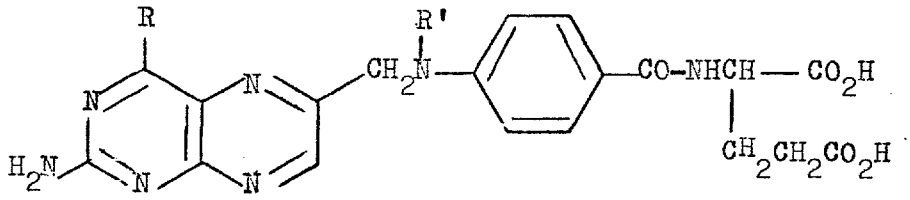
Many plant products and antibiotics have been examined for their potential as anti-cancer drugs and some have proved effective. Similarly, hormone therapy is of value in the treatment of certain tumours but it is not proposed to review the large field of anti-cancer drugs. Excellent reviews have been published[1,2] and these give a detailed coverage of this subject.

Certain tumours have been found sensitive to the enzyme L-asparaginase[3]. This is because of their inability to synthesize asparagine and their consequent dependence on the blood as a source of this amino acid. The therapeutic value of L-asparaginase is rather limited but this rare example of a fundamental difference between tumour and normal cells is worth noting.

Anti-metabolites are essentially anti-growth agents and as such have proved effective in the treatment of some

forms of cancer in which the cells are rapidly proliferating. However side effects have proved hard to avoid.

As their name implies, the anti-metabolites act by interfering with the metabolism of compounds essential for cell growth. Usually the anti-metabolite has a structure which resembles that of the compound with which it interferes. This is illustrated by the case of methotrexate (1a) which is an analogue of folic acid (1b) with which it interferes by blocking the active site of the enzyme responsible for its reduction.



1 a R= NH_2 ; R' = Me

b R= OH ; R' = H

Some anti-metabolites which interfere with purine and pyrimidine are also known to be effective anti-tumour agents[4].

Possibly the largest group of compounds that has been examined for anti-tumour properties are those known as biological alkylating agents. Ethylene imines, epoxides and methanesulphonates all come under this heading and the chemistry

and biological properties of these and other alkylating agents are discussed in great detail by Ross[5].

Sulphur mustard gas has long been known as a chemical warfare agent and the related nitrogen mustards, of general formula 2, were extensively examined during the war. The nitrogen mustard known as HN2 (2,R=Me) was found to have some value in the treatment of leukemia and a search was made for more effective nitrogen mustards for the treatment of cancer. The similar effects of nitrogen mustards and X-rays caused the former to be called 'radio-mimetic agents' but Alexander[6] has now called for the abandonment of this concept.

Many modifications of the structure of nitrogen mustards have been made in the search for more effective drugs and most of those prepared have been of the so-called two-armed type - that is with two reactive 2-chloroethyl groups attached to nitrogen, as in 2. The lack of selectivity of these compounds and their high toxicity have proved to be great obstacles and the number of clinically useful compounds remains low. However, the design of selectively acting nitrogen mustards by suitable structural modifications is an interesting challenge.

$$R\text{-}N(CH_2CH_2Cl)_2$$

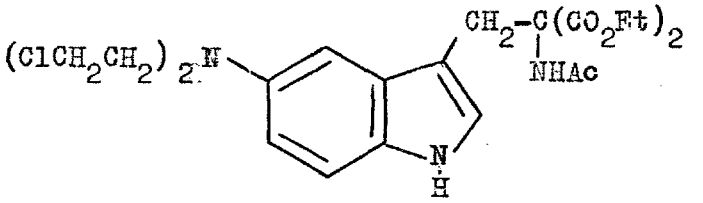
(2)

THE CHEMISTRY OF NITROGEN MUSTARDS

Preparation;

The usual method of preparation of nitrogen mustards involves the chlorination of the corresponding ethanolamine using conventional chlorinating agents[7,10]. Phosphorus oxychloride and phosphorus pentachloride are the most commonly used such reagents although DeGraw et. al.[8] report the use of methane-sulphonyl chloride in pyridine for the preparation of the compound (3) from the corresponding diol. The use of thionyl chloride is also quite usual but the formation of cyclic sulphites is then possible[9].

The diols required for these preparations are usually prepared by the action of ethylene oxide on the parent primary amine using aqueous acetic acid as solvent.

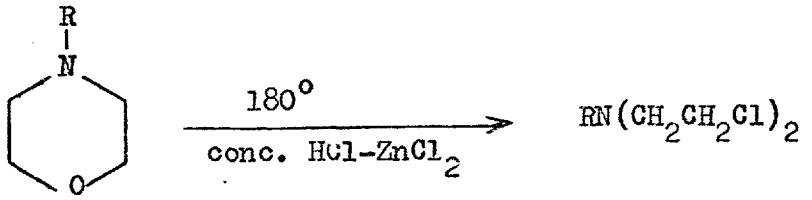


(3)

A recent report[12] concerns the preparation of some aromatic nitrogen mustards by the hydrolysis of the corresponding substituted morpholines, fig. 1.

The bromo analogues of these compounds may be prepared by similar methods but the exchange of bromine for chlorine using lithium bromide has been reported[13]. The displacement of toluene-p-sulphonate by fluoride was used to prepare some aryl-2-fluoroethylamines[28].

Fig. 1



R= 4-BrC_6H_4 , 4-tolyl ,
1-naphthyl.

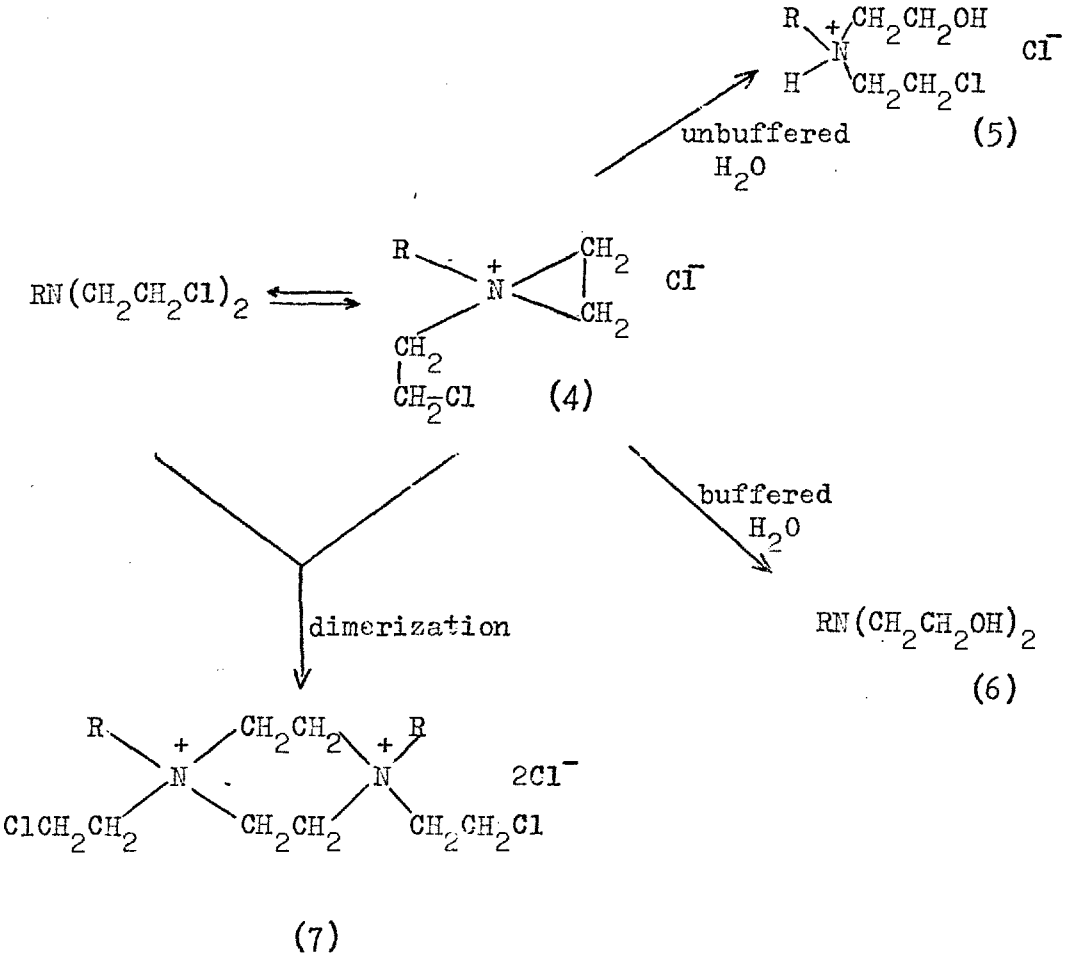
Reactions with nucleophiles;

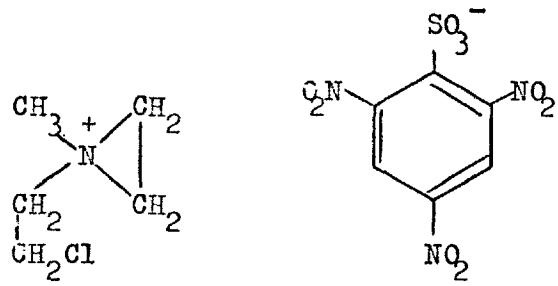
The work of Hanby and Rydon[14] showed that simple alkyl-di-2-chloroethylamines, when dissolved in water, rapidly cyclized to give aziridinium ions of general formula (4), fig.2. The instantaneous thiosulphate titre of such solutions showed the presence of free chloride ion- nearly one equivalent - and Golumbic[15] succeeded in isolating the picryl sulphonate (8) from a solution of methyl-di-2-chloroethylamine. N.m.r. spectroscopy has shown the presence of a cyclic ion in the deuterium oxide solution of diethyl-2-chloroethylamine[17].

In unbuffered solution, alkyl-di-2-chloroethylamines give a half hydrolysis product (5) which is presumably stabilized as the hydrochloride. The use of bicarbonate buffer causes the hydrolysis to go to completion[15] with the formation of the diol (6). Dimerization can also occur[14] resulting in the formation of piperazinium dichlorides (7). In dilute solution however, the hydrolysis products predominate.

Although the formation of three or four membered rings is energetically unfavourable, the entropy requirements are less than those necessary for bimolecular displacement reactions in which two separate molecules are involved[16]. It is generally accepted then, that the reactions of alkyl nitrogen mustards proceed with the formation of an intermediate

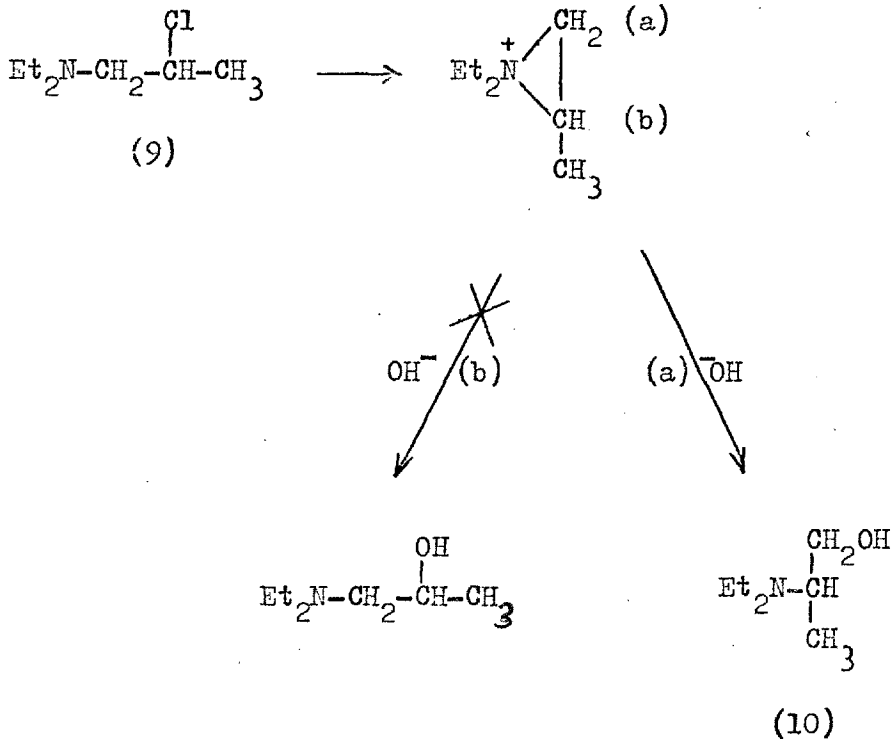
Fig.2.


unbuffered
H_2O
(5)
$RN(CH_2CH_2Cl)_2$
(4)
buffered
H_2O
$RN(CH_2CH_2OH)_2$
(6)
dimerization
$2Cl^-$
(7)



(8)

Fig. 3.



(9)

(10)

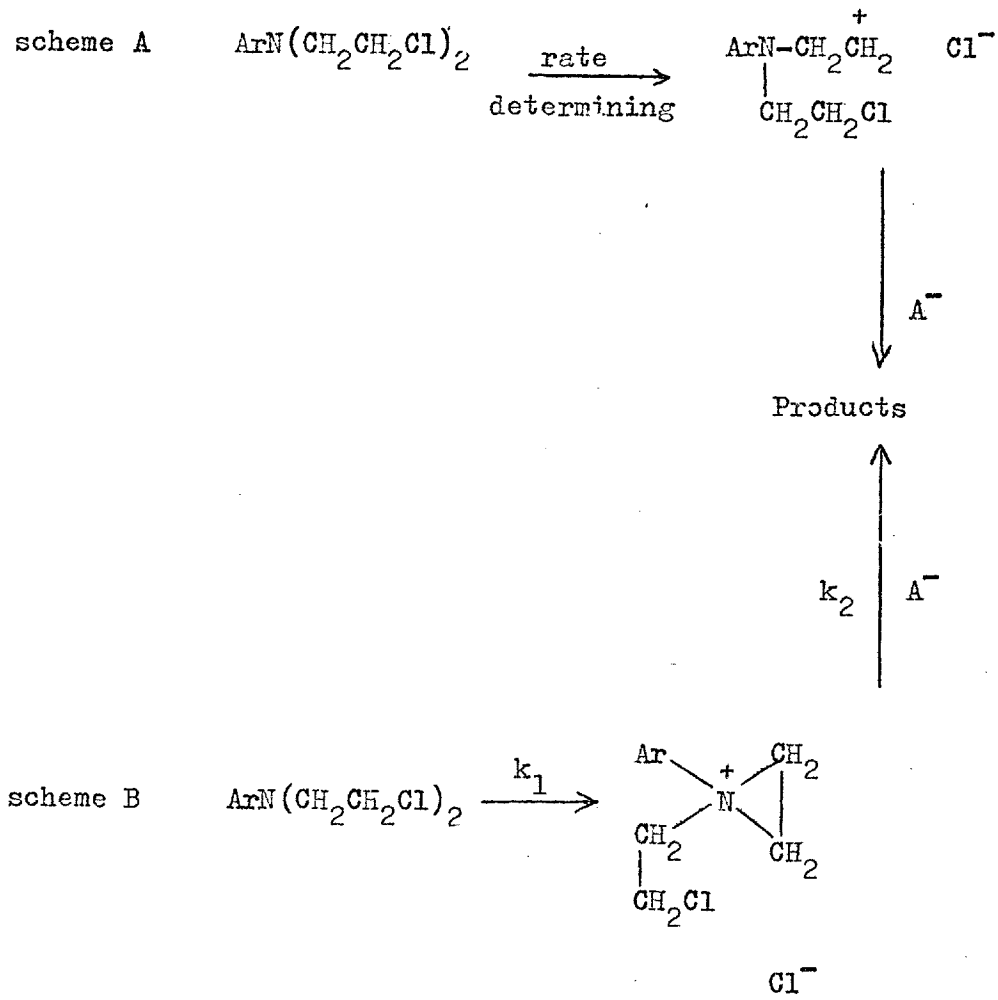
aziridinium ion (4). In principle this ion may react by collapse to a carbonium ion which can then react with a nucleophilic species but Price[17] doubts the intermediacy of carbonium ions in the reactions of either alkyl or aryl nitrogen mustards.

When the intermediate aziridinium ion is of an unsymmetrical nature a mixture of products or a rearranged product may be formed depending on the site(s) of attack by the nucleophile. Thus, S.D. Ross[18] found that 1-diethylamino-2-chloropropane (9) reacted with aqueous base to give the rearranged product (10). This resulted from attack at the primary carbon atom (a) of the intermediate, see fig.3.

The rates of hydrolysis of alkyl nitrogen mustards have been found to increase with their basicity[16]. Although greatly reduced, the basicities of aromatic nitrogen mustards also parallel their rates of hydrolysis as measured by the standard method of Ross[10]. However, the mechanism of reaction of aromatic nitrogen mustards has been considered to involve a carbonium ion intermediate as shown in scheme A, fig. 4. The formation of the carbonium ion is considered to be rate determining and the following evidence was advanced in support of this scheme[10]:

i) the hydrolysis reaction followed first order kinetics.

Fig.4


scheme A
ArN(CH2CH2Cl)2
rate determining
ArN-CH2CH2+
CH2CH2Cl
Cl−
A−
Products
k2
A−
scheme B
ArN(CH2CH2Cl)2
k1
Ar
N+
CH2
CH2
CH2
CH2Cl
Cl−

ii) added chloride ion reduced the degree of hydrolysis.

iii) there was an approximate correlation between the basicities of the parent amines and the ease of hydrolysis of the mustards.

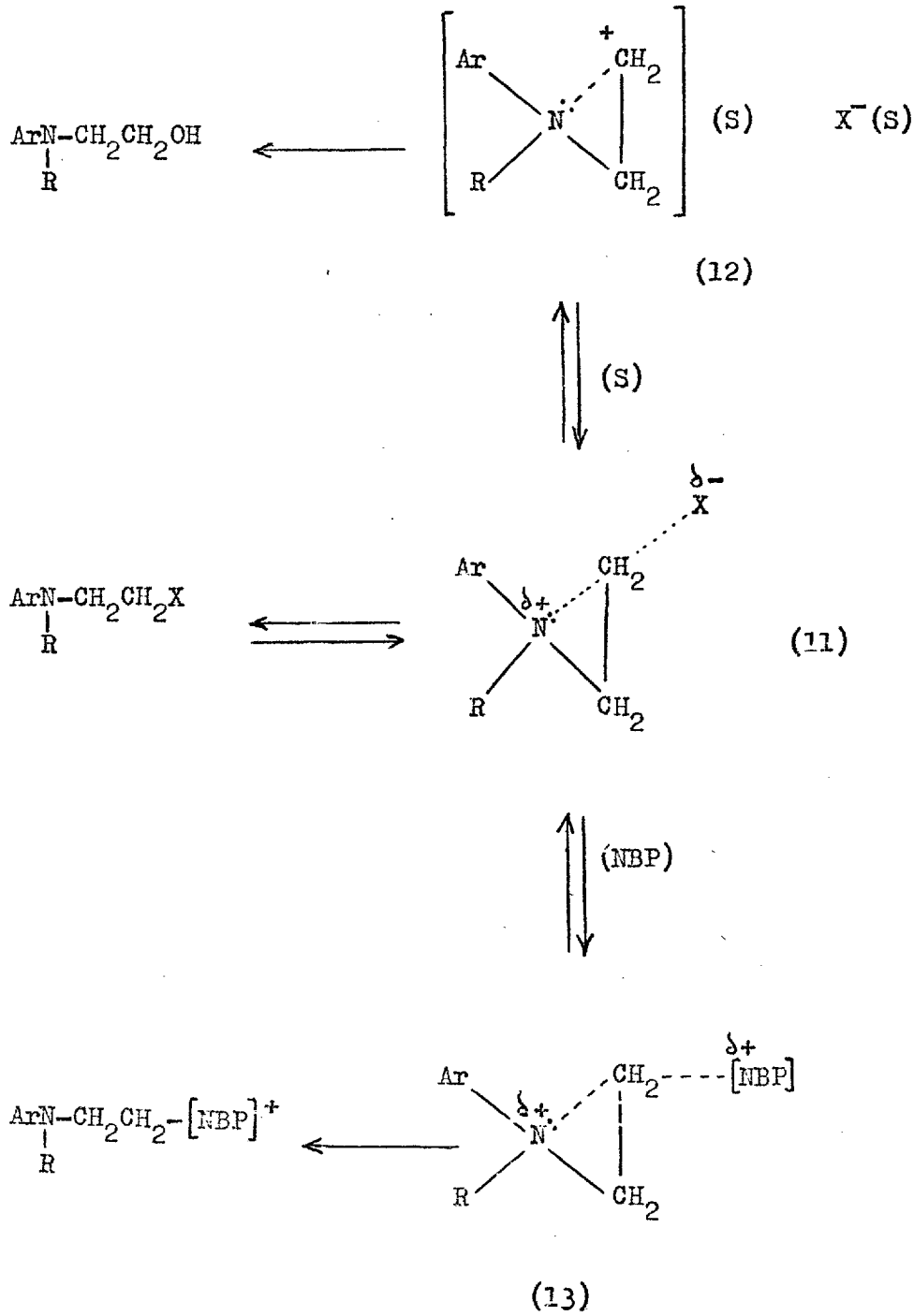
iv) chloride and hydrogen ions were liberated simultaneously.

Other authors have criticized this scheme and suggested scheme B, fig. 4, in its place[17,19]. The observation of first order kinetics does not distinguish between these possibilities if one considers that $k_2 > k_1$. For the same reason one would expect simultaneous liberation of chloride and hydrogen ion to result from either mechanism. The observed common ion effect would only be indicative of an S_N1 mechanism if a simple displacement reaction were under consideration and it seems more reasonable to correlate the basicity of the nitrogen atom with the rate of reaction on the basis of scheme B, fig. 4, which involves participation by the lone pair of electrons of the nitrogen atom.

Certainly the difference between the basicities of alkyl and aryl nitrogen mustards appears to have an effect on the reactions of these compounds. It seems reasonable, however, to suppose that this will greatly decrease the rate of cyclization of aromatic mustards thereby causing a situation in which $k_2 > k_1$.

The fact that bis-(3-chloro-n-propyl)aniline and bis-(6-chloro-n-hexyl)aniline underwent hydrolysis at rates slower than 2-chloroethylanilines[11] also lends support to a mechanism represented by scheme B. An increased number of carbon atoms between the chlorine and nitrogen atoms would be expected to make the entropy requirements for cyclization very high and thus make cyclization a less favourable process[16], so that on the basis of scheme B one would now expect a slower reaction, since participation by nitrogen would at least be diminished and probably non-existent.

In a detailed study of the reactions of aromatic nitrogen mustards with water and with 4-(p-nitrobenzyl)pyridine (NBP), Bardos et. al.[20] considered that both reactions passed through the same intermediate (11), fig. 5, which they likened to the transition state necessary for aziridinium ion formation. However, with water, this intermediate reacted in an 'S_N1 type reaction', via. a solvated carbonium ion -nitrogen dipole (12), to give the product of hydrolysis. On the other hand, with NBP an 'S_N2 complex' (13) was formed which gave the product of alkylation. Such a mechanism is in agreement with the previous proposals regarding the intermediacy of a cyclic species, the only difference being the depth of treatment given to the subject. It seems reasonable to believe that the nature of the

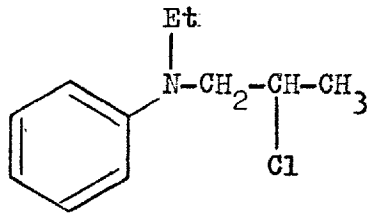

ArN-CH2CH2OH
R
Ar
N
CH2
R
CH2
(S)
X⁻(S)
(12)
(S)
ArN-CH2CH2X
R
δ-
X
Ar
δ+
N
CH2
R
CH2
(11)
(NBP)
ArN-CH2CH2-[NBP]+
R
Ar
δ+
N
CH2
[NBP]
R
CH2
(13)

intermediate, whether aziridinium ion or transitional complex (11), will depend on the nature of the nucleophile involved.

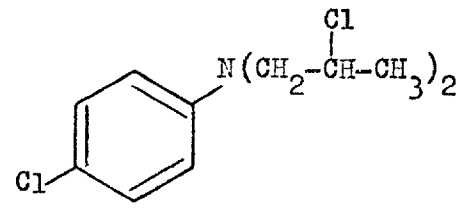
The fact that the aryl-2-chloroethylamines (14) and (15) underwent hydrolysis in aqueous acetone without rearrangement[11], may be explained by assuming the solvolysis of the cyclic intermediate to be S_N1 in character. Thus, positive charge is localized on the secondary carbon atoms giving rise to unrearranged products. Reactions with aqueous sodium hydroxide, on the other hand, might proceed by an S_N2 type mechanism giving rise to a mixed or rearranged product as was the case with 1-diethylamino-2-chloropropane[18] (see above).

The scrambling of label found upon hydrolysis or acetolysis of the deuterium labelled nitrogen mustards (16) provides excellent evidence for the intermediacy of aziridinium ions in the reactions[21]. At the same time it is suggested that the reaction with powerful nucleophiles (such as thio-cresolate) proceeds by direct displacement of chloride with no participation by nitrogen. Certainly a clearer, more detailed understanding of the mechanism of the reactions of nitrogen mustards is now emerging.

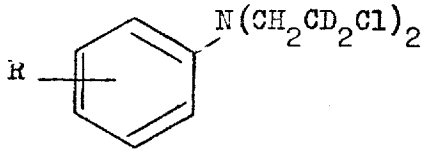
All of the work so far described relates to the more usual mustards in which the halogen is chlorine. The so-called bromo-mustards are less common but they are in general more



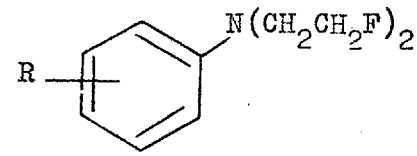
(14)



(15)



(16) R= H; p-MeO;
2,4$(NO_2)_2$.



(17) R= m- and p-Cl;
p-MeO;
p-CO_2Et.

readily hydrolyzed than their chloro counterparts[22,5]. Fluorine containing mustards (17) have been reported and they appear to be less effective anti-tumour agents and quite resistant to solvolysis with methanol[28].

Nitrogen mustards are efficient alkylating agents, reacting with primary amines to give substituted piperazines[23] and with thiols and thioethers at various pH values[24]. However, it is the reactions which occur within the narrow pH range found in biological systems that are the most important when considering the mode of action of nitrogen mustards as cytotoxic compounds.

Reactions in biological systems;

A multitude of nucleophilic centres exist in living cells but at physiological pH not all will be equally reactive. Some tumour cells, because of increased lactic acid production, tend to be more acidic than normal[26] cells but the normal pH of the biological medium is 7·5. Under these conditions not all of the functional groups of amino-acids, proteins and nucleic acids will be in a reactive, ionised form[5]. The fraction of such functional groups that are ionised is dependent on the pK_A value and Table 1 shows the fraction (f) of some of the more common groups that are in an ionised form. Sterols and carbohydrates will not be ionised while heterocyclic nitrogen bases such as purine and pyrimidine should be highly reactive.[5]

Thus, many nucleophiles, including water, are able to react with nitrogen mustards but it is important to consider with which centre significant biological reaction occurs. Alkylating agents in general, and nitrogen mustards in particular, are known to affect cells in three ways;

i) delay or prevent cell division (mitosis).

ii) cause mutations.

iii) cause irreparable cell damage and so exhibit a cytotoxic effect.

