

**SYNTHESIS AND USE OF AN IMMOBILIZED
CATALYST FOR THE N-OXIDATION OF
2-CHLOROPYRIDINE**

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DECLARATION

I hereby certify that this material, which I now submit for assessment on the programme of study leading to the award of M.Sc. is entirely my own work and has not been taken from the work of others save and to the extent that such work has been cited and acknowledged within the text of my work.

Signed: Patrick Nobbs Date: 25/10/94

Date: _____

DEDICATION

TO MY WIFE PAULINE, DAUGHTER LOUISE
AND SON ROBERT FOR THEIR SUPPORT,
PATIENCE AND ENDURANCE.

ACKNOWLEDGEMENTS

I wish to acknowledge with deepest sincerity the following without whose assistance and cooperation, this work could not have been made possible:-

Olin Chemicals B.V. for the supply of facilities, chemicals and equipment. Rohm and Haas UK, Ltd., for the supply of resins used for this work. Professor A.C. Pratt for his help, suggestions and encouragement throughout this Thesis preparation.

ABSTRACT.

N-oxides were defined, their history and chemistry surveyed. Conventional N-oxidising reagents, such as the aliphatic and aromatic percarboxylic acids were examined. Immobilized catalysts, their applications and synthesis were extensively reviewed and examples noted. Immobilized percarboxylic acids or carboxylic acids in conjunction with hydrogen peroxide were identified as potential N-oxidising reagents. The literature survey yielded eight routes which have been utilized for introduction of a carboxyl group into polystyrene. A number of these routes were investigated experimentally. Two routes proved useful, (i) modification of Merrifield resin to carboxylated resin and (ii) chloroacylation of polystyrene, then formation of the phenyl pyridinium chloride derivative followed by cleavage afforded carboxylated polystyrene.

The criteria for a useful support resin were reviewed and a porous macroreticular polystyrene-divinylbenzene crosslinked resin was found to offer a number of advantages over conventional gel-type resins. A sample of such a resin, XE-305 was procured from a commercial company and used for synthesis. The carboxylated derivative with carboxylate loading from 42% to 88% were used to oxidise 2-chloropyridine to its N-oxide in the presence of excess hydrogen peroxide and mineral acid. Yields of the order of 33-35% were achieved. 2-Chloropyridine-N-oxide is used for the manufacture of a number of commercially important antifungal and anti-bacterial biocides.

Despite numerous changes and modifications to the reaction conditions, including the use of a peroxide stabiliser, the yield could not be increased above 33-35%. For commercial success, yields greater than 60% would have to be achieved in order to compete with existing processes such as the peracetic acid process reported in the literature. A mass balance examination showed that up to 24% of the initial 2-chloropyridine was unaccounted for at the end of oxidation. A further study of 2-chloropyridine and its N-oxide stability, demonstrated that product N-oxide and not 2-chloropyridine was unstable and decomposed under conditions likely to prevail in the oxidations. No way was found to prevent this decomposition and so it was concluded that this process using immobilized catalyst could not compete with existing batch processes utilising peracetic or acetic acid/hydrogen peroxide.

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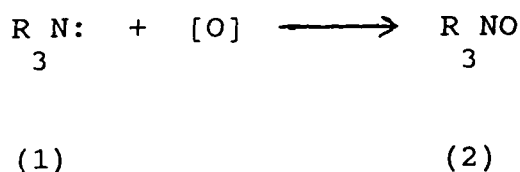
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Chapter 1

INTRODUCTION

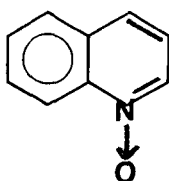
The product formed by the reaction of peroxide compounds such as hydrogen peroxide or a percarboxylic acid with tertiary amine (1) is known as an N-oxide:



The amine oxide (2) may be represented by structures (3) or (4) in which the lone pair electrons of the nitrogen atom of the tertiary amine (1) are utilized in bonding to the oxygen.