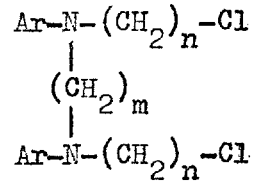
Table 1.

Group	pK_A	f at pH 7·5
Proteins; ∝-carboxyl	3·0–3·2	0·9999
carboxyl (aspartyl)	3·0–4·7	0·9999–0·999
phenolic OH (tyrosine)	10·4	0·001
sulphydryl (cysteine-terminal)	7·9–8·5	0·01–0·06
∝-ammonium	7·6–8·4	0·44– 0·11
Nucleic acids;		
primary phosphoryl	2·0	0·9999
hydroxyl (guanine)	10·1	0·0025
amine (guanine)	2·3	0·9999
sugar hydroxyl	13	10^{-5}

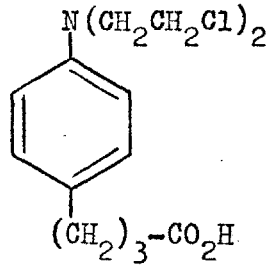
In order to explain such facts it was proposed by Goldacre et.al.[27] that the mustards linked strands of DNA with receptor sites in the same, or possibly different, molecule.[5,38] This cross-linking hypothesis has been of major significance and it is easy to see how the process of mitosis would be affected and how mutations could occur.

Evidence for the validity of this hypothesis has come from many quarters. By the preparation of the series of nitrogen mustards (18), in which n and m were varied, Kon and Roberts[29] strikingly demonstrated the dependence of the biological properties on the presence of two 2-chloroethyl groups attached to nitrogen. Few monofunctional nitrogen mustards have in fact shown any anti-tumour properties although cases have been reported[31].

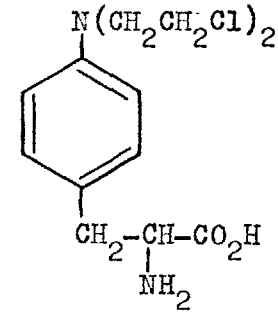
In vitro studies of the reaction of DNA with different mustards have provided the most direct evidence in support of the cross-linking theory. Rutman[32] demonstrated that HN2 caused the cross-linking of DNA strands while Alexander and Lett[30] demonstrated the same effect in the case of the mustard (19) and other aromatic nitrogen mustards. The failure of the one-armed mustards (21) and (22) to cause cross-linking of DNA was also reported[30]; the two-armed analogues of these compounds are the drugs chlorambucil and melphalan, (19) and (20) respectively.



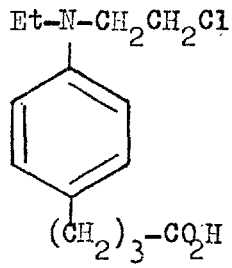
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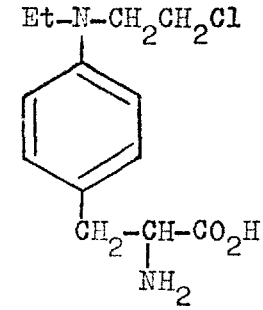
(19)



(20) L-isomer



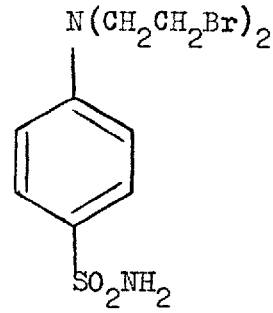
(21)



(22)

In more detail it has been suggested that the N-7 position of the guanine moiety in DNA is alkylated by nitrogen mustards[17]. The isolation of N-7 alkylated products from the reaction of guanylic acid with HN2 is of some significance in this respect[33]. However, the reaction of phosphoryl groups might also be important and it has been suggested that this could be followed by transalkylation of the N-7 position of guanine moieties[17].

While there is much evidence that cross-linking of DNA might be the significant biological reaction of nitrogen mustards, some further process could be of great importance[6]. Other 'targets' might also undergo reaction with mustards in a significant way and some authors have suggested that blocking of enzyme sites can occur. Thus it has been speculated that the activity of the L-phenylalanine mustard (20) and of chlorambucil (19) is due to the blocking of enzymes involved in protein synthesis[34]. The unusual toxic effects displayed by the sulphonamide mustard[35] (23) have also been attributed to the alkylation of an enzyme site, possibly one concerned with folic acid metabolism[36].



(23)

DRUG DESIGN

Some quantitative differences between normal and tumour cells are known to exist (e.g. enzyme levels) and one approach to the design of drugs attempts to exploit such differences in order to achieve selectivity of action. It has been suggested that simultaneous exploitation of several such variables will increase the selectivity of drugs[40]. In the search for more effective nitrogen mustards for the treatment of cancer many approaches to drug design have been made and some are outlined briefly below.

Modification of reactivity;

The highly reactive nature of the alkyl nitrogen mustards, such as HN2, can make their administration a somewhat hazardous procedure[5]. Aromatic nitrogen mustards are generally less reactive and their structure is easily modified by substitution. Ross examined some mustards derived from substituted anilines and found their reactivity to vary in relation to the ability of the nitrogen atom to donate its lone pair of electrons. There also appeared to be a correlation between the rates of hydrolysis of these compounds in aqueous acetone and their anti-tumour activity[10,41].

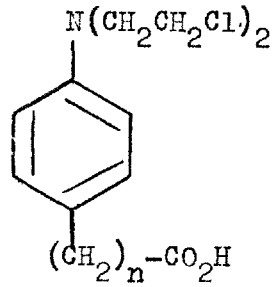
Solubility and charge;

In order to examine the effect of increasing water solubility, Everett et. al.[42] prepared the series of compounds (24), n= 1-4, and from this work the clinically useful drug 'chlorambucil', (24) n= 3, resulted. An extension of this study was made in order to examine the phenoxy-alkyl acids (25), n= 1-4, of which the propionic acid derivative (25), n= 2, showed outstanding anti-tumour activity[43]. It is interesting to note that this is an isostere of 'chlorambucil'.

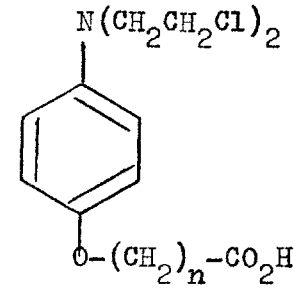
The anionic character introduced into the molecule by the carboxyl group of compounds such as (24) and (25), will affect their reactivity as well as their solubility. Thus, one would expect the anionic forms to be the more reactive as alkylating agents while the undissociated forms will diffuse more easily through cell walls[45]. On the other hand, amino derivatives such as (26), prepared by Bergel[48], would be protonated at physiological pH and thus inactive, while the uncharged form would diffuse more easily and be more reactive.

A recent report[44] correlates the anti-tumour activity of some substituted aniline mustards with the appropriate Hammett substituent constant and the partition coefficient of the compound between water and 1-octanol (a measure of lipophilicity). This mathematical relationship between easily

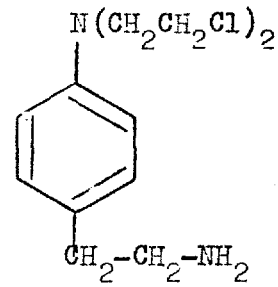
measured physical constants and the chemotherapeutic value of a compound could be of great use in the future screening of potential drugs.



(24)



(25)



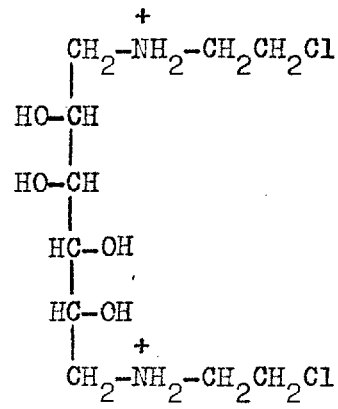
(26)

Active transport;

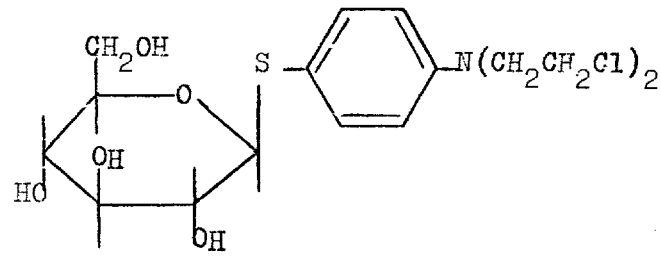
The incorporation of nitrogen mustard functions into 'carrying structures' based on biologically significant compounds has been extensively examined. It is hoped that by so doing, the transport of the alkylating functions to their sites of action inside the cell will be facilitated. With this aim in mind Bergel and Stock[46] prepared the L-phenylalanine mustard (20) which was also described by Larionov[47]. This compound proved to have a very high anti-tumour activity but its D-isomer was not as good. The o- and m-isomers of this compound (20) have given favourable biological results[34,5].

Nitrogen mustards have also been described in which amino acids such as serine[49] and tyrosine[58] have been incorporated but the success of the L-phenylalanine compound has not been repeated. Similarly the examination of steroidal nitrogen mustards has not met with great success[50,51,22].

The mannitol derivative (27) was shown to display useful anti-tumour properties[52] and other carbohydrate-carrying mustards, such as (28), have been reported[22,62].



(27)

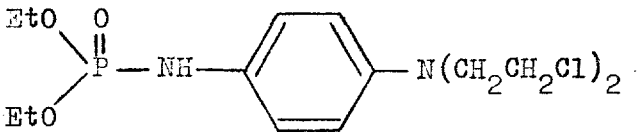


(28)

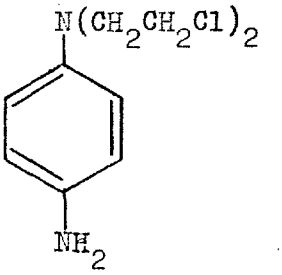
Latent activity;

The slightly different enzyme content of tumour cells makes it possible to design compounds that, by chemical transformation in such cells, will be changed from an inactive to an active form. This is the principle of latent activity and much effort has been directed to the development of drugs that work in this way.

Reports that phosphoramidase activity in malignant tumours was higher than in normal tissue prompted the investigation of compounds that depended for their action on prior hydrolysis by such enzymes. Thus, the relatively non-toxic mustard (29), prepared by Ross and Warwick[53] would be selectively activated *in vivo* to give the potently active *p*-mustard amine (30).

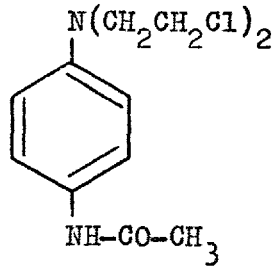


(29)

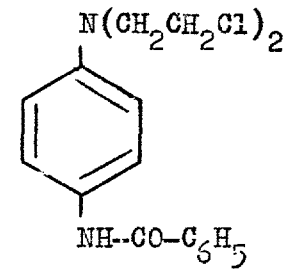


(30)

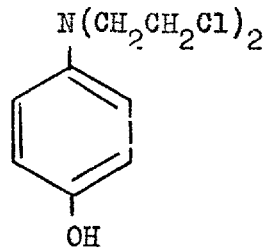
Some amides of the p-mustard amine (30) provide an interesting demonstration of the principle of latent activity. The electron-withdrawing nature of the amide function decreases the activity of the mustard group in both (31) and (32) but only the N-acetyl compound (31) proved effective against the Walker 256 tumour in test animals. Hebborn and Danielli[54] attributed this to the presence of an enzyme capable of hydrolyzing an acetamido but not benzamido function. Simlarly, acylation of the p-mustard phenol (33), as in the compounds (34), was shown to increase the selectivity and this was also attributed to enzymic activation[54,59].



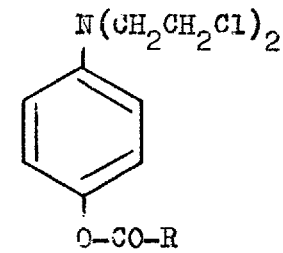
(31)



(32)

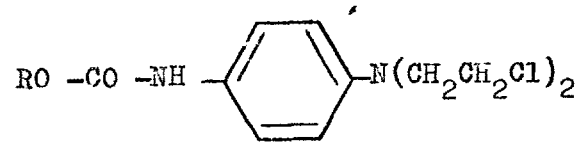


(33)

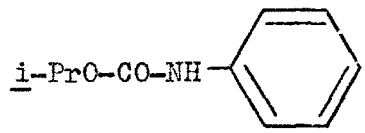


(34) R= CH_3 ; aryl

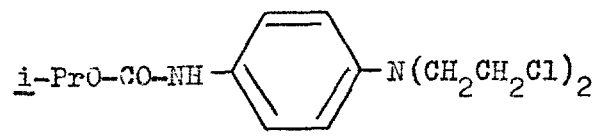
Carbamate compounds of the general formula (35) would be less toxic than the parent amine (30) in much the same way as the amide compounds discussed above. Some non-mustard carbamates have long been known to inhibit tumour growth but resistance develops because of the formation of adaptive enzymes capable of hydrolyzing them[55]. It was reasoned, therefore, that prior administration of a suitably designed carbamate such as (36), followed by the corresponding mustard compound (37), would bring about selective release of the toxic p-mustard amine (30) inside the tumour. The administration of (37) alone was found to cause no complete regressions of tumours whereas after prior potentiation by (36), 75% complete regressions were recorded[5].



(35)



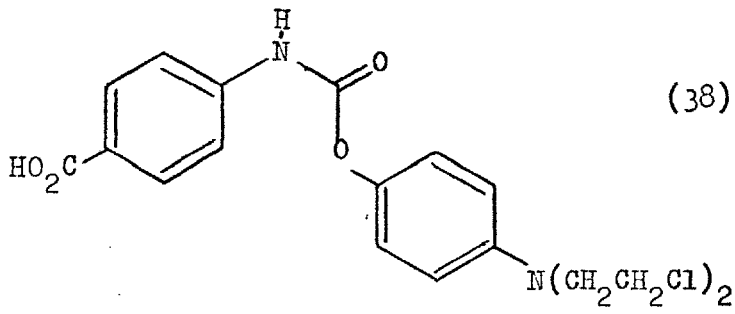
(36)



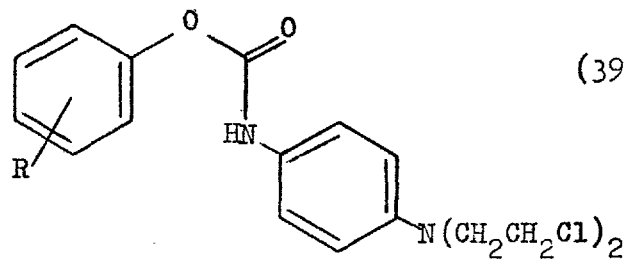
(37)

The four nitrogen mustard carbamates (38) and (39) all showed a high degree of anti-tumour activity as measured by their chemotherapeutic indices. (Chemotherapeutic index, or C.I., is the ratio of the median lethal dose to the minimum dose required for 90% tumour regression; i.e. $\frac{LD_{50}}{ED_{90}}$). The non-alkylating analogue (40) of the compound (38) did not, however, display any anti-tumour activity. The compounds (38) and (39) were originally designed[56,62] to be activated by enzymic hydrolysis *in vivo*, thus giving rise to the cytotoxic mustards (33) and (30) respectively, but no evidence for such a reaction could be found[39]. Hebborn[37,39] proposed, therefore, that the high degree of selectivity displayed by the four compounds (38) and (39) arose from their alkylation of specific receptor sites in tumour cells. Much of the work described in this thesis was directed to the examination of some nitrogen mustard carbamates which might act in a similar way to the compounds (38) and (39).

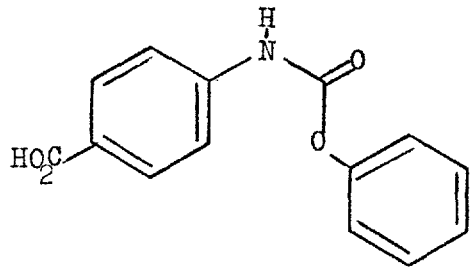
In a further development of the above ideas concerning the principle of latent activity, Pringle[61] and Owen and Sridhar[56] prepared some carbamates derived from amino acids such as the DL serine derivative (41). It was hoped that such compounds would benefit from an active transport mechanism as well as enzymic activation but the results proved to be disappointing.



(38) C.I. =17



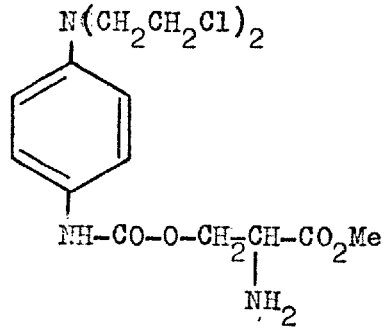
		C.I.
(39)	a R= o-CO_2Me	126
	b R= p-CO_2Me	137
	c R= p-CO_2H	46



(40) C.I. = 1

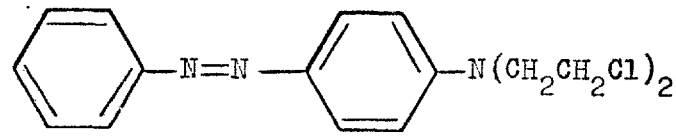
Ross[57] examined a range of phenyl-substituted compounds related to the azo-benzene mustard (42) and some promising results were obtained. The biological action of these azo-benzene derivatives was attributed to their reduction *in vivo* to the *p*-amino mustard. In a related case, the selective deactivation of the mustard thiol (43) by oxidative enzymes in normal tissue (giving the less active disulphide), has been suggested as the reason for its biological activity[60].

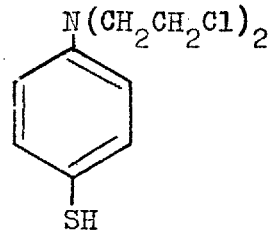
For a very detailed account of the factors involved in the design of selectively acting nitrogen mustards the reader is directed to the excellent work of Ross[5].



(41)

(42)





(43)

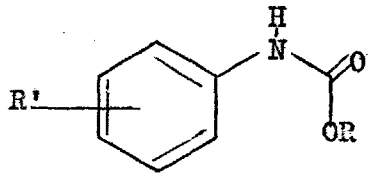
D I S C U S S I O N

A N D

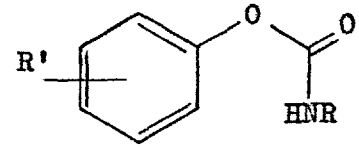
R E S U L T S

Part 1: Some Carbamates Derived from Aromatic Nitrogen Mustards.

The remarkably high chemotherapeutic indices of the carbamates (38) and (39) have already been mentioned (P.37). In view of the suggestion[37,39] that this might be due to the alkylation of specific receptor sites in tumour cells, it was thought desirable to examine a wider range of compounds, (44), derived from the p-mustard phenol (33) and the reversed carbamates (45) derived from the p-mustard amine (30).



(44)



(45)

R= p-$C_6H_4N(CH_2CH_2Cl)_2$

p-(Bis-2-chloroethylamino)phenol.

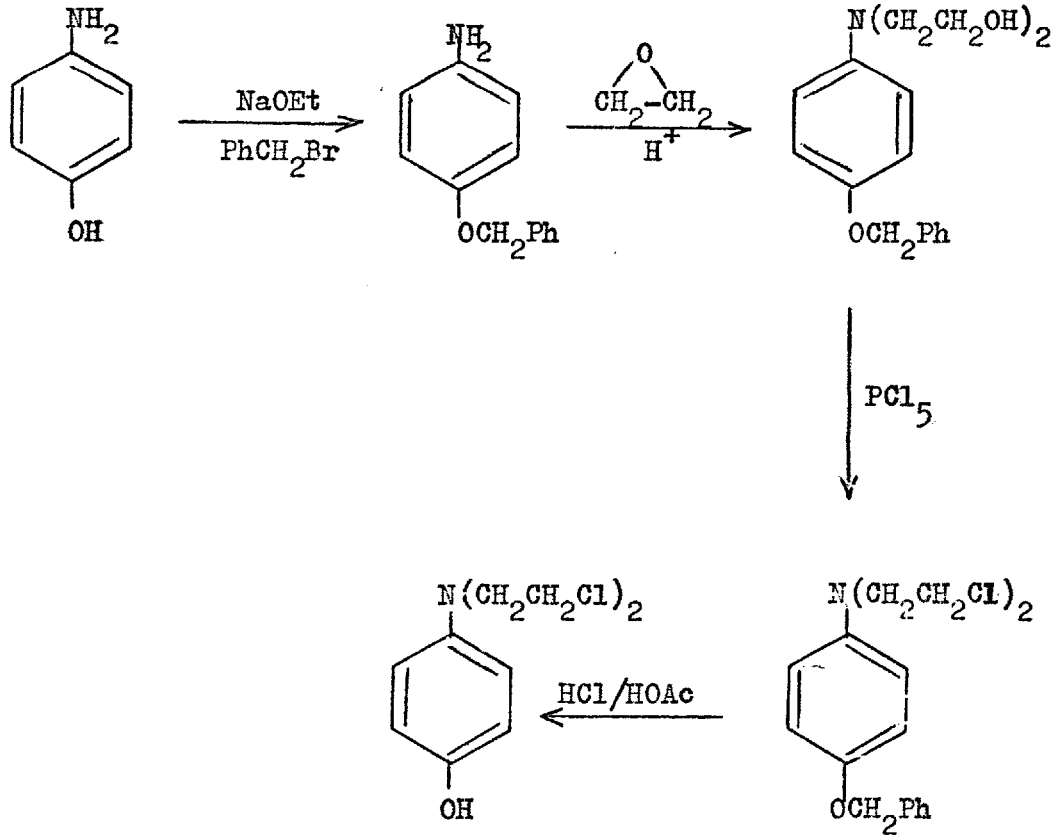
p-(Bis-2-chloroethylamino)phenol - the p-mustard phenol - was prepared from p-aminophenol by the known procedure[61,62] shown in fig. 6. The condensation of the p-mustard phenol with o-, m- and p-tolyl isocyanates in the presence of triethylamine, afforded the series of compounds (44), R'= Me.

The reaction of o- and m-chloroaniline with phosgene yielded the corresponding isocyanates[63] which, with commercially available p-chlorophenyl isocyanate, were condensed with the p-mustard phenol to give the three carbamates (44), R'= Cl.

m-Aminoanisole was prepared from m-aminophenol by acetylation, methylation with dimethyl sulphate and removal of the N-acetyl group by acid hydrolysis[64]. The reaction of this amine with phosgene gave m-methoxyphenyl isocyanate[65] which, with o- and p-methoxyphenyl isocyanates, reacted with the p-mustard phenol to give the three carbamates (44), R'= MeO.

The nitrogen mustard sulphonamide (23) (see P.28) displayed unusual toxic effects on test animals[36] and so it was thought worthwhile examining the effect, if any, of the sulphonamide group on the activity of a mustard carbamate. p-Sulphonamidophenyl isocyanate[66] was prepared by the reaction of sulphanilamide with phosgene in ethyl acetate solution and reaction of the crude isocyanate with the p-mustard phenol

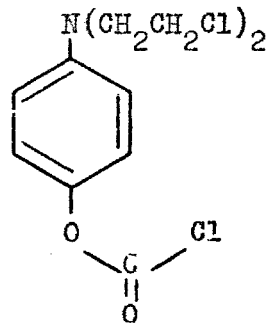
Fig. 6


NH2
OH
NaOEt
PhCH2Br
NH2
OCH2Ph
O
CH2-CH2
H+
N(CH2CH2OH)2
OCH2Ph
PCl5
N(CH2CH2Cl)2
OCH2Ph
HCl/HOAc
N(CH2CH2Cl)2
OH

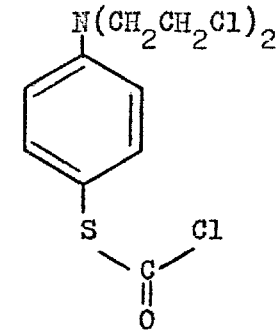
(33)

yielded a sample of the desired carbamate (44), R'= p-SO_2NH_2 , which was purified by column chromatography.

The mustard chloroformate (46) has an obvious potential as an intermediate in the preparation of carbamates in cases where the appropriate isocyanate is unobtainable or difficult to prepare. The chlorothiolformate (47) has already been described[13]. The p-mustard phenol reacted with phosgene in the presence of quinoline to give the chloroformate (46) as an oil which, by reaction with sulphanilamide, afforded a second, more pure sample of the sulphonamide carbamate (44), R'= p-SO_2NH_2.

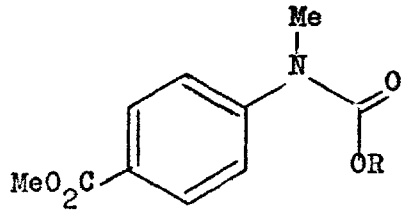


(46)



(47)

Nitrogen mustard carbamates of the type (44) were originally designed to be activated by enzymic hydrolysis *in vivo*[62]. Although this is not now considered to be the case[37,39] it appeared worthwhile examining the tertiary carbamate (48) which is an N-methyl analogue of the compound (38) (see P.38). Such a tertiary carbamate might be expected to act differently from its secondary analogue especially if enzymic hydrolysis is in fact important for its activation. The reaction of methyl p-methylaminobenzoate[67] with the mustard chloroformate (46) afforded the tertiary carbamate (48).



R = p-$C_6H_4N(CH_2CH_2Cl)_2$

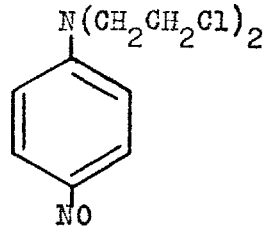
(48)

NN-Bis-(2-chloroethyl)-p-phenylenediamine and its m- isomer.

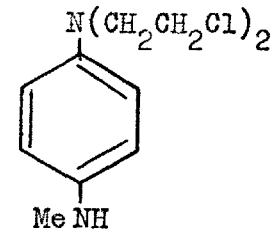
NN-Bis-(2-chloroethyl)-p-phenylenediamine (30) was prepared from NN-bis-(2-chloroethyl)aniline by the method of Ross[11]. Samples prepared in this way were invariably contaminated by coloured impurities arising from the intermediate nitroso compound (49) and the successful preparation of the secondary mustard amine (50) (see below) prompted the investigation of a similar route for the preparation of the primary amine. It was hoped, in this way, to prepare a colourless product.

The diol (51), which has been described by DeGraw et. al.[68], reacted with thionyl chloride in dimethylformamide to give a 25% yield of the N'-acetyl compound (52). This was shown to be identical to a sample prepared by acetylation of the p-mustard amine. (The use of the thionyl chloride - dimethyl-formamide chlorinating agent is discussed in detail in the next section). Acid hydrolysis gave the p-mustard amine (isolated as the hydrochloride) as a white solid and although the overall yield was low (12%) the purity of the product justified the use of this method.

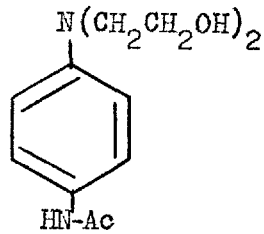
In order to prepare the series of carbamates (45), R'= Me, MeO and Cl, it was necessary to prepare the nine corresponding aryl chloroformates. Without exception these were



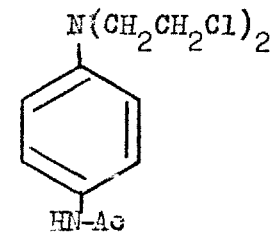
(49)



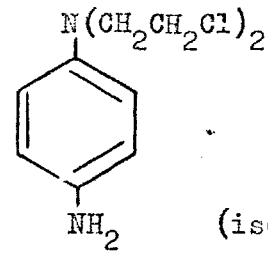
(50)



(51)



(52)



(isolated as hydrochloride)

(30)

obtained by the reaction of the substituted phenols with phosgene in the presence of quinoline. All have been described before (see Experimental section) except m-methoxyphenyl chloroformate; this compound was characterized as the N-phenyl-carbamate derivative because it could not be adequately purified by distillation.

Condensation of the substituted phenyl chloroformates with the p-mustard amine then afforded the series of compounds (45), R'= Me, MeO, Cl (o-, m- and p-).

Preliminary biological results suggested further modification of the p- substituent of these carbamates (45) and the compound in which R' = p-tert-butyl was prepared from p-tert-butylphenyl chloroformate[69]. Also, p-nitrophenyl chloroformate[70] was prepared and from it, the carbamate (45),R'=p-NO_2.

Diazotization of p-aminophenol followed by reaction with potassium ethyl xanthate and base hydrolysis, yielded p-hydroxythiophenol[71] from which p-hydroxythioanisole[72,73] was prepared by reaction with sodium hydroxide-methyl iodide in ethanol. Thus, p-(methylthio)phenyl chloroformate was obtained and from this the carbamate (45), R' = p-SMe.

The reaction of m-dimethylaminophenol with phosgene afforded m-dimethylaminophenyl chloroformate in the form of a distillable oil which rapidly darkened and decomposed when stored.

The reaction of this chloroformate with the p-mustard amine gave the carbamate (45), R'= m-NMe_2.

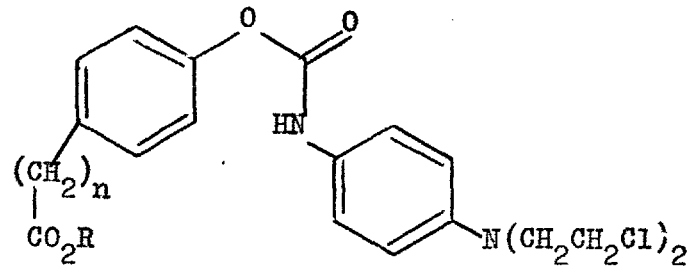
The series of nitrogen mustards (24), described by Ross[42], has already been mentioned (see P. 30). It appeared worthwhile examining a similar modification of the compounds (39) b and c which, of course, had prompted this programme of work. It was intended, therefore, to prepare the carbamates (53), n= 1, 2 and 3, R= H and Me.

p-Hydroxyphenylacetic acid[74] was prepared by hydrolysis of p-methoxyphenylacetic acid (commercially available) with hydrobromic acid. The methyl ester[75] of this acid reacted with phosgene in the presence of quinoline to give the chloroformate (54), n= 1, and from this chloroformate the carbamate (53), n= 1, R= Me, was obtained.

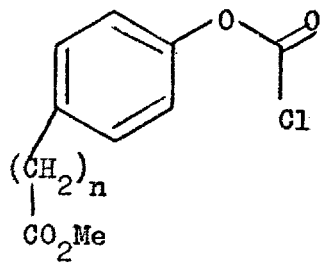
Methyl 3-(p-hydroxyphenyl)propionate[76] was used to prepare the chloroformate (54), n= 2. Distillation of this compound left a solid residue which was purified by column chromatography and identified as di-(p-(2-methoxycarbonylethyl)-phenyl)carbonate, (55), on the basis of its analysis and ir. spectrum. The p-mustard amine reacted with the chloroformate to give the desired carbamate (53), n= 2, R= Me.

The method of Kharasch and Khalfayan[77] was used to prepare 4-(p-hydroxyphenyl)butyric acid, fig. 7. The methyl ester (56) of this acid could not be obtained in an analytically pure

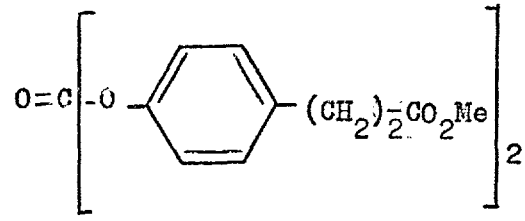
form although the n.m.r. spectrum and thin layer chromatography showed no impurity. This compound was characterized by conversion to the p-nitrobenzoate ester (57). Similarly, the chloroformate (54), n= 3, could not be obtained as an analytically pure liquid and it was characterized by reaction with aniline to give the N-phenylcarbamate derivative. The reaction of the chloroformate with the p-mustard amine furnished the desired product (53), n= 3, R=Me.



(53)

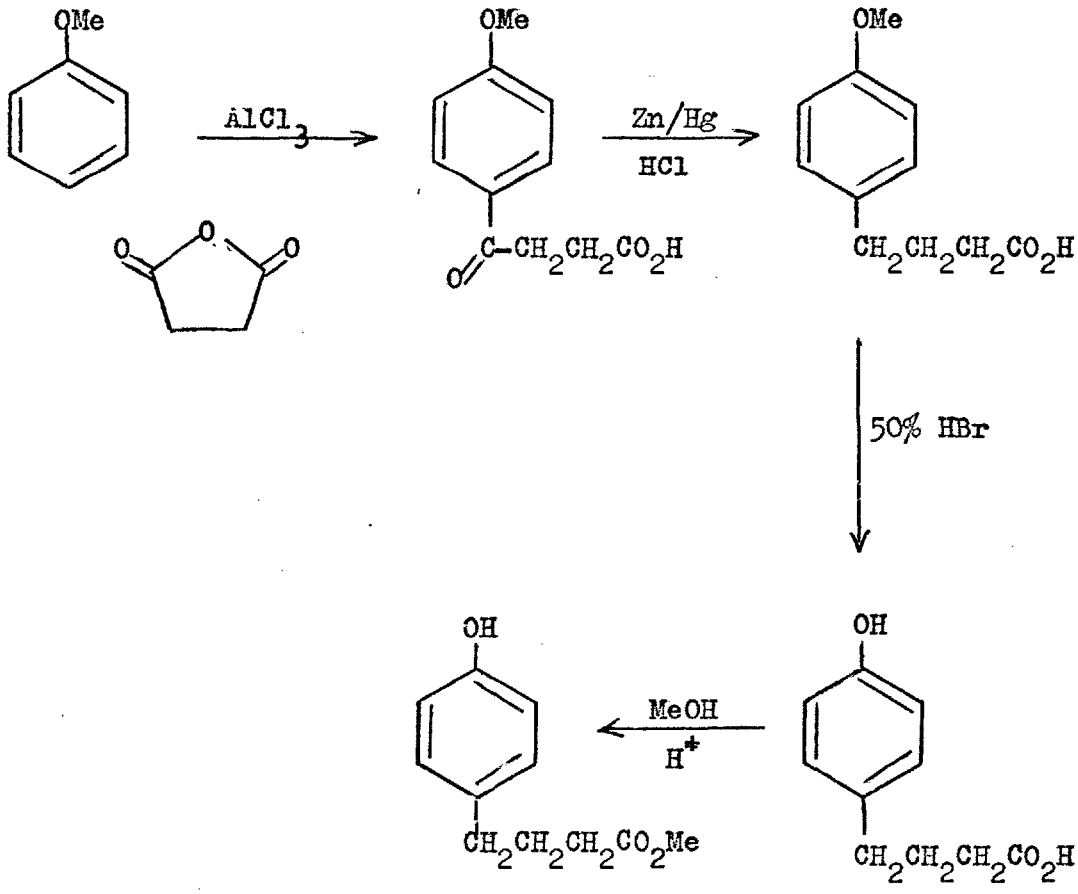


(54)

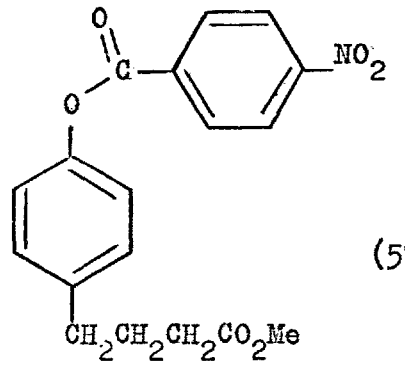


(55)

Fig. 7


OMe
AlCl3
OMe
Zn/Hg
HCl
OMe
C-CH2CH2CO2H
CH2CH2CH2CO2H
50% HBr
OH
MeOH
H+
OH
CH2CH2CH2CO2Me
CH2CH2CH2CO2H

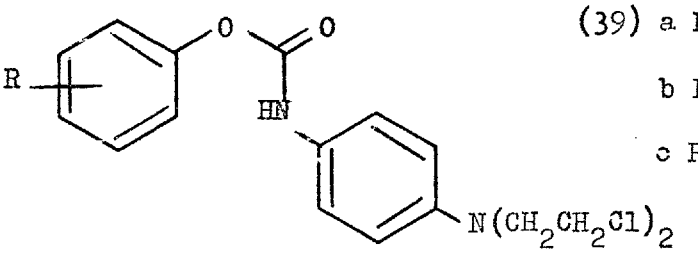
(56)


NO2
CH2CH2CH2CO2Me

(57)

Hydrolysis of the above esters in a 1:1 mixture of acetic and hydrochloric acids[56], furnished the series of acid compounds (53), n= 1, 2 and 3, R= H. These three compounds showed a remarkable tendency to occlude solvent whether recrystallized from benzene-petroleum or ether-petroleum. The n.m.r. spectra of two of the acids are reproduced below, fig. 8, and the resonances attributable to diethyl ether are clearly visible. Drying under high vacuum could not remove the solvent of crystallization which considerably affected the analytical results obtained.

The mono-substituted carbamate (39)a was described by Owen and Sridhar[56] and it was thought that further substitution in the phenyl ester ring, for example by methyl, might increase the selectivity of what was already an active anti-tumour agent. To this end 2-methoxycarbonyl-4-methylphenyl chloroformate (58) was prepared from methyl 5-methylsalicylate and from this

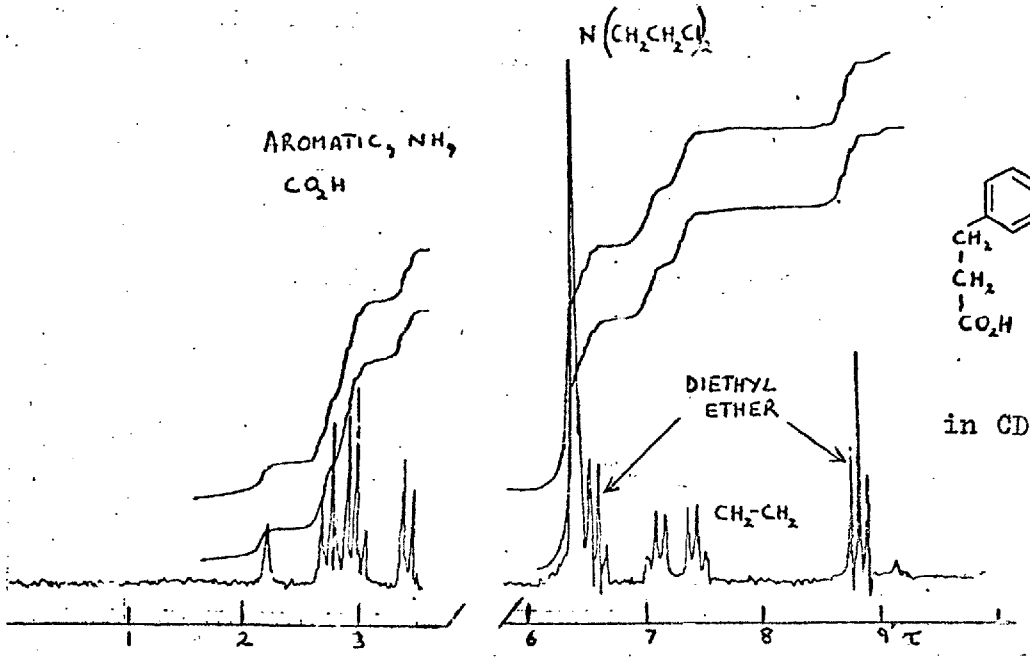


(39) a R= o-CO_2Me

b R= p-CO_2Me

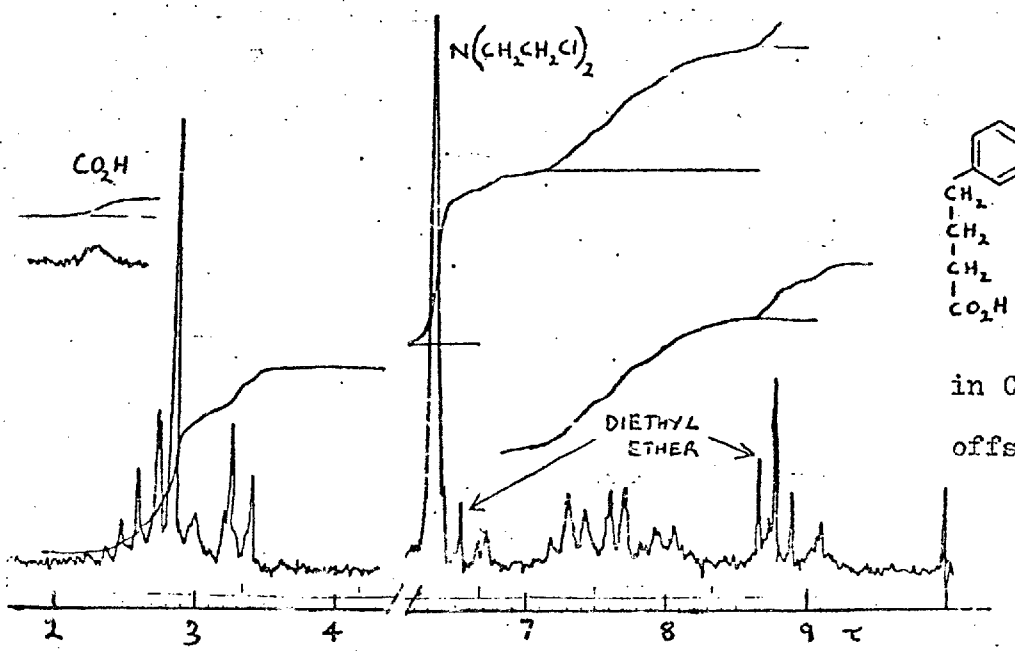
c R= p-CO_2H

Fig. 8



in $CDCl_3$–d_6-DMSO

R= p-$C_6H_4N(CH_2CH_2Cl)_2$



in $CDCl_3$

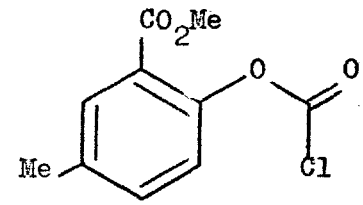
offset 0 and

100 Hz

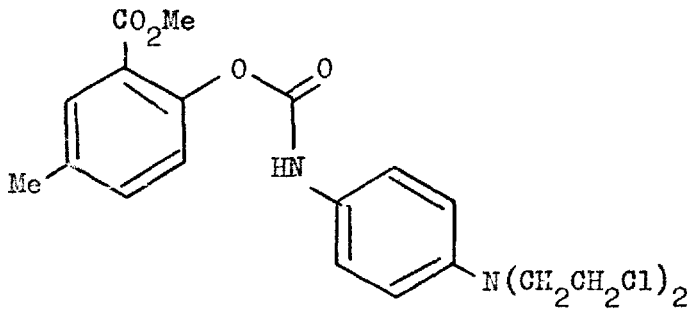
chloroformate the carbamate (59) was obtained in the usual way.

Another potentially interesting disubstituted mustard carbamate was (60), R= Me. Both the o- and p- monosubstituted compounds, (39)a and b respectively, are known anti-tumour agents[56] and combination of the two substituents might have a favourable effect.

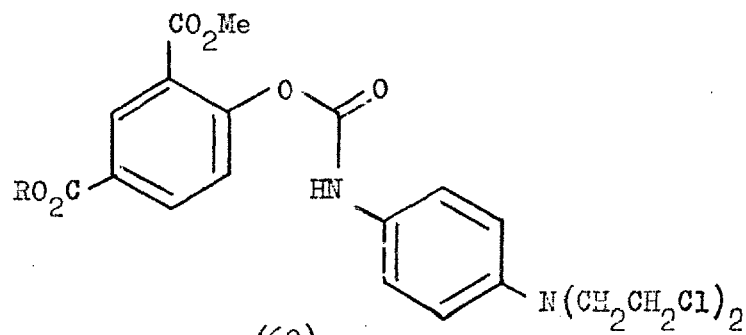
4-Hydroxyisophthalic acid (61) was prepared by permanganate oxidation of 2,4-dimethylanisole followed by hydrolysis



(58)



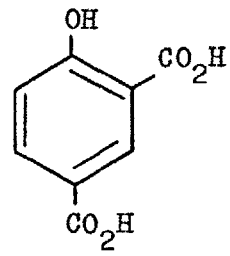
(59)

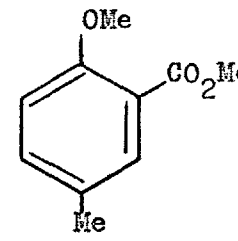


(60)

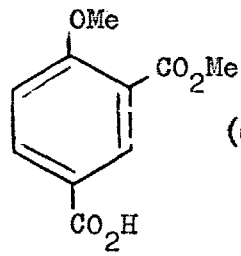
with hydrobromic acid, essentially as described by Jacobsen[102]. In another approach the permanganate oxidation of methyl 2-methoxy-5-methylbenzoate[103] (62) gave a mixture of the two acids (63) and (64) from which 4-hydroxyisophthalic acid could also be obtained by the action of hydrobromic acid. Methyl 4-hydroxyisophthalate[104] reacted slowly with phosgene to give the chloroformate (65) as a crude oil which could not be purified but which reacted with aniline and the p-mustard amine to give the corresponding carbamate compounds (66) and (60), R= Me, respectively.

(61)



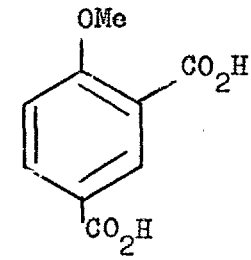


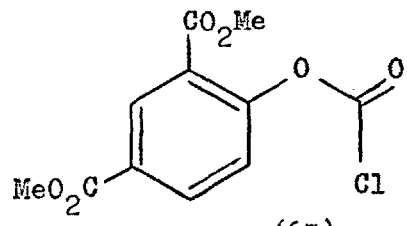
(62)



(63)

(64)



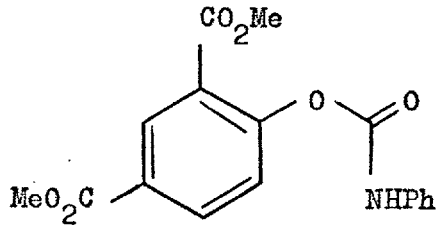


(65)

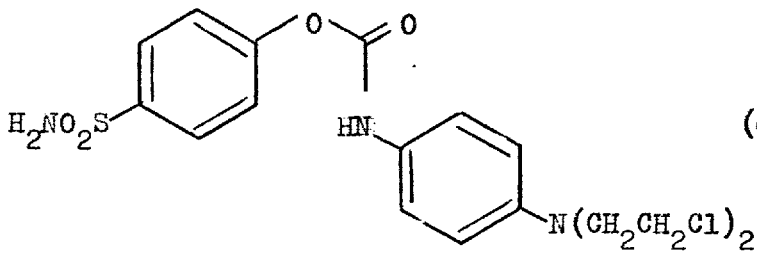
Unfortunately, attempts to selectively hydrolyse the p-ester function of the carbamate (60), R= Me, to obtain the half ester (60), R= H, were not successful. Sridhar[56] found the o-ester (39)a resistant to hydrolysis in a mixture of acetic and hydrochloric acids while the p-ester (39)b was readily hydrolyzed. When the disubstituted carbamate (60), R= Me, was treated in a similar way a mixture of products was formed.

In order to prepare the sulphonamido-carbamate (67) (c.f. the previous section) an attempt was made to prepare p-sulphonamidophenyl chloroformate. p-Hydroxybenzenesulphonamide, prepared by the method of Kermack and Spragg[78], was reacted with phosgene in the presence of quinoline in the usual way but the crude products so obtained could not be purified or identified and the attempts were abandoned.

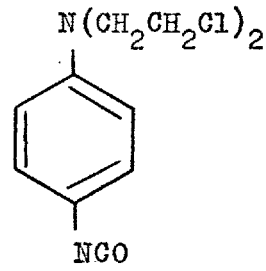
An alternative method for the preparation of this compound, (67), involved the preparation of the mustard isocyanate (68) from the p-mustard amine[62]. Unfortunately, when this isocyanate was treated with p-hydroxybenzenesulphonamide in ethyl acetate containing a little pyridine, none of the desired product could be isolated.



(66)

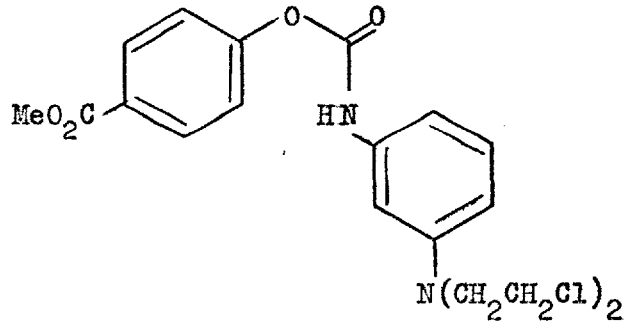


(67)

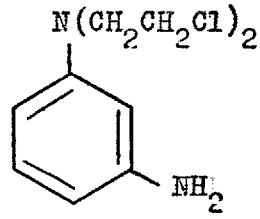


(68)

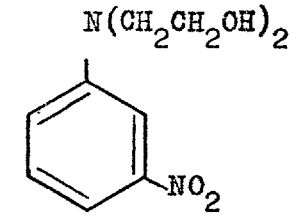
The carbamate (69), derived from the m-mustard amine (70), has not been described before but is of some interest because it is an isomer of the known anti-tumour agent (39)b (see P. 38). In order to prepare this carbamate the m-mustard amine was prepared essentially as described by Degutis and Bieksa[9] with the exception that the diol (71) was chlorinated by reaction with thionyl chloride using dimethylformamide as solvent. An excellent yield of the chloro compound (72) was obtained in this way and the use of thionyl chloride-dimethylformamide is discussed in detail in the next section. Stannous chloride reduction of the nitro compound (72) gave the m-mustard amine which reacted with p-methoxycarbonylphenyl chloroformate to give the desired carbamate (69).


MeO2C
O
O
HN
N(CH2CH2Cl)2

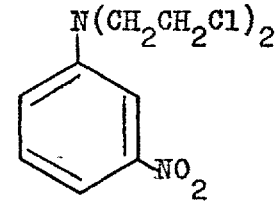
(69)


N(CH2CH2Cl)2
NH2

(70)


N(CH2CH2OH)2
NO2

(71)


N(CH2CH2Cl)2
NO2

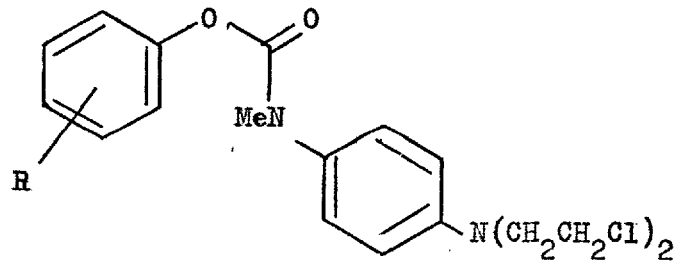
(72)

NN-Bis-(2-chloroethyl)-N'-methyl-p-phenylenediamine.

The desirability of preparing some tertiary nitrogen mustard carbamates has already been mentioned in the context of the compound (48) derived from the p-mustard phenol (P. 46). Tertiary carbamates of the type (73) might also be expected to show a different biological activity from their secondary counterparts and so it was proposed to examine some carbamates derived from the secondary mustard amine (50). This compound has been reported in the literature[79] but this now appears to have been a mistake and it has not in fact been prepared before.[80]

Although the primary p-mustard amine is readily available it was not thought that mono-methylation of this compound could be easily achieved and the route shown in fig. 9 was examined for the preparation of this secondary amine.

Reduction of N-methyl-p-nitroacetanilide with stannous chloride in conc. hydrochloric acid gave a product of superior quality to that obtained by the use of iron-formic acid as described by Morgan and Grist[81]. The resulting substituted phenylenediamine (74) reacted with ethylene oxide in dilute acetic acid to give the diol (75) in high yield as a thick oil, apparently quite pure (n.m.r. and t.l.c.). It was characterized by preparation of the crystalline dibenzoate (76).

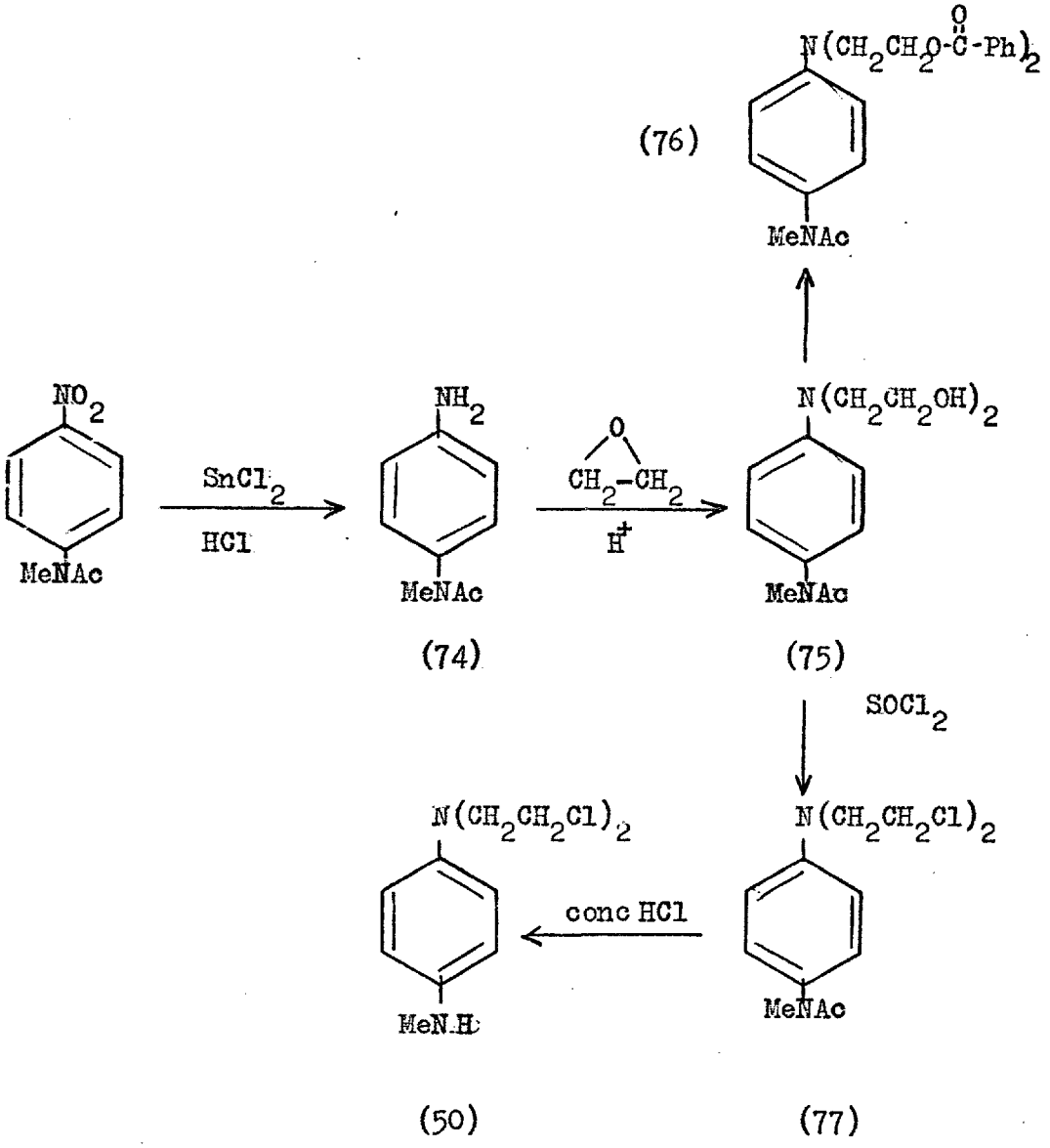


(73)

It was anticipated that chlorination of the diol (75) would present difficulties. Conventional chlorinating agents such as thionyl chloride, phosphorus oxychloride and phosphorus pentachloride are known to react with amides [82] and undesirable side reactions seemed inevitable.

The Bosshard group[83] suggested that the thionyl chloride - dimethylformamide reagent might react with sulphonic and carboxylic acids by way of the intermediate (chloromethylene)-dimethylammonium chloride (78) which they were able to isolate. They did not, however, discount the possibility that reaction was by way of the chlorosulphite (79). It has subsequently been reported that the chlorosulphite (79) has been isolated and that it reacts with alcohols to give high yields of alkyl chlorides[84a] and with acids to give acid chlorides[84b].

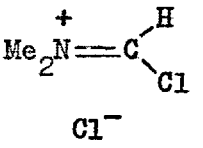
Fig, 9


NO2
MeNAc
SnCl2
HCl
NH2
MeNAc
(74)
O
CH2-CH2
H+
N(CH2CH2OH)2
MeNAc
(75)
(76)
N(CH2CH2O-C-Ph)2
O
MeNAc
SOCl2
N(CH2CH2Cl)2
MeNAc
(77)
conc HCl
N(CH2CH2Cl)2
MeN.H
(50)

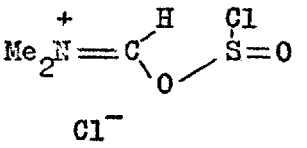
It was proposed, therefore, to allow the reaction of thionyl chloride and a slight excess of dimethylformamide to take place and to react the resulting intermediate, whether (78) or (79), with the diol (75). The charred product obtained in this way gave, after chromatography, a 20% yield of a compound identified as the cyclic sulphite (80) on the basis of its elemental analysis. This suggests that the reaction proceeded by way of the intermediate (79), as proposed by Palomo[84a], with cyclization of the resulting ester (81) occurring instead of displacement by chloride. The possibility remains, however, that the sulphite resulted from reaction of the diol with thionyl chloride itself although it seems unlikely that any would remain after the prior reaction with dimethylformamide; both Bosshard[83] and Palomo[84a,b] claim that this reaction is facile.

It must be pointed out that it is not proposed that the reactions of the diols (51) and (71) (see Pp. 47 and 59) necessarily proceeded by the same mechanism as that discussed here. In these cases no attempt was made to react thionyl chloride with dimethylformamide before addition of the diols and also, the dimethylformamide was used in large excess as a solvent and not in 'reagent quantities'.

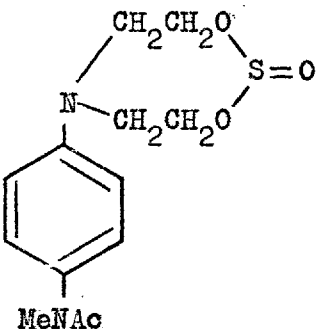
The chlorination of the diol (75) was eventually



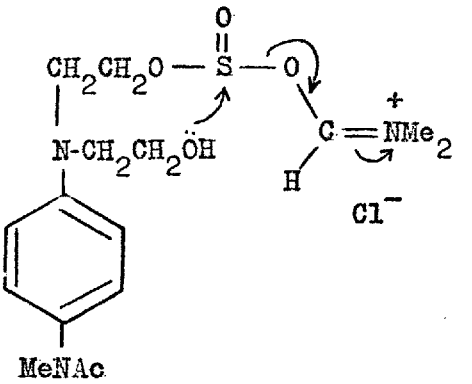
(78)



(79)



(80)



(81)

achieved by reaction with thionyl chloride in boiling chloroform. A little of the sulphite (80) was also formed and the yield of chloro compound (77) was ca. 20%. Removal of the N-acetyl group of (77) by acid hydrolysis gave the desired secondary mustard amine (50), isolated in the form of a white, crystalline hydrochloride.

The tertiary carbamate (73), R= p-$CH_2CH_2CO_2Me$, was prepared by reaction of this secondary amine with p-(2-methoxycarbonylethyl)phenyl chloroformate, but it could not be obtained in a crystalline form. Acid hydrolysis furnished the acid compound (73), R= p-$CH_2CH_2CO_2H$, but this was also obtained only as an oil.

Biological Results.

Many of the nitrogen mustard carbamates described in this thesis were tested for their activity against the Walker 256 tumour. The results, expressed as chemotherapeutic index ($\frac{LD_{50}}{ED_{90}}$) were kindly made available by Dr. P. Hebborn, State University of New York, Buffalo.

Some of the compounds, eg. I.C. 286, 290, 292 and 296, have high chemotherapeutic indices but no obvious structure - activity relationship can be seen. In general the compounds in Table 1 are less active than those in Table 2 and this probably reflects the relative reactivities of the p-mustard phenol and the p-mustard amine from which they were derived.

Comparisons with other compounds prepared in these laboratories are interesting. In Table 4, I.C. 301, derived from the m-mustard amine, is isomeric with the compound I.C. 220, derived from the p-mustard amine, but it has a considerably lower C.I. (but see note on P. 68). The compound I.C. 294 has a C.I. similar to the related compound I.C. 221 but I.C. 298 is remarkably less effective than the two related compounds I.C. 220 and I.C. 221.

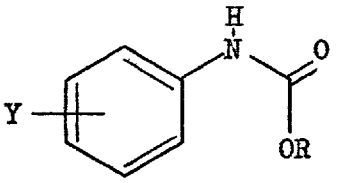
Perhaps the most interesting trend is that shown by

the compounds I.C. 280 and 293 (Table 2) and those in Table 3. The presence of a carboxyl group at the para position (cf. I.C. 213) has a great effect on the chemotherapeutic index even when it is separated from the phenyl ester ring as in I.C. 303, 297 and 305. The similarity of these compounds to the drug 'chlorambucil' (see P. 30) is worth noting.

Note:

In the following Tables, the results recorded, were determined using the Walker 256 tumour in rats except where marked by an asterisk in which cases mice were used.

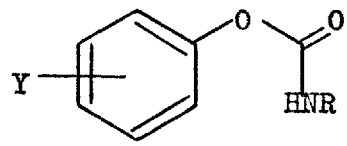
Table 1.



R= p-$C_6H_4N(CH_2CH_2Cl)_2$

I.C.No.	Y	LD_{50}	ED_{90}	C.I.
278	o-Me	90mg/kg	6·5mg/kg	14
277	m-Me	140	8	17
276	p-Me	45	5	9
285	o-Cl	80	2·5	35
286	m-Cl	800	15	52
287	p-Cl	500	110	4·5
282	o-MeO	56	20	2·8
283	m-MeO	200	7·5	26
284	p-MeO	800	120	6·5
299	p-SO_2NH_2	1000	1000	1*

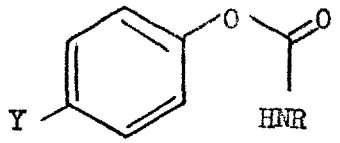
Table 2.



R= p-$C_6H_4N(CH_2CH_2Cl)_2$

I.C.No.	Y	LD_{50}	ED_{90}	C.I.
281	o-Me	> 300mg/kg	50mg/kg	ca.12
279	m-Me	170	5	34
280	p-Me	170	7	24
288	o-Cl	60	20	3
289	m-Cl	140	15	9·3
290	p-Cl	140	2	70
292	o-MeO	140	1	140
296	m-MeO	600	5	120
291	p-MeO	600	35	17
293	p-tert-Bu	700	50	14
307	p-SMe	500	300	ca.1*
306	p-NO_2	80	2·2	36*
308	m-NMe_2	800	600	ca.1*

Table 3.

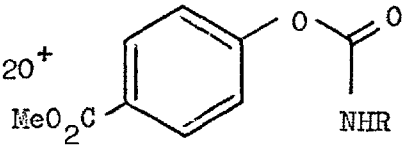
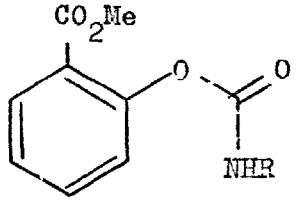
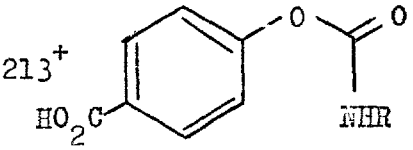


R= p-$C_6H_4N(CH_2CH_2Cl)_2$

I.C.No.	Y	LD_{50}	ED_{90}	C.I.
302	CH_2CO_2Me	ca.500 mg/kg	ca.400 mg/kg	ca. 1*
303	CH_2CO_2H	80	5	16*
295	$CH_2CH_2CO_2Me$	500	15	33
297	$CH_2CH_2CO_2H$	140	1	140
		ca.100	2·3	ca.30*
305	$CH_2CH_2CH_2CO_2H$	125	2·5	50*

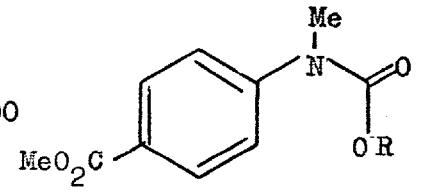
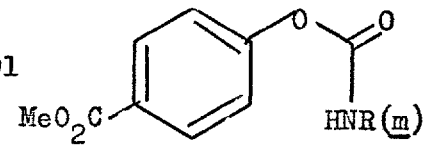
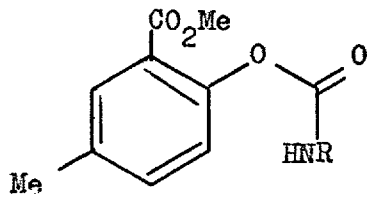
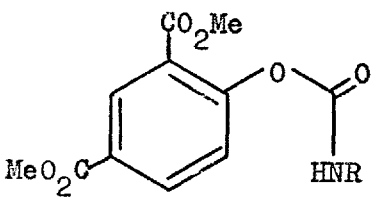
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Table 4.

I.C.No.		LD_{50}	ED_{90}	C.I.
220^+		110 mg/kg	0·8 mg/kg	131
221^+		115	ca.1	ca.100
213^+		58	1·2	46

+ described by Owen and Sridhar[56].

Table 4cont.

I.C.No.		LD_{50}	ED_{90}	C.I.
300		1000mg/kg	1000mg/kg	ca.1*
301		500	400	ca.1*
294		500	5	100
298		310	300	ca.1*

In the above Table, R= p-$C_6H_4N(CH_2CH_2Cl)_2$ except for the compound I.C.301 which is derived from the m-mustard amine.

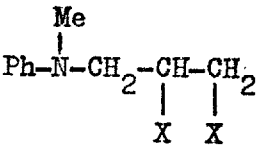
* See note on P. 68.

Part 2: Studies on the Mechanism of the Alkylation Reactions of Compounds of the Nitrogen Mustard Type.

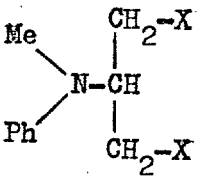
The Dimethanesulphonates of 2-N-methylanilinopropane-1,3-diol and 3-N-methylanilinopropane-1,2-diol.

Aminodichloropropanes such as (82) and(83), X= Cl, are of interest as potentially cytotoxic compounds[85,86] and their similarity to the more usual nitrogen mustards is evident. The unsymmetric nature of such compounds makes it possible for rearranged products to arise from reactions with nucleophiles if such reactions proceed by way of a cyclic intermediate. In this respect these dichloropropanes resemble the compounds (14) and (9) which have already been mentioned (P. 20,15). It was proposed, therefore, to prepare the dichloropropanes (82) and (83), X= Cl, and to study their reactions with different nucleophiles.

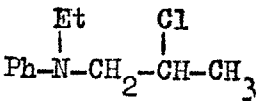
Unfortunately, the preparation of the 1,2-dichloride (82), X= Cl, from the corresponding diol (82), X= OH, proved to be difficult. The use of phosphorus pentachloride and thionyl chloride has already been reported as being unsuccessful[87] but a low yield of the 1,2-dichloride could be obtained by the use of methanesulphonyl chloride in pyridine (cf. DeGraw[8]), as established by Mr. G. Durrant of this Department[87].



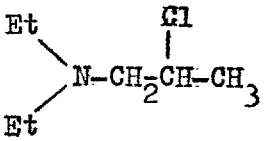
(82)



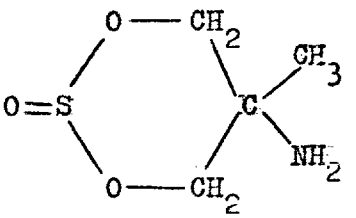
(83)



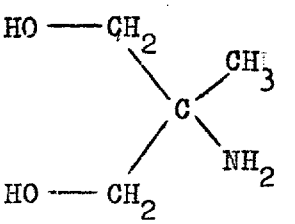
(14)



(9)



(84)



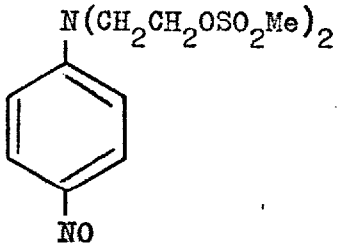
(85)

The difficulty of converting 2-aminopropane-1,3-diols and 3-aminoprcpane-1,2-diols to their dichlorides has been reported by Cromwell and Hassner[85] while Jones and Wilson[88] isolated the cyclic sulphite (84) from the reaction of the diol (85) with thionyl chloride.

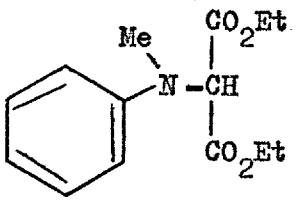
Because of these facts, attention was turned to the more easily prepared dimethanesulphonates (82) and (83), X=OSO_2Me. The value of methanesulphonates in general, as anti-tumour agents is well established[5] and some 'mustard-like' compounds, such as (86), have been reported[89,25]. In their reactions with nucleophiles, the dimethanesulphonates (82) and (83), X= OSO_2Me, would be expected to behave in a similar manner to the dichlorides of the same type with the possibility of rearranged products arising from any cyclic intermediate.

3-N-Methylanilinopropane-1,2-diol[90] reacted with methanesulphonyl chloride in the presence of triethylamine to give the dimethanesulphonate (82), X= OSO_2Me, as a clear, viscous oil which could be stored indefinitely (at 0°) without decomposition.

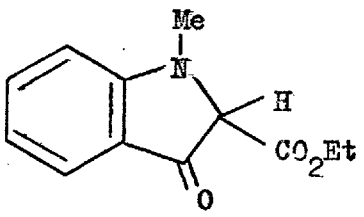
The preparation of 2-N-methylanilinopropane-1,3-diol (83), X= OH, has already been described[91]. The reaction of N-methylaniline with diethyl bromomalonate gave a good yield of diethyl 2-N-methylanilinomalonate (87). This compound has been described by Nnadi and Wang[92] as a crystalline solid of m.p. 105°.



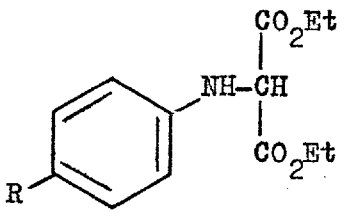
(86)



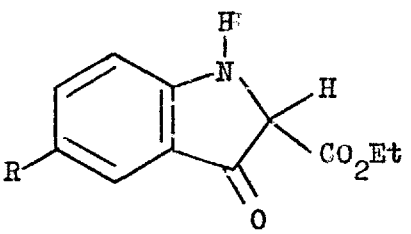
(87)



(88)



(89) R= H, Me



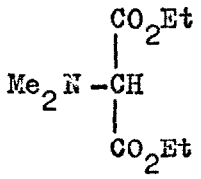
(90)

In several preparations the present author obtained this compound as a pale yellow liquid which was chromatographically and spectrally (n.m.r.) pure and had the correct molecular weight (mass spectrum).

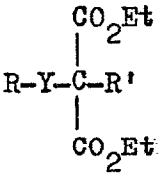
Prolonged heating of the ester (87) during distillation, caused the formation of a white crystalline solid which was also formed when the ester was heated in refluxing xylene or nitrobenzene. This unknown compound showed four aromatic protons, one ethoxy group, one N-methyl group and a one proton singlet (τ 1·30) in the n.m.r. spectrum and two carbonyl absorptions in its i.r. spectrum. The molecular weight (mass spectrum) was 219 and analysis figures suggested a formula of $C_{12}H_{13}NO_3$ and on this evidence the compound was formulated as 2-ethoxycarbonyl-N-methylindoxyl (88). The thermally induced cyclization of the malonates (89), to give the corresponding 2-ethoxycarbonylindoxyl compounds (90), has been reported by Blank[93].

Diethyl 2-N-methylanilinomalonate (87) proved resistant to Bouveault-Blanc reduction, which compares with the resistance of the ester (91) to reduction by this method[88]. The reduction of the ester (87) with lithium aluminium hydride in boiling tetrahydrofuran gave a low (18%) yield of the 1,3-diol[91] (83),X=OH. The formation of unwanted products in the LAH reduction of 1,3-diketones[94] and malonate esters[95] is known and Yale et. al.[96]

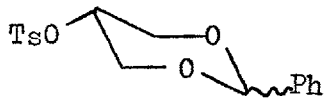
report poor yields in the LAH reduction of malonates of the type (92), Y= O or S.



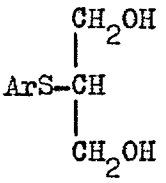
(91)



(92)



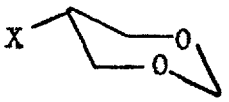
(93)



(94)

Khan[97] and Baig[98] used the mixture of cis and trans-toluene-p-sulphonates (93), obtained from the tosylation of 1,3-O-benzylideneglycerol, for the preparation of the 2-arylthio-propane-1,3-diols of the type (94). However, the cis-form of the toluene-p-sulphonate (93) was often recovered unchanged after reaction with various thiols[97]. It was decided, therefore, to

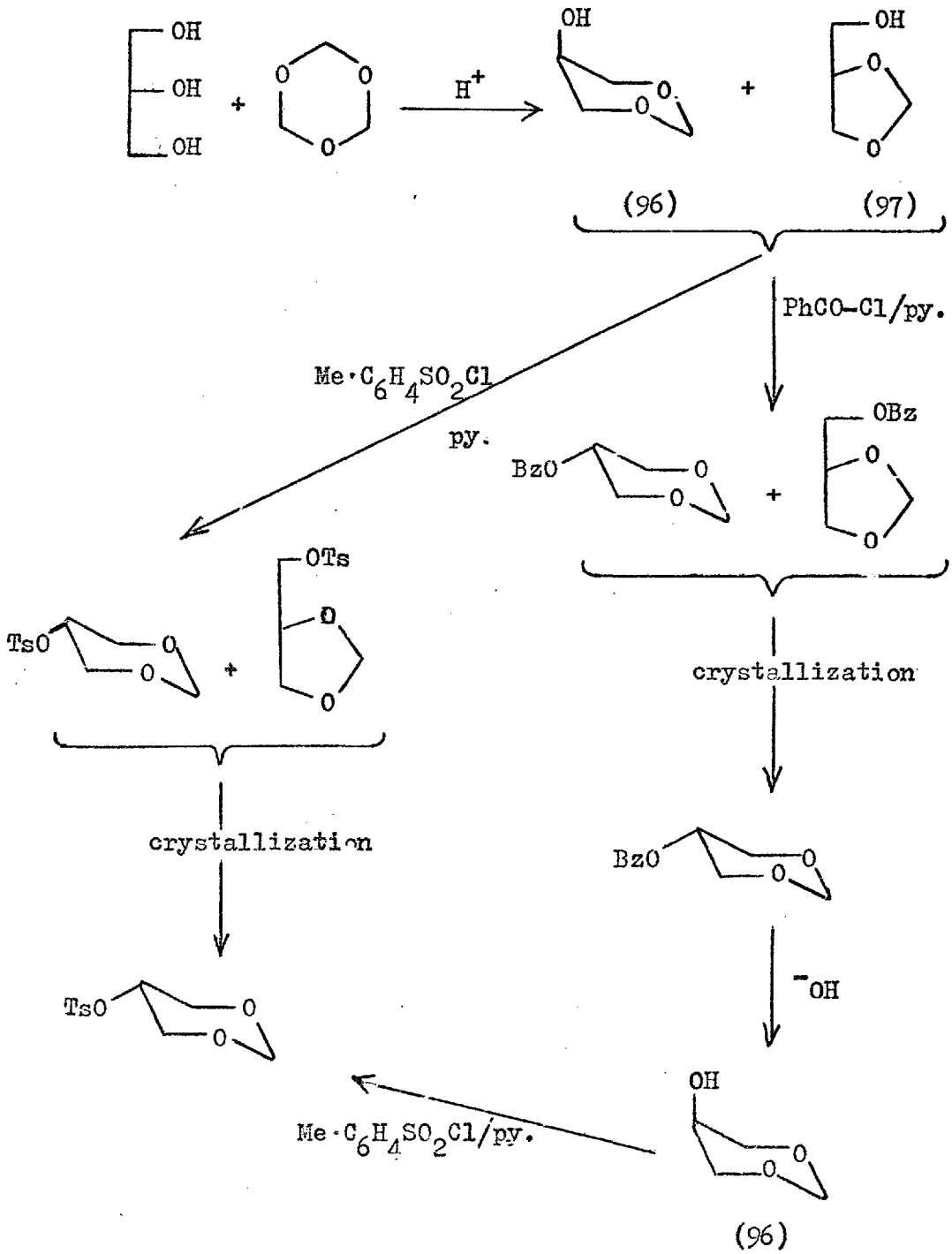
examine the use of some 5-substituted m-dioxans (95), X= Cl, OTs, for the preparation of the 1,3-diol (83), X= OH. The absence of any cis-trans isomerism, with its apparent effect on the reactivities of the isomers, makes the 5-substituted m-dioxans (95) more attractive intermediates for the preparation of such 1,3-diols.



(95)

5-Hydroxy-m-dioxan (96) was prepared by the well established procedure of Hibbert and Carter[99], fig. 10. The mixture of alcohols (96) and (97) , from the acid catalysed reaction of glycerol with sym. trioxan, was benzoylated and then crystallization from ether yielded pure 5-benzoyloxy-m-dioxan (95), X= OBz. Base hydrolysis of this compound gave 5-hydroxy-m-dioxan (96) and thence, by tosylation, the required tosylate (95), X= OTs. Alternatively, tosylation of the mixture of alcohols (96) and (97) gave a mixture of tosylates from which 5-toluene-p-sulphonyloxy-m-dioxan (95), X= OTs, could be separated by crystallization

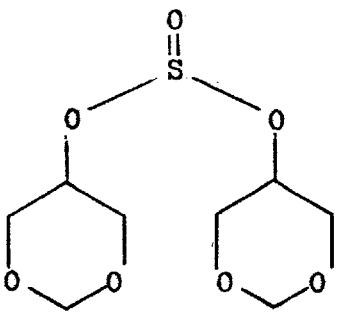
Fig. 10


OH
OH
OH
H+
(96)
(97)
PhCO-Cl/py.
Me·C6H4SO2Cl
py.
OBz
BzO
crystallization
OTs
TsO
crystallization
TsO
BzO
-OH
OH
Me·C6H4SO2Cl/py.
(96)

from chloroform-petroleum. The tosylate prepared in this way was identical to that prepared from pure 5-hydroxy-*m*-dioxan and its n.m.r. spectrum was identical to that recorded by other authors[100] who did not, however, describe any other properties or the preparation of the compound.

When 5-toluene-*p*-sulphonyloxy-*m*-dioxan and *N*-methyl-aniline were heated together in dimethylformamide at 105° or in refluxing dioxan in the presence of sodium hydride, none of the desired product could be detected.

Tsatsas[101] reports the preparation of 5-chloro-*m*-dioxan (95), X= Cl, from the reaction of the alcohol (96) with thionyl chloride in pyridine. Using this method an 8% yield of the chloride was obtained but when the reaction was carried out using chloroform (containing a little pyridine) as solvent, a sulphur containing product was isolated in 70% yield; this product was identified as the sulphite (98). Because of the difficulty of preparing the chloride (95), X= Cl, its examination as an intermediate for the preparation of the 1,3-diol (83), X= OH, was discontinued; the only source of this diol remained the LAH reduction of the ester (87).



(98)

1,3-Dimethanesulphonyloxy-2-N-methylanilinopropane (83), X= OSO_2Me, was prepared from the 1,3-diol by reaction with methanesulphonyl chloride in the presence of triethylamine. Unlike its 1,2-isomer, this compound could not be purified by preparative thin layer chromatography but a 'crude' sample proved to be of adequate analytical purity. Surprisingly, the four methylene protons of this compound appeared as a sharp singlet in the n.m.r. spectrum (see P.93); however, the methine proton could not be seen as a singlet probably because it was masked by signals resulting from the small amounts of impurity present. The 1,3-dimethanesulphonate was, however, of sufficient purity for a study to be made of its reactions with different nucleophiles. In order to identify the products of these reactions it was necessary to prepare, from the 1,3-diol, the 1,3-diacetate (83), X= OAc, (with acetic anhydride-pyridine[98]) and the 1,3-dimethyl ether (83),

X= OMe, (with dimethyl sulphate - sodium hydroxide in THF[98]). The corresponding compounds derived from the 1,2-diol were already available, having been prepared by Mr. G.Durrant[87].

The n.m.r. spectra of the compounds (82) and (83), X= OMe, OAc and OSO_2Me, are recorded on Pp. 92 and 93. Products of the displacement reactions of the two dimethanesulphonates were identified on the basis of these authentic spectra while the ratios of isomeric products (when a mixture was obtained) were estimated from the relative strengths of the N-methyl signals which were always well separated for pairs of isomers.

Reactions of the dimethanesulphonates of 2-N-methylanilino-propane-1,3-diol and 3-N-methylanilinopropane-1,2-diol.

i) with methanol;

Solvolysis of the two dimethanesulphonates in methanol, buffered with calcium carbonate, gave exclusively 1,2-dimethoxy-3-N-methylanilinopropane in both cases.

ii) with sodium methoxide;

Both dimethanesulphonates reacted with sodium methoxide in boiling methanol to give a mixture of the 1,2-and 1,3-dimethyl ethers (82) and (83), X= OMe, in the ratio 1:1.

iii) with potassium acetate;

Both dimethanesulphonates reacted with potassium acetate in acetic anhydride at 100° to give a mixture of the 1,2- and 1,3-diacetates (82) and (83), X= OAc, in the ratio 3:2.

iv) with sodium thiophenate;

The 1,2-dimethanesulphonate reacted with sodium thiophenate in boiling methanol to give a

mixture of the 1,2- and 1,3-bisphenylsulphides (82) and (83), X= SPh, in the ratio 7:3. These isomeric products were separated by preparative thin layer chromatography and examination of their n.m.r. spectra (Pp. 92 and 93) enabled the individual isomers to be identified. In all other authentic compounds the N-methyl resonance appeared at higher field for the 1,3-isomer and so the 1,3-bisphenylsulphide (83), X= SPh, was identified as that with the N-methyl resonance at τ 7·26, the 1,2-isomer as that with the N-methyl at τ 7·00. The complex splitting pattern of the methylene protons of the 1,2-isomer and distorted AB system of the methylene protons of the 1,3-isomer are in agreement with this assignment.

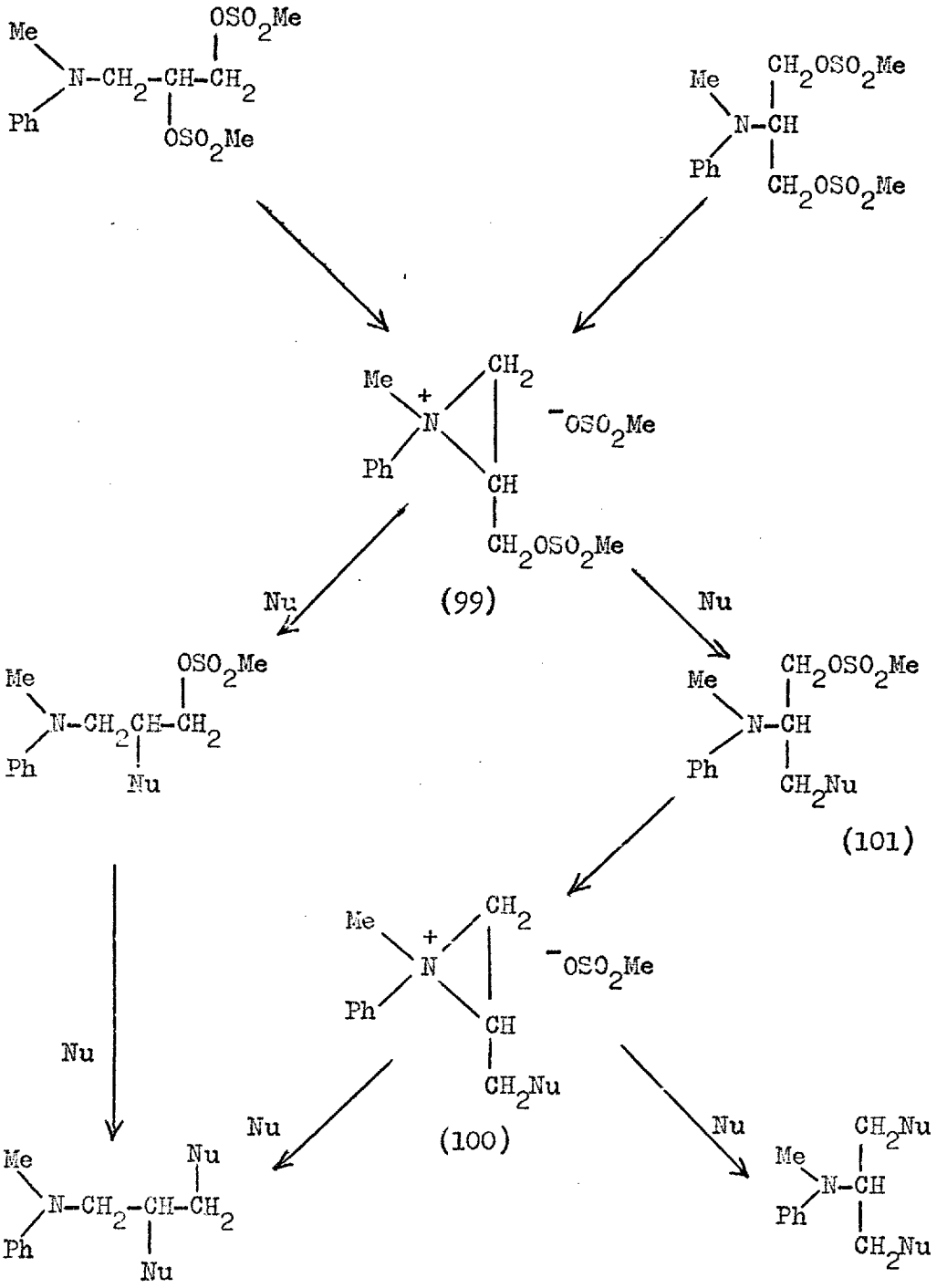
The 1,3-dimethanesulphonate reacted with sodium thiophenate to give a mixture of the 1,2- and 1,3-bisphenylsulphides in the ratio 2:3.

Control reactions established the stability of the 1,3-dimethyl ether and the 1,2-diacetate to the conditions of i) and ii) above and by heating both of the dimethanesulphonates in boiling acetone it was shown that they were not interconvertible.

It was found, then, that the two dimethanesulphonates reacted with sodium methoxide and with potassium acetate to give, in each case, products of identical composition and this can be interpreted on the basis of a scheme involving common intermediates which are best formulated as aziridinium ions (99) and (100), fig. 11. The direction of ring opening of such cyclic intermediates will depend both on electronic and steric factors and the latter appear to dominate the course of the reactions with sodium methoxide and potassium acetate. If the primary and secondary positions of the ions (99) and (100) were attacked equally by nucleophiles then a product ratio of 3:1 (1,2- to 1,3- disubstituted product) would result. The observed product ratios are nearer to unity and the conclusion must be that acetate and methoxide ions preferentially attack the less hindered primary positions thus increasing the proportion of the 1,3- disubstituted product.

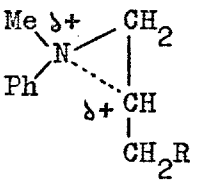
In contrast to the above, the two dimethanesulphonates reacted with methanol to give only the 1,2-dimethyl ether while the 1,3-dimethyl ether was shown to be stable to the reaction conditions. This indicates either that the aziridinium ion (99) is opened only at the secondary position or, that if any of the aziridinium ion (100) is formed then it reacts with methanol exclusively at the secondary position. (It is unlikely that

Fig. 11

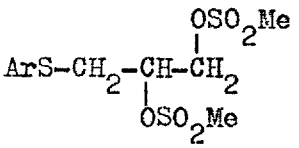

Me
OSO2Me
N-CH2-CH-CH2
Ph
OSO2Me
Me
CH2OSO2Me
N-CH
Ph
CH2OSO2Me
Me
CH2
+
N
-OSO2Me
Ph
CH
CH2OSO2Me
(99)
Nu
Nu
Me
OSO2Me
N-CH2CH-CH2
Ph
Nu
Me
CH2OSO2Me
N-CH
Ph
CH2Nu
(101)
Me
CH2
+
N
-OSO2Me
Ph
CH
CH2Nu
(100)
Nu
Nu
Nu
Me
Nu
N-CH2-CH-CH2
Ph
Nu
Me
CH2Nu
N-CH
Ph
CH2Nu

methanol would react with the monosubstituted intermediate (101) except by way of the cyclic ion (100). The stronger nucleophiles methoxide and acetate gave no evidence of such direct displacement reactions with the two dimethanesulphonates, as shown by the observed product ratios). It is proposed, therefore, that the selective opening of the aziridinium ions (99) and (100) by methanol, occurs by means of an S_N1 type mechanism involving partial localization of charge at the secondary position, as in (102). The stabilization of charge at this position would be greater than at the primary position although its extent would be affected by the inductive and hyperconjugative properties of the function CH_2R in (102).

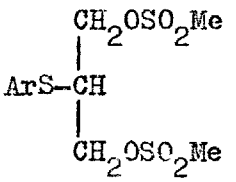
The situation described above is not unlike that proposed by Bardos et.al.[20] in their study of the solvolysis reactions of some aromatic nitrogen mustards. They suggested that these were 'S_N1 type reactions' involving a solvated carbonium ion - nitrogen dipole, the collapse of which gave rise to the solvolysis product (see P.18). It does not seem unreasonable to expect that in an unsymmetrical system, such as that examined here, the electronic effects associated with any localization of charge will exert a directing influence on the site of nucleophilic attack. This, of course, will apply mainly when the nucleophile is weak, as in the case of methanol; stronger nucleophiles may react



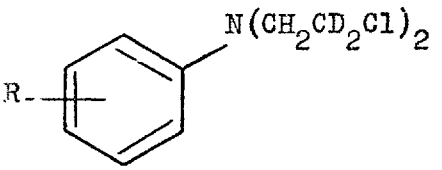
(102)



(103)



(104)



(16) R= H; p-MeO; 2,4$(NO_2)_2$.

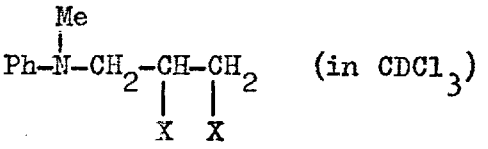
directly with the aziridinium ions (S_N2 type reaction) and be influenced by steric factors as in the case of reactions with methoxide and acetate.

The reaction scheme proposed here is directly related to that suggested to explain the reactions of the methanesulphonates (103) and (104) in which episulphonium ions are involved[105]. That these similar types of compound react with nucleophiles in a similar way is not surprising although it should be emphasized that some differences do exist. This is demonstrated particularly by the course of the reactions of the two dimethanesulphonates (82) and (83), X= OSO_2Me, with sodium thiophenate. Although rearranged products were obtained from both the 1,2- and 1,3-dimethanesulphonates, the product ratios were different showing that significant reaction occurred without the intervention of a cyclic intermediate. In contrast, the dimethanesulphonates of type (103) and (104) reacted with sodium thiophenate and other powerful nucleophiles without giving rise to any rearranged products[105]. This indicates that the tendency to form an aziridinium ion in systems such as (82) and (83), X= OSO_2Me, is greater than the tendency for formation of episulphonium ions in the compounds (103) and (104).

Direct displacement of chloride from the aromatic

nitrogen mustards (16), by thiocresolate, was reported by Bern et.al.[21] whereas weaker nucleophiles reacted by way of a cyclic intermediate. This also corresponds with the results reported here and it seems clear that the character of the nucleophile has an important influence on the mechanism of the alkylation reactions of compounds of the nitrogen mustard type.

N.m.r. spectra of authentic compounds;

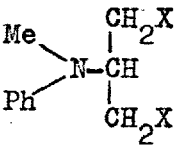


(in $CDCl_3$)

aromatic	N–CH_2–	–CH_2–	–CH–	N–CH_3	X	Group X
2·6–3·4τ m 5H	ca. 6·3τ m 2H	ca. 5·6τ m 2H	ca. 5·0τ m 1H	7·06τ s 3H	7·00τ and 6·93 two s 6H	OSO_2CH_3
ca. 3·2 m 5H	ca. 6·8 two s superimposed on m 11H			7·10 s 3H	see 6·8	OCH_3 *
ca. 3·2 m 5H	6·6 q 2H	5·9 t 2H	4·8 m 1H	7·07 s 3H	8·05 and 7·92 6H two s	OAc
2·6–3·5 m 15H	5·90 – 6·95 m 5H			7·00 s 3H	in aromatics	SPh

* This compound was prepared by Mr. G. Durrant and the spectrum recorded in CCl_4.

N.m.r. spectra of authentic compounds;



(in $CDCl_3$)

aromatic	$-CH_2-$	$-CH-$	$N-CH_3$	X	Group X
2·5–3·3τ m 5H	5·5τ s 4H	ca. 6·3τ several peaks. ca.1H	7·11τ s 3H	7·04τ s 6H	OSO_2CH_3
2·60–3·25 m 5H	6·41 d 4H	5·83 m 1H	7·15 s 3H	6·67 s 6H	OCH_3
2·50–3·25 m 5H	ca. 5·66 broad s 5H		7·16 s 3H	8·03 s 6H	OAc
2·6–3·5 m 15H	6·75 m 4H distorted AB	5·95 m 1H	7·26 s 3H	in aromatics	SPh

Reactions of 1,2-dimethanesulphonyloxy-3-N-methylanilinopropane.

n.m.r. spectra in $CDCl_3$

reagent (product)	aromatic	$-CH_2-CH-CH_2-$	$N-CH_3$	X	Group X
MeOH (1,2-di-methyl ether)	2·5–3·4τ m 5H	ca. 6·6τ two s and m 11H	7·0τ s 3H	see 6·6τ	OMe
NaOMe (1,2-and 1,3-dimethyl ethers)	2·7–3·4 m 5H	5·8–6·6 two s and m 11H	7·0s 1½H 7·15s 1½H	see 6·6	OMe
KOAc (1,2-and 1,3-diacetates)	2·7–3·4 m 5H	4·6–6·5 5H	7·05s 2H 7·18s 1H	7·92s and 8·05s 6H	OAc
NaSPh (1,2-and 1,3-bis-phenylsulphides)	2·6–3·6 m 15H	4·0–7·0 m 5H	7·0s 2·1H 7·28s 0·9H	see aromatics	SPh

Reactions of 1,3-dimethanesulphonyloxy-2-N-methylanilinopropane.

n.m.r. spectra in $CDCl_3$

reagent (product)	aromatic	$-CH_2CH-CH_2-$	$N-CH_3$	X	Group X
MeOH (1,2- di-methyl ether)	2·6–3·4τ m 5H	ca 6·6τ two s and m 11H	7·0τ s 3H	see 6·6τ	OMe
NaOMe (1,2- and 1,3-dimethyl ethers)	2·6–3·4 m 5H	5·8–6·6 two s and m 11H	7·0s 1½H 7 14s 1½H	see 6·6	OMe
KOAc (1,2- and 1,3-diacetates)	2·6–3·4 m 5H	4·6–6·5 5H	7·03s 2H 7·16s 1H	7·92s and 8·04s 6H	OAc
NaSPh (1,2 and 1,3-bis-phenylsulphides)	2·6–3·4 m 15H	4·0–7·0 m 5H	7·0s 1·2H 7·28s 1·8H	in aromatics	SPh

EXPERIMENTAL SECTION

The figures in parentheses, shown throughout this section, refer to pages in laboratory notebooks.

Infra-red spectra were recorded on Unicam SP 200 and Perkin-Elmer 700 instruments; n.m.r. spectra were recorded on Varian A 60 and HA 100 instruments using tetramethylsilane as internal reference.

Thin layer chromatograms were carried out using Kieselgel GF_{254} (E.Merck Ltd.) and column chromatography was with silica gel M.F.C. (Hopkins and Williams Ltd.).

Melting points were determined using a Kofler block and are uncorrected. Organic solutions were dried with magnesium sulphate except where stated otherwise. Petroleum refers to the fraction b.p. 60-80° unless otherwise stated.

Some carbamates derived from p-(bis-2-chloroethylamino)phenol.

p-(Bis-2-hydroxyethylamino)phenol (35).

p-Aminophenol (92 g) was suspended in water (200 ml) and glacial acetic acid (75 ml). Ethylene oxide (ca. 100 ml) was added with stirring at 0° and the reaction mixture was allowed to stand overnight when t.l.c. (chloroform) showed no starting material. Neutralization with solid sodium carbonate precipitated the triol (111 g), m.p. 135-138° (from acetone) (lit.[53], 140°).

Benzyl p-(bis-2-hydroxyethylamino)phenyl ether (37).

Sodium metal (13·1 g) was dissolved in ethanol (800 ml) and the above triol (112 g) added. Benzyl bromide (97 g) was added dropwise with stirring and the mixture boiled under reflux for 3 hours. The resultant red solution was concentrated and poured into excess water (1 litre) and the ether (137 g) filtered off and recrystallized from ethanol-water. It had m.p. 91-94° (lit.[62], 93-94°).

Benzyl p-(bis-2-chloroethylamino)phenyl ether (39).

The diol (137 g), from the previous stage, was dissolved in chloroform (750 ml) and phosphorus pentachloride (135 g) added. When the initial reaction had subsided the solution was refluxed for 2 hours, cooled, poured into water (300 ml) and washed with aqueous sodium carbonate. The dried chloroform solution was concentrated to 300 ml and the product precipitated by addition of ethanol. Yield 77 g, m.p. 101-104° (from ethanol-petroleum) (lit.[62], 105-106°).

p-(Bis-2-chloroethylamino)phenol hydrochloride (42, 134).

The above benzyl ether (43 g) was dissolved in a 1:1 mixture (300 ml) of glacial acetic acid and conc. hydrochloric acid and boiled under reflux for 1¼ hours. The solution was cooled, neutralized (sodium carbonate and a little water) and extracted with chloroform (7×100 ml). The dried extracts were concentrated and an ethanolic solution of hydrogen chloride (8 g) was added. Evaporation of solvent gave an oil which rapidly solidified. The hydrochloride (30·9 g) was recrystallized from ethanol-petroleum and had m.p. 136-141° (lit.,[53] 168°, lit.,[61] 180-181°), ν_{max}(nujol) 3300, 2410 and 1600 $cm.^{-1}$ identical to that of an authentic sample.

p-(Bis-2-chloroethylamino)phenyl N-p-tolylcarbamate (26).

The p-mustard phenol hydrochloride (1·35 g) was suspended in dry benzene (20 ml) and triethylamine (0·514 g) added, followed by p-tolyl isocyanate (0·673 g). The mixture was stirred and refluxed for 3 hours, washed with water (2×20 ml) and dried. Evaporation of solvent under reduced pressure gave the title compound (1·44 g), m.p. 126·5-128·5° (from benzene-petroleum), ν_{max}(nujol) 3350, 1710 and 1610cm.$^{-1}$ (Found: C,58·98; H,5·47; Cl,19·11; N,7·62; $C_{18}H_{20}Cl_2N_2O_2$ requires C,58·84; H,5·49; Cl,19·30; N,7·63%).

p-(Bis-2-chloroethylamino)phenyl N-m-tolylcarbamate (27).

This was prepared from the p-mustard phenol hydrochloride (2 g) and m-tolyl isocyanate (0·993 g) in a similar manner to that described above for the p-isomer. The carbamate (2·23 g) had m.p. 101-103° (from benzene-petroleum), ν_{max}(nujol) 3330, 1705 and 1610cm.$^{-1}$ (Found: C,58·95; H.5·46; Cl,19·10; N,7·48%).

p-(Bis-2-chloroethylamino)phenyl N-o-tolylcarbamate (28).

This was prepared from the p-mustard phenol hydrochloride (2 g) and o-tolyl

isocyanate (0·99 g) in the same way as the previous isomers. The carbamate (2·26 g) had m.p. 92–94° (from benzene–petroleum), ν_{max}(nujol) 3400, 1730, 1605 and 1585 cm.$^{-1}$ (Found: C,58·86; H,5·48; Cl,19·21; N,7·60%).

o-Chlorophenyl isocyanate (49).

o-Chloroaniline (6·4 g) in dry benzene (20 ml) was added to a solution of phosgene (ca. 5 g) in benzene (70 ml). A white solid was precipitated and the mixture was boiled under reflux for 5 hours when the solvent was removed by distillation. The residue was distilled giving the isocyanate (1·44 g), b.p. 80–81° at 15 mmHg (lit.,[63] 114–115° at 43 mmHg), n_D^{21} 1·5560, ν_{max}(CCl_4) 2270 cm.$^{-1}$

m-Chlorophenyl isocyanate (53).

A solution of m-chloroaniline (5·4 g) in dry benzene (50 ml) was added to a stirred solution of excess phosgene in benzene (70 ml) while a stream of the gas was bubbled through. The mixture was then boiled under reflux for 3 hours and the solvent removed. Distillation of the resulting oil gave the isocyanate (5·5 g), b.p. 82° at 15 mmHg, (lit.,[63] 113–114° at 43 mmHg), n_D^{23} 1·5558, ν_{max}(CCl_4) 2280 cm.$^{-1}$

p-(Bis-2-chloroethylamino)phenyl N-o-chlorophenylcarbamate (54).

The p-mustard phenol hydrochloride (2 g) was suspended in dry benzene (100 ml) and triethylamine (0·81 g) added, followed by o-chlorophenyl isocyanate (1·15 g). The mixture was stirred and refluxed for 3 hours when t.l.c. (benzene) showed one major product. Triethylamine hydrochloride was filtered off, the solution washed with water and dried. Evaporation of solvent gave the title compound (2·42 g), which when recrystallized from petroleum (b.p.80-100°) had m.p. 109-110°, ν_{max}(nujol) 3400, 1740cm.$^{-1}$ (Found: C,52·84; H,4·65; Cl,27·33; N,7·39; $C_{17}H_{17}Cl_3N_2O_2$ requires C,52·60; H,4·42; Cl,27·45; N,7·22%).

p-(Bis-2-chloroethylamino)phenyl N-m-chlorophenylcarbamate (55).

This was prepared from m-chlorophenyl isocyanate (1·15 g) in the same way as described above for the o-isomer. The carbamate (1·89 g) was obtained as a white solid, m.p. 133-134° (from CCl_4), ν_{max}(nujol) 3300 and 1710 cm.$^{-1}$ (Found: C,52·65; H,4·39; Cl,27·32; N,7·39%).

p-(Bis-2-chloroethylamino)phenyl N-p-chlorophenylcarbamate (43)

In a similar way to that described above for the o-isomer, p-chlorophenyl isocyanate (1·1 g) reacted to give the title compound

(1·7 g), m.p. 173–175° (from benzene–petroleum), ν_{max}(nujol) 3360, 1710 cm.$^{-1}$ (Found: C,52·78; H,4·57; Cl,27·24; N,7·24%).

p-(Bis-2-chloroethylamino)phenyl N-o-methoxyphenylcarbamate (45).

The reaction of o-methoxyphenyl isocyanate (1·15 g) and the p-mustard phenol hydrochloride (2 g) in the presence of triethylamine (0·81 g), essentially as described for preceding carbamate compounds, gave the title compound (2 g), m.p. 108–109° (from petroleum b.p. 80–100°), ν_{max}(nujol) 3380 and 1730 cm.$^{-1}$ (Found: C,56·22; H,5·40; Cl,18·53; N,7·20. $C_{18}H_{20}Cl_2N_2O_3$ requires C,56·41; H,5·27; Cl,18·50; N,7·31%).

N-Acetyl-m-aminophenol (50, 58).

m-Aminophenol was acetylated with acetic anhydride in acetic acid solution as described by Reverdin and de Luc[64], to give the acetyl compound, m.p. 147–148° (lit.,[64] 148°).

N-Acetyl-m-aminoanisole (50, 61, 65).

The above phenol (5·8 g) with dimethyl sulphate (5·2 g) in aqueous sodium hydroxide, was shaken vigorously for 6 hours. The product (3·37 g) precipitated from solution and when recrystallized from aqueous ethanol had m.p. 79–80° (lit.,[64] 80–81°).

m-Aminoanisole (68).

N-Acetyl-m-aminoanisole (6 g) was dissolved in water (30 ml) and conc. hydrochloric acid (30 ml) and the solution refluxed for 30 minutes, cooled and neutralized with conc. aqueous ammonia. The solution was extracted with chloroform (2×50 ml) and the dried extracts evaporated to give m-aminoanisole (3·8 g), b.p. 117-118° at 15 mmHg (lit.,[64] 243° at 755 mmHg), n_D^{24} 1·5777, $\nu_{max}(CCl_4)$ 3500, 3400 and 1620 $cm.^{-1}$

m-Methoxyphenyl isocyanate (70).

m-Aminoanisole (3·8 g) was dissolved in dry benzene (50 ml) and added dropwise to a solution of excess phosgene in benzene (100 ml) while a stream of the gas was bubbled through. The mixture was then refluxed for one hour when a clear solution was obtained; removal of solvent gave the isocyanate as an almost colourless oil (3·9 g), b.p. 95-96° at 15mmHg (lit.,[65] 94·6-94·8°at 10 mmHg), n_D^{24} 1·5410, $\nu_{max}(CCl_4)$ 2295 $cm.^{-1}$

p-(Bis-2-chloroethylamino)phenyl N-m-methoxyphenylcarbamate (71).

The reaction of the above isocyanate with the p-mustard phenol hydrochloride in the manner (and quantities) described for the o-chlorophenyl compound, gave a 70% yield of the carbamate,

m.p. 78–79° (from a large volume of petroleum), ν_{max}(nujol) 3300, 1705 cm.$^{-1}$ (Found: C,56·48; H,5·36; Cl,18·23; N,7·19%).

p-(Bis-2-chloroethylamino)phenyl N-p-methoxyphenylcarbamate (44).

p-Methoxyphenyl isocyanate (1·13 g), p-mustard phenol hydrochloride (2 g) and triethylamine (0·82 g) reacted in the usual way to give the title compound (2·4 g), m.p. 146·5–148° (from petroleum b.p. 80–100°), ν_{max}(nujol) 3350 and 1700 cm.$^{-1}$ (Found: C,56·54; H,5·28; Cl,18·49; N,7·30%).

p-Sulphonamidophenyl isocyanate (195, 205).

This was prepared in 80% yield by the action of phosgene on sulphanilamide in boiling ethyl acetate. The solution obtained after 2 hours was filtered and concentrated; addition of petroleum precipitated the crude isocyanate as a white solid, m.p. 147–150° (lit.,[66] 156–157°), which was used without further purification. The isocyanate had ν_{max}(nujol) 3350,3250, 3100, 2290 and 1780 cm.$^{-1}$ (impurity).

p(Bis-2-chloroethylamino)phenyl chloroformate (147, 167, 261).

The mustard phenol (obtained by treating 5 g of the hydrochloride with aqueous sodium bicarbonate) and quinoline (2·5g) in chloroform solution, were added to a cooled solution of phosgene

(ca. 5 g) in dry benzene (50 ml). The mixture was left overnight, filtered and washed with water. Drying and evaporation of solvent gave the crude chloroformate (4 g). A sample was purified by distillation and had b.p. 140° at $1 \cdot 35 \times 10^{-4}$mmHg, $\nu_{max}(CCl_4)$ 1775cm.$^{-1}$ (Found: C,44·51; H,4·19; Cl,35·98; N,4·64. $C_{11}H_{12}Cl_3NO_2$ requires C,44·53; H,4·08; Cl,35·86; N,4·72%).

p-(Bis-2-chloroethylamino)phenyl N-p-sulphonamidophenylcarbamate.

i) from p-mustard phenol hydrochloride (198).

The mustard phenol hydrochloride (2 g), p-sulphonamidophenyl isocyanate (1·6 g) and triethylamine (90 mg) were dissolved in AnalaR ethyl acetate (80 ml) and the mixture stirred and boiled under reflux for 2 hours. The solution was decanted from precipitated solid, washed with water and dried. Evaporation gave a crude solid which was purified by column chromatography (acetone-petroleum, 1:1). The carbamate (Rf 0·5; 1 g) had an ill-defined m.p. ca. 180°, ν_{max}(nujol) 3300-3200 and 1725 cm.$^{-1}$ (Found: C,47·04; H,4·59; Cl,13·56, 13·86; N,9·62. $C_{17}H_{19}Cl_2N_3O_4S$ requires C,47·22; H,4·49; Cl,16·40; N,9·72%).

ii) from mustard chloroformate (262, 168).

Sulphanilamide (400 mg) and pyridine (200 mg) were dissolved in dry acetone (20 ml) and

the mustard chloroformate (700 mg, freshly prepared and distilled) was added dropwise at room temperature. After 1½ hours the solution was poured into water, extracted with ethyl acetate and the extract dried. Evaporation of solvent gave the carbamate (0·4 g), m.p. 185-202° (from ethyl acetate-carbon tetrachloride), ν_{max}(nujol) 3300-3200 and 1725 $cm.^{-1}$, τ (d_6-acetone) 0·5(1H,s, NH-CO-O), 2·1 (4H, d, aromatic), ca. 3·0 (4H, q, aromatic), 6·2 (8H, s, $N(CH_2CH_2Cl)_2$), 6·84 (2H, s, SO_2NH_2). (Found: C, 47·22; H, 4·45; Cl,16·33; N,9·85%).

Methyl p-(methyl-amino)benzoate (137).

p-(Methylamino)benzoic acid (6 g), methanol (150 ml) and conc. sulphuric acid (1 ml) were boiled under reflux for 20 hours when t.l.c. (chloroform) showed no acid to be present. The solution was concentrated to 50 ml and poured into water (50 ml). After basification with aqueous sodium hydroxide this solution was extracted with chloroform (50 ml×3),the extracts dried and evaporated giving the ester (2·5 g), m.p. 94-95° (from aqueous ethanol) (lit.,[67] 95·5°).

p-(Bis-2-chloroethylamino)phenyl N'-p-methoxycarbonylphenyl-N'-methylcarbamate (149).

Freshly prepared mustard chloroformate (see

above; 1·7 g) was dissolved in ethanol-free chloroform (30 ml) and a solution of the preceding amine (0·94 g) and pyridine (0·5 g) in chloroform was added with stirring. After 7 hours refluxing, the reaction mixture was washed with dilute hydrochloric acid, aqueous sodium hydrogen carbonate and water. Drying and evaporation of solvent gave an oil which was crystallized from carbon tetrachloride-petroleum. Recrystallization from benzene-petroleum (b.p. 80–100°) afforded the title compound (1·23 g), m.p. 92–93°, ν_{max}(nujol) 1720cm.$^{-1}$ (Found: C,56·41; H,5·37; Cl,16·68; N,6·43. $C_{20}H_{22}Cl_2N_2O_4$ requires C,56·45; H,5·21; Cl,16·67; N,6·59%).

Substituted phenyl chloroformates.

Unless otherwise stated, the general method of preparation described below for p-tolyl chloroformate was used in the preparation of all substituted phenyl chloroformates reported here.

p-Tolyl chloroformate (36).

p-Cresol (5·4 g; 0·05 mole) and quinoline (6·5 g; 0·05 mole) were dissolved in dry benzene (50 ml) and the solution added dropwise to an ice-cooled solution of excess phosgene in benzene (ca. 50 ml) with stirring. After a total of 2½ hours (the reaction was followed by t.l.c.) the quinoline hydrochloride was filtered off, the solution was washed with a little water, dried and the solvent removed by distillation. This gave the chloroformate as a yellow oil (3·67 g), b.p. 82° at 15 mmHg (lit.,[106] 108° at 30 mmHg), n_D^{21} 1·5100, ν_{max}(film) 1775 cm.$^{-1}$

m-Tolyl chloroformate (31).

This was obtained in a 45% yield from m-cresol and it had b.p. 87-89° at 15 mmHg (lit.,[106] 103° at 22 mmHg), $n_D^{21·5}$ 1·5100, ν_{max}(film) 1780 cm.$^{-1}$

o-Tolyl chloroformate (32).

o-Cresol gave a 35% yield of the chloroformate, b.p. 81-82°at 15 mmHg (lit.,[106] 110-120° at 28 mmHg), n_D^{23} 1·5100, ν_{max}(film) 1780 $cm.^{-1}$

o-Chlorophenyl chloroformate (69).

This was obtained from o-chlorophenol and phosgene in the presence of quinoline, the yield being 43%. The chloroformate had b.p. 94° at 15 mmHg (lit.,[107] 113° at 27 mmHg), n_D^{23} 1·5238, $\nu_{max}(CCl_4)$ 1780 $cm.^{-1}$

m-Chlorophenyl chloroformate (59).

This was prepared essentially as described for the o-isomer (yield 58%) and had b.p. 104-105° at 20 mmHg (lit.,[108] 98-100° at 13 mmHg), n_D^{21} 1·5300, ν_{max}(film) 1775$cm.^{-1}$

p-Chlorophenyl chloroformate (74).

A 64% yield of this chloroformate was obtained from p-chlorophenol using the general method. The compound had b.p. 97-98° at 15 mmHg (lit.,[107] 114° at 20 mmHg), n_D^{26} 1·5306, $\nu_{max}(CCl_4)$ 1785 and 1770 $cm.^{-1}$ (shoulder).

o-Methoxyphenyl chloroformate (82).

The general method gave a 67% yield of this chloroformate, b.p. 110-112° at 15 mmHg (lit.,[109] 110° at 10 mmHg), n_D^{24} 1·5170, $\nu_{max}(CCl_4)$ 1785 $cm.^{-1}$

m-Methoxyphenyl chloroformate (118).

The reaction of m-methoxyphenol (3·35 g) with excess phosgene in the presence of quinoline (3·89 g) in the usual way, gave the chloroformate (2 g), b.p. 128-129° at 25 mmHg, $\nu_{max}(CCl_4)$ 1780 $cm.^{-1}$ The compound was characterized as the N-phenylcarbamate derivative described below.

m-Methoxyphenyl N-phenylcarbamate (119).

The above chloroformate (200 mg) was dissolved in dry benzene (10 ml) and aniline (220 mg) added. The mixture was stirred and heated under reflux for 20 minutes, filtered, washed with dil. hydrochloric acid, aq. sodium hydrogen carbonate and water and finally dried. Evaporation gave the derivative (120 mg), m.p. 123-124° (from benzene-petroleum), $\nu_{max}(CHCl_3)$ 3420 and 1745 $cm.^{-1}$ (Found: C,69·12; H,5·47; N,5·59. $C_{14}H_{13}NO_3$ requires C,69·13; H,5·39; N,5·76%).

p-Methoxyphenyl chloroformate (81).

This was prepared from p-methoxyphenol (6·2 g), quinoline (6·5 g) and phosgene in dry benzene in the usual way. The product was obtained as an oil (6·9 g), b.p. 118–119° at 15 mmHg (lit.,[115] 49° at 0·27 mmHg), n_D^{21} 1·5225 (lit.,[115] n_D^{19} 1·5237), $\nu_{max}(CCl_4)$1780 cm.$^{-1}$ (Found: C,51·17; H,3·78; Cl,19·20. $C_8H_7ClO_3$ calc. C,51·50; H,3·78; Cl,19·00%).

p-tert-Butylphenyl chlorformate (92).

The reaction of p-tert-butylphenol with phosgene in the usual way gave a 63% yield of the chloroformate; it had b.p. 121–123° at 15 mmHg (lit.,[69] 124° at 12 mmHg), n_D^{21} 1·5035, $\nu_{max}(CCl_4)$ 1775 cm.$^{-1}$

p-Nitrophenyl chloroformate (334).

p-Nitrophenol (7 g) was treated with phosgene in the usual way. The chloroformate was obtained as a pale yellow solid (8·1 g) which had m.p. 69–79° (lit.,[70] 80–81°), $\nu_{max}(CHCl_3)$ 1780 cm.$^{-1}$ The chloroformate was used without further purification.

m-(NN-Dimethylamino)phenyl chloroformate (342,347).

m-(NN-Dimethylamino)phenol (8·8 g) in dry benzene (100 ml containing a little chloroform to aid solubility) was added to a cooled, stirred solution of excess phosgene in benzene (80 ml). After 3 hours the solution was filtered and the solvent removed to give the chloroformate[110] (4·7 g) which was distilled under reduced pressure and had b.p. 70-80° at 10^{-5}mmHg, $\nu_{max}(CHCl_3)$ 1780 cm.$^{-1}$ (Found: C,53·37; H,4·89; Cl,17·82. calc. for $C_9H_{10}ClNO_2$ C,54·16; H,5·05; Cl,17·76%).

p-Hydroxythiophenol (251,332).

p-Aminophenol (10 g) was dissolved in water (100 ml) and conc. HCl (20 ml) and a solution of sodium nitrite (6·5 g) in water (20 ml) added dropwise with stirring. The temperature was maintained at approximately 5°.

The solution of the diazonium salt so obtained, was neutralized with solid sodium hydrogen carbonate and then added to a solution of ethyl potassium xanthate (20 g) in water (25 ml) which was heated to 60-70°. The crude xanthate ester separated as a thick oil which was dissolved in 2N sodium hydroxide (50 ml) and boiled under reflux in an atmosphere of nitrogen for 2½ hours. The solution was then acidified with conc. HCl, extracted with chloroform (50 ml×2) and the extracts dried. Evaporation of solvent then gave a yellow oil which was suspended in dilute HCl containing

some zinc and refluxed for 30 minutes after which further extraction and drying gave p-hydroxythiophenol (4 g), b.p. 72–74° at 10^{-4} mmHg (lit.,[71] 133–137° at 11 mmHg), ν_{max}(film) 3350 (broad) and 2560 $cm.^{-1}$

p-Hydroxythioanisole (258,335).

The above thiol (4·4 g), sodium hydroxide (1·4 g) and methyl iodide (5·5 g) were dissolved in ethanol (50 ml) and the solution refluxed for 1½ hours in an atmosphere of nitrogen. The solution was then concentrated, poured into water (100 ml) and the product (2·85 g) filtered off and dried; when recrystallized from carbon tetrachloride–petroleum it had m.p. 83–84° (lit.,[72] 83–84°, lit.,[73] 84–85°).

p-(Methylthio)phenyl chloroformate (320, 337).

p-Hydroxythioanisole reacted with phosgene in the usual way to give a 72% yield of the chloroformate, b.p. 65–67° at 10^{-4} mmHg, n_D^{20} 1·5750, $\nu_{max}(CHCl_3)$ 1780 and shoulder at 1760 $cm.^{-1}$ (Found: C,47·25; H, 3·41; Cl,17·46; S,15·76. $C_8H_7ClO_2S$ requires C,47·42; H,3·48; Cl,17·49; S,15·79%).

Methyl 5-methylsalicylate (102).

5-Methylsalicylic acid (30 g) was dissolved in methanol (200 ml) containing conc. sulphuric acid (5 ml) and

the solution refluxed for 17 hours. The solution was then concentrated, poured into excess water and extracted with chloroform (100 ml and 50 ml × 2). The dried extracts were evaporated to give the ester (26·5 g), b.p. 120–121° at 18mmHg (lit.,[111] 120–121° at 18 mmHg), n_D^{20} 1·5330, $\nu_{max}(CCl_4)$ 3200 and 1675 $cm.^{-1}$

2-Methoxycarbonyl-4-methylphenyl chloroformate (107).

The above phenol (10 g) was treated with excess phosgene in the usual way for a period of 6 hours. Work up gave the chloroformate (5·6 g) as an oil, b.p. 96–98° at 0·3 mmHg, n_D^{23} 1·5191, $\nu_{max}(CCl_4)$ 1780 and 1725 $cm.^{-1}$ (Found: C,52·73; H,4·09; Cl,15·72. $C_{10}H_9ClO_4$ requires C,52·53; H,3·97; Cl,15·51%).

p-Hydroxyphenylacetic acid (236).

p-Methoxyphenylacetic acid (17 g) was suspended in aqueous hydrobromic acid (45%, 80 ml) and the mixture boiled under reflux for 7 hours. After standing overnight, the mixture was filtered and the product was washed with water. When recrystallized from water it had m.p. 153–155° (lit.,[74] 147–149°).

Methyl p-hydroxyphenylacetate (239).

The above acid (11 g) was dissolved in dry methanol (200 ml) containing conc. sulphuric acid (2 ml) and

the solution refluxed for 15 hours. The solution was then concentrated to 50 ml, poured into water (100 ml) and neutralized with sodium hydrogen carbonate solution. Extraction with chloroform (50 ml×3), drying and evaporation of solvent gave the ester (8·4 g), b.p. 104–106° at $1·3\times10^{-4}$ mmHg (lit.,[75] 310° at 760·5 mmHg), $\nu_{max}(CHCl_3)$ 3600–3200 and 1730 $cm.^{-1}$

p-(Methoxycarbonylmethyl)phenyl chloroformate (250,271).

Methyl p-hydroxyphenylacetate (4 g) and quinoline (3·14 g), in benzene solution, reacted with phosgene in the usual way to give the title compound (3·2 g), b.p. 92–96° at 10^{-4} mmHg , n_D^{20} 1·5245, $\nu_{max}(CCl_4)$ 1785 and 1740 $cm.^{-1}$ (Found: C,52·82; H,4·18; Cl,15·40. $C_{10}H_9ClO_4$ requires C,52·53; H,3·97; Cl,15·51%).

Methyl 3-(p-hydroxyphenyl)propionate (101, 106).

3-(p-Hydroxyphenyl)propionic acid (20 g), conc. sulphuric acid (3 ml) and methanol (150 ml) were heated under reflux for 40 hours. The solution was cooled, concentrated to 50 ml and poured into water (200 ml). Extraction with chloroform (100 and 50 ml), drying and evaporation gave the ester (14·5 g), b.p. 129–132° at 0·3 mmHg (lit.,[76] 186–187° at 17 mmHg). The ester was crystallized from ether–petroleum (b.p. 40–

60°) and had m.p. 37-39°(lit.,[76] 40-41°).

p-(2-Methoxycarbonylethyl)phenyl chloroformate (110).

The reaction of the above phenol with phosgene in the usual way gave the chloroformate (71%), b.p. 124-126° at 0·5 mmHg, n_D^{23} 1·5100, $\nu_{max}(CCl_4)$ 1780 and 1738 $cm.^{-1}$ (Found: C,54·29; H,4·65; Cl,14·62. $C_{11}H_{11}ClO_4$ requires C,54·44; H,4·57; Cl,14·62%).

The residue from the distillation of this compound was purified by chromatography (chloroform) to give di-(p-(2-methoxycarbonylethyl)phenyl)carbonate (200 mg), m.p.112-114° (from petroleum (b.p. 80-100°)), ν_{max}(nujol) 1770 and 1720 $cm.^{-1}$ (Found: C,65·50; H,5·98. $C_{21}H_{22}O_7$ requires C,65·26; H,5·74%).

3-(p-Anisoyl)propionic acid (240,270).

Anisole (20 g) and succinic anhydride (18·5 g) were dissolved in dichloroethane (200 ml) and nitrobenzene (50 ml). Aluminium trichloride (50 g) was added, with stirring and cooling in ice, over a period of 2 hours. The mixture was stored in the refrigerator for 3½ days and then poured into water (400 ml). The crude solid so obtained was dissolved in aqueous sodium hydroxide and the solution washed with small portions of chloroform and then filtered. Acidification of the clear

solution with conc. hydrochloric acid gave 3-(p-anisoyl)propionic acid (27·9 g), m.p. 147-149° (from ethanol) (lit.,[112] 146-147°).

4-(p-Methoxyphenyl)butyric acid (244, 275).

Reduction of the preceding anisoyl acid (15·6 g) using the procedure described by Martin[113] gave the title compound (10·4 g), m.p. 58-59·5° (from ether-petroleum) (lit.,[113] 60-61°).

4-(p-Hydroxyphenyl)butyric acid (245, 277).

4-(p-Methoxyphenyl)butyric acid (10·3 g) and hydrobromic acid (50%; 60 ml plus 10 ml water) were boiled under reflux for 6 hours. The red solution was poured into water (150 ml) and the product filtered off, dried and recrystallized from benzene containing a little chloroform. The phenol-acid (7·3 g) had m.p. 108·5-109·5° (lit.,[77] 107-108°).

Methyl 4-(p-hydroxyphenyl)butyrate (248, 286).

A solution of the above acid (7·2 g) and conc. sulphuric acid (1 ml) in dry methanol (130 ml) was refluxed overnight, concentrated to 20 ml and poured into water (50 ml). Extraction with chloroform (50 ml×2) and drying gave the ester (6·36 g), b.p. 135° at 10^{-3} mmHg, n_D^{20} 1·5300,

$\nu_{max}(CHCl_3)$ 3590, 3330 (broad) and 1725 $cm.^{-1}$, $\tau(CDCl_3)$ ca. 3·1 (4H, q, aromatic), 3·54(1H, s, OH), 6·31 (3H, s, CO_2Me), 7·2–8·2 (6H, m, $CH_2CH_2CH_2$). (Found: C,67·17, 67·27; H,7·22, 7·19. $C_{11}H_{14}O_3$ requires C,68·03; H,7·27%).

This ester was characterized by preparation of the p-nitrobenzoate derivative from p-nitrobenzoyl chloride. The derivative had m.p. 103–104° (from methanol), ν_{max}(nujol) 1735 $cm.^{-1}$ (Found: C,62·83; H,5·19; N,3·85. $C_{18}H_{17}NO_6$ requires C,62·98; H,4·99; N,4·08%).

p-(3-Methoxycarbonylpropyl)phenyl chloroformate (295,274).

Methyl 4-(p-hydroxyphenyl)butyrate was treated with phosgene in the usual way except that the time of reaction was increased to 12–24 hours. The chloroformate (40–50% yield) had b.p. 102–106° at 10^{-4} mmHg, $\nu_{max}(CHCl_3)$ 1775 and 1725 $cm.^{-1}$ (Found: C,56·71; H,5·38; Cl,13·35. $C_{12}H_{13}ClO_4$ requires C,56·14; H,5·11; Cl,13·81%).

The N-phenylcarbamate derivative of this chloroformate was also prepared, essentially in the same manner as that described for the derivative of m-methoxyphenyl chloroformate. p-(3-Methoxycarbonylpropyl)phenyl N-phenylcarbamate had m.p. 111° (from carbon tetrachloride-petroleum), $\nu_{max}(CHCl_3)$1730 $cm.^{-1}$ (broad). (Found: C,68·75; H,6·01; N,4·49. $C_{18}H_{19}NO_4$ requires C,69·00;

H,6·11; N,4·47%).

2,4-Dimethylanisole (170, 173).

2,4-Dimethylphenol (89·7 g) was dissolved in aqueous sodium hydroxide (2N , 400 ml) and dimethyl sulphate (97 g) added dropwise with cooling. The solution was then refluxed for 1½ hours and excess sodium hydroxide solution was added. The cooled reaction mixture was extracted with chloroform (200 ml), the extracts washed with water and dried. Evaporation of solvent gave the product (76 g), b.p. 80° at 15 mmHg, n_D^{24} 1·5200, (lit.,[114] b.p. 73-74° at 13 mmHg).

Methyl 2-methoxy-5-methylbenzoate (200, 207, 210).

5-Methylsalicylic acid (15 g) was dissolved in dry acetone (200 ml) and potassium carbonate (35 g) and dimethyl sulphate (33 g) added. The mixture was stirred and refluxed under nitrogen for a total of 20 hours during which time more dimethyl sulphate (24 g) and potassium carbonate (15 g) were added. After this time, t.l.c. (chloroform) showed only one component and no starting material. The solid was filtered off and the solvent evaporated to give an oil which was distilled to give the product (14 g), b.p. 146-149° at 15 mmHg (lit.,[103] 128-130° at 14 mmHg), n_D^{23} 1·5363, $\nu_{max}(CCl_4)$ 1730 and 1715 $cm.^{-1}$

4-Methoxyisophthalic acid.

i) from 2,4-Dimethylanisole (171, 175, 185).

2,4-Dimethylanisole (15 g) was suspended in water (350 ml) and finely ground potassium permanganate (80 g) added over a period of 1½ hours while the mixture was heated on a steam bath. After a further 2½ hours the manganese dioxide was filtered off and washed with hot water. The clear solution was concentrated to 300 ml and then acidified with conc. hydrochloric acid. 4-Methoxyisophthalic acid (10·9 g) was dried in vacuo and used without further purification; it had m.p. 233-234° (sealed tube) (lit.,[102] 245°, corrected).

ii) from Methyl 2-methoxy-5-methylbenzoate (203, 215).

Methyl 2-methoxy-5-methylbenzoate (31·5 g) was suspended in water (800 ml) and finely ground potassium permanganate (60 g) added in the manner described in the previous preparation. Acidification of the filtrate after removal of manganese dioxide gave a mixture of 1-hydrogen 3-methyl 4-methoxyisophthalic acid and 4-methoxyisophthalic acid (16 g), m.p. 214-216°, E.W.= 158 (calculated for the dibasic acid 98, for the monobasic acid 210). The n.m.r. spectrum also indicated a mixture of products.

4-Hydroxyisophthalic acid (183, 191, 218).

The reaction of the mixture of acids prepared above or of 4-methoxyisophthalic acid with 50% aqueous hydrobromic acid, essentially as described for 4-(p-hydroxyphenyl)-butyric acid, gave the acid-phenol in yields of 70-80%. It had m.p. 308-310°(sealed tube) (lit.,[116] 283-285° corrected; lit.,[104] 314°).

Methyl 4-hydroxyisophthalate (186, 192, 219).

The above phenol (7·5 g) and conc. sulphuric acid (1 ml) were dissolved in methanol (100 ml) and the mixture refluxed for 18 hours when t.l.c. (ethanol) showed one spot. The solution was concentrated, poured into water (150 ml) and the precipitated solid recrystallized from ethanol to give the product (5 g), m.p. 93-96° (lit.,[104] 97·5°), $\nu_{max}(CHCl_3)$ 3150 (broad), 1715 and 1680 $cm.^{-1}$

2,4-Bismethoxycarbonylphenyl chloroformate (231).

Methyl 4-hydroxyisophthalate (4·8 g) and quinoline (3·1 g) were dissolved in chloroform (ethanol-free, 80 ml) and added to a solution of excess phosgene in dry benzene (50 ml). The mixture was stirred for 3 days at approximately 15°. The clear solution so obtained was worked-up in

the usual way to give the title compound (6·1 g), $\nu_{max}(CHCl_3)$ no hydroxyl peak, 1785, 1725 and 1680 $cm.^{-1}$ (The latter peak was weak and attributable to unreacted phenol).

The chloroformate could not be distilled and was characterized by preparation of the N-phenylcarbamate derivative:-

The crude chloroformate (250 mg) and aniline (200 mg) were stirred together at room temperature for 50 minutes in ethanol-free chloroform (10 ml). The solution was washed with dil. hydrochloric acid, aq. sodium hydrogen carbonate and with water, dried and evaporated to give the derivative (200 mg), m.p. 92-94° (from carbon tetrachloride-petroleum), ν_{max}(nujol) 3330 and 1720 $cm.^{-1}$ (Found: C,61·91; H,4·52; N,3·95: $C_{17}H_{15}NO_6$ requires C,62·00; H,4·56; N,4·25%).

p-Hydroxybenzenesulphonamide (217, 242, 97).

This was prepared from sulphanilamide essentially as described by Kermack et. al.[78] Column chromatography (ether) gave the product in 50-60% yield as a white crystalline solid, m.p. 175-177° (from ethyl acetate-carbon tetrachloride) (lit.,[78] 178°).

Attempted preparation of p-sulphonamidophenyl chloroformate (326, 222, 104, 98).

Equimolar amounts of p-hydroxybenzenesulphonamide and quinoline were reacted with excess phosgene in ethyl acetate-benzene solution for periods of ca. 5 hours. An oil separated and the clear solution was decanted, washed with water, dried and the solvent evaporated. The crude product obtained in this way (an oily solid) had an i.r. spectrum showing absorption in the region of 1780 $cm.^{-1}$ No purification could be achieved nor could a derivative be prepared.

p-Methoxycarbonylphenyl chloroformate (157).

Methyl p-hydroxybenzoate (10 g) reacted with excess phosgene in the presence of quinoline, as described for previous chloroformates. Distillation of the crude product gave a fraction b.p. 102° at 0·4 mmHg which had m.p. 53° when recrystallized from petroleum (lit.,[109] 58°).

Some carbamates derived from NN-bis-(2-chloroethyl)-p-phenylene-diamine and its m-isomer.

NN-Bis-(2-chloroethyl)aniline (313, 232, 66).

NN-Bis-(2-hydroxyethyl)aniline (100 g) was dissolved in chloroform (250 ml) and added dropwise to a cooled (ice) suspension of phosphorus pentachloride (135 g) in chloroform (100 ml). When the addition was complete, the solution was allowed to warm and then refluxed for $3\frac{1}{2}$ hours. T.l.c. (chloroform) showed no diol to be present and the solution was poured into ice-water (200 ml), washed with more water (100 ml) and dried. Evaporation of solvent followed by distillation, gave the product (89·3 g), b.p. 119-123° at 0·05 mmHg (lit.,[117] 164° at 14 mmHg). The clear oil solidified on cooling , to a mass of white crystals having m.p. 41-42° (lit.,[117] 45°).

NN-Bis-(2-chloroethyl)-p-nitrosoaniline (319, 255, 114, 67, 26a).

Nitrosation of the preceding compound by the method of Ross[11] gave the nitroso compound in 50-70% yield. Typical samples had m.p. 80-81°, 77-80° (lit.,[11] 79-80°).

N'-Acetyl-NN-bis-(2-hydroxyethyl)-p-phenylenediamine (301).

N-Acetyl-p-phenylenediamine (20 g) was dissolved in acetic acid (80 ml) and water (120 ml), cooled to 0-3° and ethylene oxide (10 g×2) added over a period of 3 hours. The solution was allowed to warm to room temperature overnight when t.l.c. (ethyl acetate) showed one spot, Rf 0·1, and a trace of starting material. Neutralization of the solution with solid sodium carbonate precipitated an almost quantitative yield of the crude diol. Recrystallization (charcoal) from water gave white crystals of the product (21·2 g), m.p. 145-147° (lit.,[68] 142·5-144·5°), ν_{max}(nujol) ca. 3200 (broad) and 1645 cm.$^{-1}$

N'-Acetyl-NN-bis-(2-chloroethyl)-p-phenylenediamine (324, 318).

The preceding diol (11·7 g) was dissolved in dry dimethylformamide (100 ml) and thionyl chloride (13 g) added dropwise. The solution was then heated to 90° for 30 minutes, poured into water (400 ml) and extracted with chloroform (50 ml×4). The chloroform extracts were washed with sodium hydrogen carbonate solution and then water. Drying and evaporation of solvent gave the crude product which was recrystallized (charcoal) from benzene-petroleum and had m.p. 122-125° (lit.,[11] 124-126°) which was undepressed by mixing with a sample prepared by acetylation of the mustard amine prepared by the method of Ross[11]. The product (3·4 g) was also chromatographically identical with such a sample.

NN-Bis-(2-chloroethyl)-p-phenylenediamine hydrochloride.

i) by reduction of NN-bis-(2-chloroethyl)-p-nitroso-aniline (327, 257, 140, 115, 80, 78).

Reduction of the nitroso compound (described above) with tin (II) chloride in conc. HCl, as described by Ross[11], gave an ethereal solution of NN-bis-(2-chloroethyl)-p-phenylenediamine which was precipitated as the hydrochloride by addition of a methanolic solution of hydrogen chloride. Various preparations gave yields in the region of 60-75% and the product was invariably discoloured. Most samples appeared to decompose at ca. 230°; one, with rapid heating, had m.p. 245-250° d (lit.,[11] 250-260°). The i.r. spectrum of the amine hydrochloride had ν_{max}(nujol) 2600 and 1615 cm.$^{-1}$

Acetylation of a sample, as described by Ross[11], gave the N'-acetyl derivative which had m.p. 123-125° (from benzene-petroleum) (lit.,[11] 124-126°).

ii) from N'-acetyl-NN-bis-(2-chloroethyl)-p-phenylene-diamine (325).

The N'-acetyl compound (4·3 g) was dissolved in conc. hydrochloric acid (40 ml) and boiled under reflux for 2 hours when t.l.c. (chloroform) showed no starting material. The solution was diluted with water (50 ml), neutralized with solid sodium bicarbonate and extracted with ether (25 ml×4). The ether

solution was dried and the hydrochloride precipitated by addition of methanolic hydrogen chloride. The product was recrystallized by dissolution in methanol followed by addition of ether. The off-white product (2·9 g) decomposed at ca. 230° and had ν_{max}(nujol) 2600 and 1615 cm.$^{-1}$ identical to that of a sample prepared by the method of Ross[11].

NN-Bis-(2-hydroxyethyl)-m-nitroaniline (143, 153).

Ethylene oxide (80 g) was added to an ice-cold solution of m-nitroaniline (103 g) in 40% acetic acid (800 ml). A further portion of ethylene oxide was added after 12 hours and after a total of 36 hours the solution was neutralized (solid sodium carbonate). The product (68 g) was filtered off and when recrystallized from ethanol it had m.p. 99-102° (lit.,[118] 98°).

NN-Bis-(2-chloroethyl)-m-nitroaniline (158, 159).

A solution of the above diol (20 g) in dimethylformamide (80 ml) and chloroform (50 ml) was added to a boiling solution of thionyl chloride (27 g) in ethanol-free chloroform (100 ml). After 4 hours t.l.c. (ethyl acetate) showed only one component and the reaction mixture was poured into water (200 ml) and the organic phase washed with further portions

of water (50 ml × 3). The dried solution was evaporated to give the title compound (17 g), m.p. 112–114° (lit.,[9] 112–113°) when recrystallized from petroleum (b.p. 80–100°) containing a little benzene.

NN-Bis-(2-chloroethyl)-m-phenylenediamine hydrochloride (160, 164).

This was prepared in 65% yield by the tin (II) chloride reduction of the above nitro compound, in the same way as described for the p-isomer. The hydrochloride was obtained as an off-white solid having an ill-defined m.p. 188–193° (lit.,[9] 201–205°), ν_{max}(nujol) 2640 and 1625 $cm.^{-1}$

p-Methoxycarbonylphenyl N-m-(bis-2-chloroethylamino)phenylcarbamate (161).

The m-mustard amine hydrochloride (1·7 g) was suspended in dry benzene (80 ml) and dry pyridine (1·1 g) added, followed by a solution of p-methoxycarbonylphenyl chloroformate (1·38 g) in benzene (20 ml). The mixture was stirred and refluxed for 2 hours when t.l.c. (chloroform) showed no chloroformate. The suspended solid was filtered off and the solution washed with 2N hydrochloric acid, aq. sodium hydrogen carbonate and water. Drying and evaporation gave an oil which was crystallized from carbon tetrachloride-petroleum . Recrystallization from petroleum

(b.p. 100-120°) gave the product (1 g), m.p. 97-99°, ν_{max}(nujol) 3320, 1740 and 1700 cm.$^{-1}$ (Found:C,55·66; H,4·92; Cl,17·56; N,6·80. $C_{19}H_{20}Cl_2N_2O_4$ requires C,55·50; H,4·90; Cl,17·25; N,6·81%).

Carbamates derived from the p-mustard amine were prepared by the general method described below for p-tolyl N-p-(bis-2-chloroethylamino)phenylcarbamate, except where indicated.

p-Tolyl N-p-(bis-2-chloroethylamino)phenylcarbamate (40).

p-Tolyl chloroformate (1·29 g, 7·5 mmole) was added to a stirred suspension of NN-bis-(2-chloroethyl)-p-phenylenediamine hydrochloride (2·02 g, 7·5 mmole) and pyridine (1·2 g, 15 mmole) in dry benzene (50 ml). The mixture was boiled under reflux for 3 hours, filtered and washed with 2N hydrochloric acid, aq. sodium hydrogen carbonate and with water. The solution was dried and concentrated to 30 ml when addition of petroleum precipitated the title compound (1·4 g), m.p. 120-120·5° (from benzene-petroleum), ν_{max}(nujol) 3350, 1700 and 1720 cm.$^{-1}$(shoulder). (Found: C,58·84; H,5·47; Cl,19·54; N,7·77. $C_{18}H_{20}Cl_2N_2O_2$ requires C,58·84; H,5·49;Cl,19·30; N,7·63%).

m-Tolyl N-p-(bis-2-chloroethylamino)phenylcarbamate (33).

This was prepared from m-tolyl chloroformate (1·7 g) in a manner similar to that described for the p-isomer. The carbamate (2·7 g) had m.p. 116-117° when recrystallized from benzene-petroleum, ν_{max}(nujol) 3300, 1700 and 1720 cm.$^{-1}$(shoulder). (Found: C,58·91; H,5·54; Cl,19·45; N,7·62%).

o-Tolyl N-p-(bis-2-chloroethylamino)phenylcarbamate (41).

The reaction of the mustard amine hydrochloride (1·5 g) and o-tolyl chloroformate (0·96 g) in the presence of pyridine (0·88 g) in the usual way, gave the title compound (0·8 g), m.p. 129-131° (from petroleum (b.p. 80-100°)), ν_{max}(nujol) 3350, 1710 and 1730cm.$^{-1}$ (shoulder). (Found: C,59·02; H,5·71; Cl,19·38; N,7·63%).

o-Chlorophenyl N-p-(bis-2-chloroethylamino)phenylcarbamate (72).

o-Chlorophenyl chloroformate (1·7g) and the p-mustard amine hydrochloride (2·3 g) reacted in the usual way to give the carbamate (1·5 g), m.p. 107-108° (from carbon tetrachloride), ν_{max}(nujol) 3350, 1710 cm.$^{-1}$ (Found: C,52·42; H,4·48; Cl,27·72; N,7·20. $C_{17}H_{17}Cl_3N_2O_2$ requires C,52·60; H,4·42; Cl,27·45; N,7·22%).

m-Chlorophenyl N-p-(bis-2-chloroethylamino)phenylcarbamate (63).

m-Chlorophenyl chloroformate gave, in the usual way,

a crude product which was crystallized from petroleum (b.p.80–100°) and then from carbon tetrachloride, to give the pure carbamate (62%), m.p. 126–127°, ν_{max}(nujol) 3320 and 1715 cm.$^{-1}$ (Found: C,52·49; H,4·52; Cl,27·62; N,7·39%).

p-Chlorophenyl N-p-(bis-2-chloroethylamino)phenylcarbamate (76).

The reaction of p-chlorophenyl chloroformate (1·77 g) and the p-mustard amine hydrochloride (2·4 g) in the usual way gave the carbamate (1·95 g), m.p. 121–122° (from carbon tetrachloride), ν_{max}(nujol) 3300, 1700 and 1720 cm.$^{-1}$ (shoulder). (Found: C,52·66; H,4·53; Cl,27·26; N,7·15%).

o-Methoxyphenyl N-p-(bis-2-chloroethylamino)phenylcarbamate (84,141).

o-Methoxyphenyl chloroformate (1·6 g) and the p-mustard amine hydrochloride (2·2 g), in the presence of pyridine (1·4 g), reacted in the usual way to give the carbamate (2·1 g), m.p. 123–124° (from benzene–petroleum (b.p. 80–100°)), ν_{max}(nujol) 3300, 1715 and 1740 cm.$^{-1}$ (shoulder). (Found: C,56·54; H,5·24; Cl,18·69; N,7·32. $C_{18}H_{20}Cl_2N_2O_3$ requires C,56·41; H,5·27; Cl,18·50; N,7·31%).

m-Methoxyphenyl N-p-(bis-2-chloroethylamino)phenylcarbamate (123).

The reaction of the p-mustard amine hydrochloride (2·1 g),

pyridine (1·32g) and m-methoxyphenyl chloroformate (1·65 g) in boiling dry benzene (100 ml) for 90 minutes, gave after the usual work-up, the title compound (1·5 g), m.p. 125-127° (from benzene-petroleum), ν_{max}(nujol) 3360 and 1720 cm.$^{-1}$ (Found: C,56·32; H,5·23; Cl,18·27; N,7·26%).

p-Methoxyphenyl N-p-(bis-2-chloroethylamino)phenylcarbamate (83).

p-Methoxyphenyl chloroformate (1·54 g) and the p-mustard amine hydrochloride (2·2 g) reacted together in the usual way to give the product (1·98 g), m.p. 125-126·5° (from carbon tetrachloride), ν_{max}(nujol) 3320, 1700 and 1720 cm.$^{-1}$(shoulder). (Found: C,56·29; H,5·42; Cl,18·75; N,7·33%).

p-tert-Butylphenyl N-p-(bis-2-chloroethylamino)phenylcarbamate (96).

This was prepared in the usual way from p-tert-butylphenyl chloroformate (1·7 g) and the p-mustard amine hydrochloride (2·1 g). The carbamate (2·2 g) had m.p. 137-138° when recrystallized from petroleum (b.p. 80-100°) and ν_{max}(nujol) 3400 and 1725 cm.$^{-1}$ (Found: C,61·70; H,6·41; Cl,17·31; N,6·78. $C_{21}H_{26}Cl_2N_2O_2$ requires C,61·60; H,6·41; Cl,17·32; N,6·84%).

p-Nitrophenyl N-p-(bis-2-chloroethylamino)phenylcarbamate (336).

Pyridine (1·56 g) and the p-mustard amine hydrochloride

(2·3 g) were suspended in dry benzene (100 ml) and p-nitrophenyl chloroformate (1·8 g) in dry benzene (20 ml) was added. The mixture was stirred and refluxed for 1 hour. Work-up in the usual way gave a brown oil which was dissolved in hot carbon tetrachloride and treated with charcoal. A red oil separated from solution and this slowly crystallized to give the carbamate (1·2 g) which had an indistinct m.p. 50-60°. The carbamate was chromatographically pure and had $\nu_{max}(CHCl_3)$ 1750 cm.$^{-1}$, $\tau(CDCl_3)$ ca. 1·5-3·4 (9H,m, aromatic and NH), 6·3 (8H, s, $N(CH_2CH_2Cl)_2$). (Found: C,51·00; H,4·49; Cl,18·03; N,10·52. $C_{17}H_{17}Cl_2N_3O_4$ requires C,51·28; H,4·30; Cl,17·80; N,10·55%).

m-(NN-Dimethylamino)phenyl N'-p-(bis-2-chloroethylamino)phenylcarbamate (345, 348).

The p-mustard amine hydrochloride was treated with aqueous sodium hydrogen carbonate and the solution of the free amine in chloroform (20 ml) added to a stirred solution of freshly prepared m-(NN-dimethylamino)phenyl chloroformate (400 mg) in dry benzene (20 ml). The solution was refluxed for 1 hour when t.l.c. (chloroform) showed only one component. The solution was washed with aqueous sodium hydrogen carbonate then with water and dried. Evaporation gave a crude solid which was recrystallized from benzene-petroleum to give the carbamate (600 mg), m.p. 159-

161°, $\nu_{max}(CHCl_3)$ 3420 and 1740 cm.$^{-1}$ (Found: C,57·65; H,5·90; Cl,17·84; N,10·47. $C_{19}H_{23}Cl_2N_3O_2$ requires C,57·58; H,5·85; Cl,17·89; N,10·60%).

p-Methylthiophenyl N-p-(bis-2-chloroethylamino)phenylcarbamate (338).

p-Methylthiophenyl chloroformate (1·5 g) and the p-mustard amine hydrochloride (1·9 g) reacted together in the usual way in benzene solution. After 2 hours refluxing the mixture was filtered, washed with dil. hydrochloric acid, aq. sodium hydrogen carbonate and then with water and finally dried. Evaporation of solvent gave an oil which crystallized when cooled. The product (1·6 g) was recrystallized from carbon tetrachloride and had m.p.117-119°. T.l.c. (chloroform) showed a trace of impurity,Rf 0·35. The carbamate had $\nu_{max}(CHCl_3)$ 1740 cm.$^{-1}$, $\tau(CDCl_3)$ 7·52 (3H, s, SCH_3), 6·35 (8H, s, $N(CH_2CH_2Cl)_2$), 2·5-3·5 (9-10H, m, aromatic and NH). (Found: C,54·08; H,4·91; Cl,17·82; N,6·91. $C_{18}H_{20}Cl_2N_2O_2S$ requires C,54·16; H,5·05; Cl,17·76; N,7·02%).

2-Methoxycarbonyl-4-methylphenyl N-p-(bis-2-chloroethylamino)phenylcarbamate (109).

2-Methoxycarbonyl-4-methylphenyl chloroformate (1·8 g) and the p-mustard amine hydrochloride (2·1 g) reacted in the usual way to give the carbamate (2·3 g), m.p. 124-126°(from benzene-

petroleum), ν_{max}(nujol) 3300, 1730 and 1690 cm.$^{-1}$ (Found: C,56·44; H,5·41; Cl,16·73; N,6·41. $C_{20}H_{22}Cl_2N_2O_4$ requires C,56·45; H,5·21; Cl,16·67; N,6·59%).

p-(Methoxycarbonylmethyl)phenyl N-p-(bis-2-chloroethylamino)phenylcarbamate (273).

p-(Methoxycarbonylmethyl)phenyl chloroformate (1·8 g) and the p-mustard amine hydrochloride (2·1 g) reacted in the usual way to give the carbamate (1·2 g), m.p. 131-134° (from benzene-petroleum), ν_{max}(nujol) 3290, 1735 and 1700 cm.$^{-1}$ (Found: C,56·21; H,5·36; Cl,16·58; N,6·48; $C_{20}H_{22}Cl_2N_2O_4$ requires C,56·45; H,5·21; Cl,16·67; N,6·59%).

p-(Carboxymethyl)phenyl N-p-(bis-2-chloroethylamino)phenylcarbamate (294).

Hydrolysis of the above ester (50 mg) essentially as described for p-(2-carboxyethyl)phenyl N-p-(bis-2-chloroethylamino)-phenylcarbamate (see below), gave the title compound (40 mg), m.p. 134-137° (from benzene), ν_{max}($CHCl_3$) 3420 and 1740 cm.$^{-1}$(broad), τ($CDCl_3$-d_6-DMSO) 6·35 and 6·4 (10H, two s, $N(CH_2CH_2Cl)_2$ and CH_2-CO_2H), ca. 2·4-3·4 (11H, m, aromatic, NH, CO_2H and benzene). (Found: C,56·34; H,4·98; Cl,16·79; N,6·47. $C_{20}H_{21}Cl_2N_2O_4$ i.e. $C_{19}H_{20}Cl_2N_2O_4 \cdot \frac{1}{6}(C_6H_6)$ requires C,56·61; H,4·99; Cl,16·71; N,6·60%).

See note on P. 139.

p-(2-Methoxycarbonylethyl)phenyl N-p-(bis-2-chloroethylamino)phenylcarbamate (113).

The reaction of p-mustard amine hydrochloride (1·9 g) and p-(2-methoxycarbonylethyl)phenyl chloroformate (1·8 g) in the usual way for 1 hour gave the title compound (1·5 g), m.p. 131-132° (from benzene-petroleum), ν_{max}(nujol) 3320, 1730 and 1705 cm.$^{-1}$ (Found: C,57·47; H,5·49; Cl,16·14; N,6·29. $C_{21}H_{24}Cl_2N_2O_4$ requires C,57·38; H,5·51; Cl,16·14; N,6·38%).

p-(2-Carboxyethyl)phenyl N-p-(bis-2-chloroethylamino)phenylcarbamate (125).

The above ester (1·2 g) was dissolved in a 1:1 mixture (10 ml) of glacial acetic and hydrochloric acids and the solution boiled under reflux for 5 minutes. The solution was cooled, poured into water (50 ml) and extracted with chloroform (25 ml × 3). The dried chloroform solution was evaporated to give the acid (840mg), m.p. 150-152° (from ether-petroleum (b.p. 40-60°)), ν_{max}(nujol) 3320, 1705 and 1690 cm.$^{-1}$ (For n.m.r. spectrum see P.54). (Found: C,57·64, 57·56; H, 5·75, 5·61; Cl,15·17, 15·58; N,5·95, 5·94. $C_{22}H_{27}Cl_2N_2O_{4\frac{1}{2}}$ i.e. $C_{20}H_{22}Cl_2N_2O_4 \cdot \frac{1}{2}((C_2H_5)_2O)$ requires C,57·15; H, 5·89; Cl,15·33; N,6·06%).

See note on P.139.

p-(3-Methoxycarbonylpropyl)phenyl N-p-(bis-2-chloroethylamino)-phenylcarbamate (300).

This was prepared in the usual way from the corresponding chloroformate. The product (47%) had m.p. 106-108° when recrystallized from ether-petroleum (b.p. 40-60°), $\nu_{max}(CHCl_3)$ 3400 and 1730 cm.$^{-1}$(broad). (Found: C,58·18; H,5·77; Cl,15·38; N,6·10. $C_{22}H_{26}Cl_2N_2O_4$ requires C,58·26; H,5·78; Cl,15·64; N,6·18%).

p-(3-Carboxypropyl)phenyl N-p-(bis-2-chloroethylamino)-phenylcarbamate (310, 315).

Hydrolysis of the above ester in the usual way gave the acid (54% and 90% on two occasions), m.p.102-106° (from benzene), $\nu_{max}(CHCl_3)$ 3400, ca. 2400-3600, 1700-1740 cm.$^{-1}$ (broad). (Found: C,60·50, 60·44; H,5·72, 5·64; Cl,15·04; N,5·88, 5·82. $C_{24}H_{27}Cl_2N_2O_4$ i.e. $C_{21}H_{24}Cl_2N_2O_4 \cdot \frac{1}{2}(C_6H_6)$ requires C,60·27; H,5·69; Cl,14·82; N,5·99%).

In the second preparation, the acid was recrystallized from ether-petroleum (b.p. 40-60°) and had m.p. 105·5-106·5°, $\nu_{max}(CHCl_3)$ as above, n.m.r. spectrum (P. 54) shows ether of crystallization. (Found: C,58·38; H,6·23; Cl,15·43; N,6·21. $C_{21}H_{24}Cl_2N_2O_4 \cdot \frac{1}{3}((C_2H_5)_2O)$ req. C,57·81; H,5·94; Cl,15·29; N,6·04%).

See note on P.139.

2,4-Bismethoxycarbonylphenyl N-p-(bis-2-chloroethylamino)-phenylcarbamate (234).

2,4-Bismethoxycarbonylphenyl chloroformate (3·6 g), p-mustard amine hydrochloride (3·5 g) and pyridine (1 g) were stirred together in ethanol-free chloroform (90 ml) at ca. 50° for 4 hours. Unreacted amine hydrochloride (500 mg) was filtered off and the solution washed with 2N hydrochloric acid, aq. sodium bicarbonate and then with water. Drying and evaporation gave an oil which was crystallized from benzene-petroleum. The product had m.p. 124-126°, $\nu_{max}(CHCl_3)$ 3420, 1750 and 1720 cm.$^{-1}$ (Found: C,53·96; H,4·60; Cl,15·17; N,5·69. $C_{21}H_{22}Cl_2N_2O_6$ req. C,53·75; H,4·73; Cl,15·11; N,5·97%).

Attempted preparation of 4-carboxy-2-methoxycarbonylphenyl N-p-(bis-2-chloroethylamino)phenylcarbamate (321, 322).

Hydrolysis of the above ester with acetic acid-hydrochloric acid gave mixtures of starting material and products, as shown by t.lc. (ethyl acetate).

NN-Bis-(2-chloroethylamino)-p-phenyl isocyanate (166, 221, 349).

The p-mustard amine (from 1 g of hydrochloride by treating with aq. sodium bicarbonate) in chloroform (30 ml) was added to a solution of phosgene in benzene (50 ml). Phosgene was bubbled through the mixture and a pink solid was formed.

The mixture was refluxed until a clear blue solution was obtained and this solution was decanted from some solid residue and evaporated to give the crude isocyanate[62] (1 g), $\nu_{max}(CCl_4)$ 2300 $cm.^{-1}$ (slight impurity at 1740 $cm.^{-1}$).

The isocyanate was used without further purification.

The reaction of the 'mustard isocyanate' with p-hydroxybenzenesulphonamide (223, 350).

The above isocyanate (1 g), p-hydroxybenzenesulphonamide (600 mg) and pyridine (2 ml) were heated at 70° in AnalaR ethyl acetate (50 ml). After 4 hours the mixture was washed with dilute hydrochloric acid, aq. sodium hydrogen carbonate and water. None of the desired carbamate could be isolated and identified - some of the unreacted phenol (150 mg) was isolated.

* * * * * * * * *

Note;

All analytical samples described in this and other sections, were dried at room temperature and 10^{-4} mmHg for 12 - 24 hours.

NN-Bis-(2-chloroethyl)-N'-methyl-p-phenylenediamine.

N-Methylacetanilide (169, 202).

N-Methylaniline (115 g), acetic acid (100 ml) and acetic anhydride (111 g) were boiled under reflux (with a little zinc dust) for 1 hour. Pouring the mixture into water (1 litre) and scratching with a spatula, precipitated N-methylacetanilide (93 g), m.p. 100° (from petroleum) (lit.,[119] 101-102°).

p-Nitro-N-methylacetanilide (172, 204).

N-Methylacetanilide (51 g) was dissolved in glacial acetic acid (30 ml) and conc. sulphuric acid (100 ml). A mixture of conc. nitric acid (25 ml) and conc. sulphuric acid (15 ml) was added with stirring and cooling such that the temperature remained <5°. After about 5 hours, the mixture was poured onto crushed ice and the precipitated solid was recrystallized from ethanol to give the product (40·8 g), m.p. 154°(lit.,[81] 153°).

N-Acetyl-N-methyl-p-phenylenediamine (176, 178, 211).

The above nitro compound (35 g) was dissolved in conc. hydrochloric acid (200 ml) and tin (II) chloride dihydrate (130 g) added with stirring. The temperature

was maintained initially at less than 15°, then at room temperature for 2 hours. The mixture was then basified by addition of aq. sodium hydroxide and extracted with chloroform (100 ml × 5). Evaporation of solvent gave an oil which was crystallized from benzene-carbon tetrachloride. Yield of product was 22·1 g and it had m.p. 70-71° (lit.,[81] 63°), $\nu_{max}(CCl_4)$ 3470, 3400, 1660 and 1620 cm.$^{-1}$

N'-Acetyl-NN-bis-(2-hydroxyethyl)-N'-methyl-p-phenylenediamine (181, 260).

The above amine (20 g) and ethylene oxide (42 g) were allowed to react together in 40% acetic acid (200 ml) in the same way as described for N'-acetyl-NN-bis-(2-hydroxyethyl)-p-phenylenediamine. After neutralization of the mixture with solid sodium carbonate, extraction with ethyl acetate (100 ml × 4), drying and evaporation gave the title compound (21 g) as a thick red oil, $\tau(CDCl_3)$ 3·2 (4H,q, aromatic), 5·39 (2H, s, OH), 6·18 and 6·42 (8H, two t, CH_2), 6·82 (3H, s, NCH_3), 8·2 (3H, s, CH_3CO) and ca. 7·8 (2H, m, impurity), $\nu_{max}(CHCl_3)$ ca. 3400 and 1650cm.$^{-1}$

The diol could not be purified but was characterized by reaction with benzoyl chloride in aqueous sodium hydroxide. The dibenzoate derivative was recrystallized from ethanol and had m.p. 141-143°, ν_{max}(nujol) 1720 and 1700 cm.$^{-1}$(shoulder), 1660 cm.$^{-1}$

(Found: C,70·28; H,6·19; N,6·02. $C_{27}H_{28}N_2O_5$ requires C,70·41; H,6·13; N,6·08%).

N'-Acetyl-NN-bis-(2-chloroethyl)-N'-methyl-p-phenylenediamine (256, 278, 443).

The crude diol prepared above, (17 g) in chloroform solution (50 ml), was added to a solution of thionyl chloride (26 g) in chloroform (100 ml) at a temperature of 60–70°, over a period of 90 minutes. The solution was then heated for a further 1 hour , cooled, neutralized with sodium hydrogen carbonate solution, washed with water and dried. Evaporation of solvent gave a black oil which was purified by column chromatography (ethyl acetate). The leading fraction (Rf 0·5) was collected and recrystallized from carbon tetrachloride-petroleum. The title compound (5·4 g) had m.p. 93–94° and $\nu_{max}(CHCl_3)$ 1640 $cm.^{-1}$ (Found: C,53·95; H,6·19; Cl,24·53; N,9·60. $C_{13}H_{18}Cl_2N_2O$ requires C,53·99; H,6·24; Cl,24·52; N,9·69%).

A small amount (10%) of the cyclic sulphite (see below) was also present; it had Rf 0·3.

The reaction of N'-acetyl-NN-bis-(2-hydroxyethyl)-N'-methyl-p-phenylenediamine with thionyl chloride in the presence of dimethylformamide (225, 445, 446).

Thionyl chloride (2 g) and dry DMF (3 ml) were dissolved in ethanol-free chloroform (50 ml) and heated at ca. 70° for 1 hour. The yellow solution was then cooled in ice and a solution of the diol (2 g) in chloroform (15 ml) added. After 1 hour the solution was washed with water and dried. Evaporation of solvent gave a dark residue which was purified by column chromatography (ethyl acetate) to give, as the only isolated product, the cyclic sulphite of the diol (450 mg, see P. 64), Rf 0·3, m.p. 136-138° (from CCl_4-petroleum), $\nu_{max}(CCl_4)$ 1660 and 1200 $cm.^{-1}$, $\tau(CDCl_3)$ 3·2 (4H, q, aromatic), 5·1-6·5 (8H, m, CH_2CH_2), 6·8 (3H, s, NCH_3), 8·15 (3H, s, CH_3CC). (Found: C,52·05, 52·04; H,6·02, 5·91; N,9·22, 9·20; S,10·71. $C_{13}H_{18}N_2O_4S$ requires C, 52·30; H,6·08; N,9·47; S,10·74%).

NN-Bis-(2-chloroethyl)-N'-methyl-p-phenylenediamine hydrochloride (287, 292).

The N'-acetyl mustard (described above; 6 g) was dissolved in conc. hydrochloric acid (50 ml) and the mixture boiled for 3 hours. After cooling and pouring into water (200 ml) the mixture was neutralized by adding solid sodium

carbonate and then extracted with ether (100 ml × 3). The dried extracts were concentrated and a methanolic solution of hydrogen chloride added dropwise. The product separated as white crystals (4·5 g), m.p. 150–160° (from methanol–ether), ν_{max}(nujol) 2450 and 2700 cm.$^{-1}$ (Found: C,46·53; H,6·11; Cl,37·38; N,9·74. $C_{11}H_{17}Cl_3N_2$ requires C,46·58; H,6·04; Cl,37·51; N,9·88%).

p-(2-Methoxycarbonylethyl)phenyl N'-p-(bis-2-chloroethylamino)phenyl-N'-methylcarbamate (296, 302).

The preceding amine hydrochloride (1·5 g) and pyridine (0·53 g) were stirred together in dry benzene (100 ml) and p-(2-methoxycarbonylethyl)phenyl chloroformate (1·4 g), in a little benzene, was added dropwise. The mixture was refluxed for 1 hour, washed with dilute hydrochloric acid, aq. sodium hydrogen carbonate and with water. Drying and evaporation of solvent gave an oil which was purified by chromatography (chloroform). The product (1·86 g) was a pale yellow oil which could not be crystallized and which had ν_{max}($CHCl_3$) 2950 and 1705 cm.$^{-1}$(broad), τ($CDCl_3$) ca. 3·0 (8–9H, m, aromatic), 6·31 and 6·33 (11H, two s, $N(CH_2CH_2Cl)_2$ and CO_2CH_3), 6·53 (3H, s, NCH_3), 6·9–7·5 (4H,m, $C\underline{H}_2C\underline{H}_2CO_2Me$).

(Found: C,58·55; H,6·03; Cl,15·47; N,6·15. $C_{22}H_{26}Cl_2N_2O_4$ requires C,58·28; H,5·78; Cl,15·64; N,6·18%).

Acid hydrolysis of p-(2-methoxycarbonylethyl)phenyl N'-p-(bis-2-chloroethylamino)phenyl-N'-methylcarbamate (305, 312, 369).

The above methyl ester (250 mg) was dissolved in glacial acetic acid (2 ml) and conc. hydrochloric acid (2 ml) was added. The mixture was then boiled under reflux for 5 minutes and poured into ice-water (10 ml). Extraction with chloroform (7 ml×2), washing with aq. sodium hydrogen carbonate, saturated sodium chloride solution and water, followed by drying , gave the acid (170 mg) as a viscous oil. This could not be crystallized and had $\nu_{max}(CHCl_3)$ 1705 cm.$^{-1}$(Equivalent Weight found 427.$C_{21}H_{24}Cl_2N_2O_4$ requires 439).

The Dimethanesulphonates of 2-N-methylanilinopropane-1,3-diol and 3-N-methylanilinopropane-1,2-diol.

3-N-Methylanilinopropane-1,2-diol (276).

Glycidol (15 g) and N-methylaniline (22 g) were dissolved in benzene (100 ml) and the solution refluxed for 4½ hours. On cooling, a white solid crystallized. Recrystallization from benzene gave the product (23·5 g), m.p. 75-77° (lit.,[90] 74-75°).

1,2-Dichloro-3-N-methylanilinopropane (371).

The above diol (1 g) in pyridine (10 ml) was added dropwise to methanesulphonyl chloride (1·4 g) and the mixture heated to 100° for 30 minutes. The mixture was then dissolved in chloroform (20 ml) and the solution washed with aq. sodium hydrogen carbonate and with water. Drying, evaporation of solvent and distillation gave the dichloride (250 mg), b.p.82° at 5×10^{-4} mmHg (lit.,[87] 105-106° at 0·24 mmHg), n_D^{14} 1·5745 (lit.,[87] n_D^{21} 1·5722), τ($CDCl_3$) 6·95 (3H, s, NCH_3), 5·4-6·4 (5H, m, CH_2CHCH_2), ca. 3·0 (5H, m, aromatic).

1,2-Dimethanesulphonyloxy-3-N-methylanilinopropane (373, 374, 377).

The 1,2-diol (4 g) and triethylamine (4·85 g) were dissolved in chloroform (ethanol-free; 50 ml) and added dropwise to a solution of methane-sulphonyl chloride (5·3 g) in chloroform (ethanol-free; 20 ml). The mixture was stored in the refrigerator overnight and then washed with dilute hydrochloric acid, sodium hydrogen carbonate solution and with water. After drying, evaporation of solvent gave the product (7·7 g) as a pale yellow oil, ν_{max} ($CHCl_3$) 1370 and 1180 cm.$^{-1}$, see P.92 for n.m.r. spectrum.

A sample was purified by preparative thin layer chromatography (chloroform). (Found: C,42·00, 42·07; H,5·45, 5·70; N,4·06, 4·00. $C_{12}H_{19}NO_6S_2$ requires C,42·72; H,5·68; N,4·15%).

Diethyl bromomalonate (339, 352).

The reaction of diethyl malonate with bromine in carbon tetrachloride, as described by Palmer[120], gave diethyl bromomalonate in 65% yield.

Diethyl 2-N-methylanilinomalonate (395, 430, 267, 359).

N-Methylaniline (22 g) and diethyl bromomalonate (24 g) were dissolved in ethanol (150 ml) and boiled under reflux overnight. The solution was then

concentrated, diluted with water (150 ml) and extracted with chloroform (50 ml × 2). Evaporation of the dried extracts gave a brown oil which was distilled twice to give the product (17 g) as a yellow oil having b.p. 116-122° at 2×10^{-4}mmHg, $\nu_{max}(CHCl_3)$ 1725cm.$^{-1}$ $\tau(CDCl_3)$ 8·71 (3H, t, $C\underline{H}_3-CH_2-O$), 6·91 (3H, s, NCH_3), 5·70 (2H, q, $CH_3-C\underline{H}_2-O$), 4·83 (1H, s, $N-C\underline{H}(CO_2Et)_2$), 2·60-3·30 (5H, m, aromatic), M^+ = 265 ($C_{14}H_{19}NO_4$ req. 265).

Nnadi and Wang[92] quote m.p. 105-106° (from ethanol-petroleum).

Prolonged heating of this compound during distillation caused the formation of a white solid which separated from the above ester. When recrystallized from petroleum, 2-ethoxycarbonyl-N-methylindoxyl had m.p. 94-95°; ν_{max}(nujol) 3300, 1650 and 1615 cm.$^{-1}$ (shoulder), $\nu_{max}(CHCl_3)$ 1700 and 1650 cm.$^{-1}$, $\tau(CCl_4)$ 8·58 (3H, t, $C\underline{H}_3-CH_2-O$), 6·22 (3H, s, NCH_3), 5·61 (2H, q, $CH_3-C\underline{H}_2-O$), 2·10-3·15 (4H, m, aromatic), 1·30 (1H, s, $N-\underset{\underset{CO}{|}}{C\underline{H}}-CO_2Et$).

(Found: C,65·11, 65·15; H,5·90, 5·80; N,6·18, 6·33; M^+=219. $C_{12}H_{13}NO_3$ requires C,65·73;H,5·98; N,6·39; M^+=219).

The effect of heat on diethyl 2-N-methylanilinomalonate (401, 391).

Diethyl 2-N-methylanilinomalonate (570 mg) was dissolved in nitrobenzene (1 ml) and the solution boiled under reflux for 30 minutes. Chromatography (benzene-2% ether) gave a

fraction having Rf 0·4, which, when recrystallized from petroleum, was identified as 2-ethoxycarbonyl-N-methylindoxyl (130 mg), m.p. 94-95° undepressed by admixture with that obtained above.

A similar result was obtained when xylene was used as solvent, refluxing for 40 hours.

2-N-Methylanilinopropane-1,3-diol (431, 413, 364).

Diethyl 2-N-methylanilinomalonate (15·5 g) was dissolved in dry tetrahydrofuran (15 ml) and the solution added to a stirred suspension of lithium aluminium hydride (3·2 g) in dry tetrahydrofuran (80 ml). After the initial vigorous reaction the mixture was stirred and refluxed for 3 days.

Cautious addition of water (200 ml) and a little aqueous sodium hydroxide gave an emulsion which was partly broken by filtration. Extraction with chloroform (100 ml and 50 ml × 4), drying and evaporation gave a yellow oil which was crystallized from benzene-petroleum. The 1,3-diol (1·96 g) had m.p. 62-64° (lit.,[91] 60°), ν_{max} ($CHCl_3$) 3600-3200 and 1600 $cm.^{-1}$, τ($CDCl_3$) 7·90 (2H, broad s, two OH), 7·18 (3H, s, NCH_3), ca. 6·25 (5H, m, CH_2CHCH_2), 2·60-3·25 (5H, m, aromatic).

Concentration of the mother liquors gave a yellow oil (4·5 g) which contained several unidentifiable components.

Attempted reduction of diethyl 2-N-methylanilinomalonate by the Bouveault-Blanc method (363).

Small pieces of sodium metal (2·75 g) were suspended in dry benzene (10 ml) and warmed gently. A solution of the malonate ester (1·8g) in dry ethanol (10 ml) was added in one portion, with stirring, followed by more ethanol (40 ml). The mixture was boiled under reflux for 30 minutes when all the sodium dissolved. After cooling, the mixture was poured into water (100 ml) and extracted with chloroform (50 ml ×2). The dried extracts were evaporated to give an oil (1·8 g) identified as the starting material by t.l.c. and its i.r. spectrum.

1,3-Dimethoxy-2-N-methylanilinopropane (417).

A mixture of 2-N-methyl-anilinopropane-1,3-diol (180 mg), dimethyl sulphate (400 mg) and powdered sodium hydroxide (260 mg) in dry tetrahydrofuran (5 ml) was stirred overnight at room temperature. The mixture was poured into water (10 ml) and extracted with benzene (10 ml). The extract was washed with water and dried. Evaporation of solvent gave an oil (190 mg) which was purified by preparative t.l.c. (chloroform). The dimethyl ether (140 mg) had Rf ca. 0·5, n_D^{18} 1·5294, $\nu_{max}(CHCl_3)$ no hydroxyl, 1600 and 1100 cm.$^{-1}$(broad). See P.93 for n.m.r. spectrum. (Found: C,69·10; H,9·32; N,6·55. $C_{12}H_{19}NO_2$

requires C,68·89; H,9·32; N,6·69%).

1,3-Diacetoxy-2-N-methylanilinopropane (418).

The 1,3-diol (110 mg) and acetic anhydride (220 mg) were dissolved in dry pyridine (3 ml) and left to stand overnight at room temperature. T.l.c. (chloroform) showed no diol to be present and the solution was poured into water (10 ml) and extracted with benzene (10 ml). The extract was washed with dilute hydrochloric acid and with water, dried and evaporated to give an oil (160 mg) which was purified by preparative t.lc. (chloroform) to give the diacetate (150 mg), Rf ca. 0·5, n_D^{19} 1·5165, $\nu_{max}(CHCl_3)$ 1735 cm.$^{-1}$, see P. 93 for n.m.r. spectrum. (Found: C,63·39; H,7·22; N,5·06. $C_{14}H_{19}NO_4$ requires C,63·39; H,7·22; N,5·28%).

1,3-Dimethanesulphonyloxy-2-N-methylanilinopropane (437,432).

2-N-Methylanilinopropane-1,3-diol (190 mg) and triethylamine (235 mg) in dry dichloromethane (5 ml) were added dropwise to a stirred solution of methanesulphonyl chloride (255 mg) in dichloromethane (5 ml) cooled in ice. The mixture (some solid separated) was left in the refrigerator for 5 hours and then washed thoroughly with dilute hydrochloric acid, aqueous sodium hydrogen carbonate and with water. Drying and evaporation gave

the dimethanesulphonate (310 mg) as a pale yellow oil, $\nu_{max}(CHCl_3)$ 1370 (broad) and 1180 cm.$^{-1}$, see P. 93 for n.m.r. spectrum. (Found: C,41·82; 41·61; H,5·66, 5·54; N,4·03, 3·93. $C_{12}H_{19}NO_6S_2$ requires C,42·72; H,5·68; N,4·15%).

Preparation of a mixture of 5-hydroxy-m-dioxan and 1,3-dioxolan-4-methanol (404, 400, 308)

Condensation of sym. trioxan and glycerol in the presence of hydrochloric acid, essentially as described by Hibbert and Carter[99], gave the mixture of alcohols (45-50% yields), b.p. 64-70° at 1½ mmHg (lit.,[99] 80-90°at 11 mmHg).

5-Benzoyloxy-m-dioxan (308, 400).

The above mixture of alcohols (82 g) was dissolved in chloroform (200 ml) and pyridine (100 ml) and cooled in an ice bath. Benzoyl chloride (122 g) was added dropwise and the mixture left at room temperature for 20 hours. After this time water (200 ml) was added and the organic layer was thoroughly washed with dilute hydrochloric acid followed by aqueous sodium hydrogen carbonate and water. Evaporation of the dried solution gave an oily solid which was crystallized from ether-petroleum; recrystallization from petroleum gave pure 5-benzoyloxy-m-dioxan (75 g), m.p. 74-75° (lit.,[99] 72°).

5-Hydroxy-m-dioxan (309, 400).

The preceding benzoate (80 g) was suspended in aqueous sodium hydroxide (20%; 250 ml) and heated at 70° for 45 minutes. The resultant clear solution was cooled and adjusted to pH 9 by addition of solid carbon dioxide. After filtration from inorganic material, continuous extraction with ether for several days, drying (potassium carbonate) and evaporation of solvent, gave the alcohol (28 g), b.p. 56° at 0·2 mmHg (lit.,[99] 82° at 11 mmHg), n_D^{23} 1·4515 (lit.,[121] n_D^{20} 1·4533), $\tau(CCl_4)$ ca. 6·2 (6H, m, $C\underline{H}_2C\underline{H}C\underline{H}_2$ and O$\underline{H}$), 5·25 (2H, s, O-CH_2-O).

The reaction of 5-hydroxy-m-dioxan with thionyl chloride.

i) in chloroform (311).

The alcohol (2 g) and pyridine (5 ml) were added dropwise to a solution of thionyl chloride (2·1 g) in chloroform (30 ml) at room temperature. The solution was then refluxed for 30 minutes, poured into water and washed with dilute hydrochloric acid, aqueous sodium hydrogen carbonate and with water. Drying and evaporation of solvent gave 5,5'-sulphinyldioxy-di-(m-dioxan) (1·6 g), m.p. 104-105° (from benzene-petroleum), $\tau(CCl_4)$ 5·7-6·4(8H, m, CH-C$\underline{H}_2$-O), ca. 5·45 (2H, m, $CH_2-\underset{\underset{O}{|}}{C\underline{H}}-CH_2$), 5·21 (4H, s, O-CH_2-O). (Found: C,38·17, 38·15; H,6·00, 5·92; S,12·97; $C_8H_{14}O_7S$ requires C,37·79; H,5·55; S,12·61%).

ii) in pyridine (393).

The alcohol (12·5 g) and dry pyridine (50 ml) were added dropwise to thionyl chloride (16 g) cooled in ice. The solution was then heated at 90° for 1 hour and poured into water (200 ml). The solution was extracted with ether (50 ml×4) and the extracts washed well with dilute hydrochloric acid and water. Drying (sodium carbonate) and evaporation gave 5-chloro-m-dioxan (1·2 g; 8%), b.p. 100-110° at atmospheric pressure (lit.,[101] 52-55° at 20 mmHg), τ($CDCl_3$) 5·60-6·60 (5H, m, CH_2CHCH_2), 5·34 and 5·00 (AB quartet, O-CH_2-O, J= 7 Hz).

5-Toluene-p-sulphonyloxy-m-dioxan.

i) from 5-hydroxy-m-dioxan (402).

The alcohol (1·07 g) was dissolved in dry pyridine (25 ml), cooled in ice and p-toluenesulphonyl chloride (2·1 g) added over a period of 30 minutes. After overnight storage in the refrigerator, a small volume of water was added (to destroy any unreacted p-toluenesulphonyl chloride) and the mixture was poured into cold dilute sulphuric acid. The solution was extracted with chloroform (25 ml × 2) and the extracts washed with dilute sulphuric acid , aq. sodium hydrogen carbonate and with water. Drying and evaporation gave the product (2 g), m.p.90-91° (from chloroform-petroleum), ν_{max}($CHCl_3$) 1375 $cm.^{-1}$

ii) from the mixture of 5-hydroxy-m-dioxan and 1,3-dioxolan-4-methanol (409).

The mixture of alcohols (15 g) was added to a solution of p-toluenesulphonyl chloride (34 g) in dry pyridine (100 ml). After overnight storage at 0°, a little water was added and then the mixture was poured into dilute sulphuric acid (200 ml). An oil precipitated and this was crystallized by scratching with a spatula. The solid was then dissolved in chloroform (200 ml), washed with water and dried. Evaporation of solvent gave a mixture of tosylates which, when crystallized from chloroform-petroleum, gave 5-toluene-p- sulphonyloxy-m-dioxan (11 g), m.p. 91-92°, mixed m.p. with sample prepared above, 90-92°, $\nu_{max}(CHCl_3)$ identical to that above.

The n.m.r. spectrum (60 MHz) of this compound showed;
$\tau(CCl_4)$ ca. 2·5 (q, 4H, aromatic), 5·26 (A, J= 6 Hz, 1H, $O-CH_2-O$), 5·41 (B, J= 6 Hz, 1H, $O-CH_2-O$), 5·6 - 6·6 (m, 5H, $CH_2-CH-CH_2$), 7·56 (s, 3H, CH_3-).
$\tau(CDCl_3)$ ca. 2·5 (q, 4H, aromatic), 5·22 (s, 2H, $O-CH_2-O$), 5·55 (m, 1H, $CH_2-\underline{C}H-CH_2$), 6·15 (m, 4H, $\underline{C}H_2-CH-\underline{C}H_2$), 7·6 (s, 3H, CH_3).

The n.m.r. spectrum was identical to that recorded by other authors[100].

The reaction of 5-toluene-p-sulphonyloxy-m-dioxan with N-methylaniline (429, 416).

A solution of 5-toluene-p-sulphonyloxy-m-dioxan (1·14 g) and N-methylaniline (1·03 g) in dry DMF (20 ml) was heated at 105° for 10 hours. After pouring into water (150 ml) and extracting with chloroform, a mixture of oil and solid (2·1 g) was obtained which was identified by t.l.c. (benzene) and i.r. as being unreacted starting materials.

Similarly, no reaction was detected when the reaction was carried out in refluxing dioxan in the presence of sodium hydride - N-methylaniline was recovered from the reaction mixture.

The reactions of 1,2-dimethanesulphonyloxy-3-N-methylanilinopropane.

The n.m.r. spectra of reaction products are recorded on P. 94.

i) with methanol (405).

The 1,2-dimesylate (300 mg) was dissolved in dry methanol (25 ml) and calcium carbonate (1 g) added. The mixture was stirred and refluxed for 12 hours and then concentrated and diluted with water (100 ml). Extraction with chloroform (20 ml×3), drying and evaporation gave the 1,2-dimethyl ether (150 mg; 60 mg after distillation), b.p. 84-85° at 0·2 mmHg (lit.,[87] 104-106° at 0·45 mmHg).

ii) with sodium methoxide (376).

Sodium metal (270 mg) was dissolved in dry methanol (50 ml) and the 1,2-dimesylate (1 g) added. The solution was boiled for 2 hours and stored at room temperature overnight. After pouring into excess water, extraction with chloroform, drying and evaporation of solvent gave a mixture of 1,2- and 1,3-dimethyl ethers (1:1 ; 550 mg, 230 mg after distillation), b.p. 75-78° at 0·25 mmHg.

iii) with potassium acetate (379).

The 1,2-dimesylate (600 mg) was heated

at 100 ± 5° in acetic anhydride (20 ml) containing potassium acetate (1·06 g). After 2 hours the mixture was poured into water (50 ml) and chloroform (50 ml) and the organic phase washed with sodium hydrogen carbonate solution and water. Drying and evaporation of solvent gave 350 mg of oil which was distilled, b.p. 106–108° at 2×10^{-2} mmHg, to give a mixture of acetates (3:2 of 1,2- to 1,3-diacetate; 210 mg).

iv) with sodium thiophenate (403).

Sodium metal (100 mg) was dissolved in dry methanol (40 ml) and thiophenol (510 mg) added followed by the 1,2-dimesylate (500 mg). The solution was boiled under reflux for 5 hours while a stream of dry nitrogen was bubbled through. The solution was then diluted with water (100 ml) and extracted with chloroform (25 ml × 2) and the extracts washed with sodium hydroxide solution and with water. Evaporation of the dried extracts gave a mixture of the 1,2- and 1,3-bisphenylsulphides (7:3 , 360 mg) which were separated by preparative t.l.c. (5% ether- 95% petroleum).

1,3-bisphenylthio-2-N-methylanilinopropane (40 mg) had Rf 0·25. (Found: C,72·24; H,6·29; N,3·73. $C_{22}H_{23}NS_2$ requires C,72·23; H,6·34; N,3·83%).

1,2-bisphenylthio-3-N-methylanilinopropane (100 mg) had Rf 0·3. (Found: C,72·16; H,6·34; N,3·77%).

See R92-3 for n.m.r. spectra.

The reactions of 1,3-dimethanesulphonyloxy-2-N-methylanilinopropane.

The n.m.r. spectra of reaction products are recorded on P.95.

i) with methanol (424).

Heating the 1,3-dimesylate (30 mg) in methanol containing calcium carbonate for 15 hours, as described above for the 1,2-dimesylate, gave the 1,2-dimethyl ether (17 mg).

ii) with sodium methoxide (436, 425).

The 1,3-dimesylate (410 mg) was dissolved in dry methanol (10 ml) in which sodium (210 mg) had been dissolved. After 4½ hours the mixture was diluted with water (20 ml) and extracted with benzene (20 ml). The extract was washed with water and dried. Evaporation of solvent gave a mixture of the 1,2- and 1,3-dimethyl ethers (1:1).

iii) with potassium acetate (433).

The 1,3-dimesylate (600 mg) was dissolved in acetic anhydride (25 ml) and potassium acetate (1·3 g) added. The mixture was heated at 100 ± 5° and white crystals were precipitated. After 2 hours the mixture was worked-up as described for the 1,2-dimesylate to give an oil (335 mg) which was

distilled to give a mixture of the 1,2- and 1,3-diacetates (3:2, 160 mg), b.p. 108-110° at 5×10^{-4} mmHg.

iv) with sodium thiophenate (426).

Sodium (100 mg) and thiophenol (500 mg) were dissolved in dry methanol (10 ml) and the 1,3-dimesylate (240 mg) in methanol (10 ml) added. The solution was refluxed under nitrogen for 2½ hours and the solvent evaporated. The residue was taken up in benzene (20 ml) and washed with aqueous sodium hydroxide and with water. Evaporation of the dried benzene solution gave an oil which was purified by preparative t.l.c. (carbon tetrachloride) to give the mixture of 1,2- and 1,3-bisphenylsulphides (2:3, 200 mg) having Rf 0·15 and a little diphenyl disulphide Rf 0·5.

Control reactions.

i) 1,3-Dimethoxy-2-N-methylanilinopropane (35 mg) was dissolved in dry methanol (5 ml) containing calcium carbonate (100 mg) and the mixture was stirred and refluxed for 6 hours. Filtration and evaporation of solvent gave the unchanged 1,3-dimethyl ether.

ii) 1,2-Diacetoxy-3-N-methylanilinopropane* (70 mg) and potassium acetate (400 mg), in acetic anhydride (10 ml) were heated at 100°

* Prepared by Mr.G. Durrant

for 2 hours. Isolation of the product as described in iii) above, gave the unchanged 1,2-diacetate.

iii) 1,2-Dimethanesulphonyloxy-3-N-methylanilinopropane was unchanged when boiled under reflux in chloroform solution. When boiled in acetone solution an oil was obtained which was identified as a mixture of the unchanged 1,2-dimesylate and diacetone alcohol, $\nu_{max}(CHCl_3)$ 1700 cm.$^{-1}$, $\tau(CDCl_3)$ 8·80 (6H,s, $(CH_3)_2$-C), 7·89(3H,s, CH_3-CO-C), 7·44 (2H, s, CO-CH_2-C) and signals attributable to the unchanged 1,2-dimesylate masking the hydroxyl peak of diacetone alcohol. The n.m.r. spectrum of a mixture of the dimesylate and authentic diacetone alcohol was identical.

iv) 1,3-Dimethanesulphonyloxy-2-N-methylanilinopropane was unchanged when heated in boiling acetone for 6 hours.

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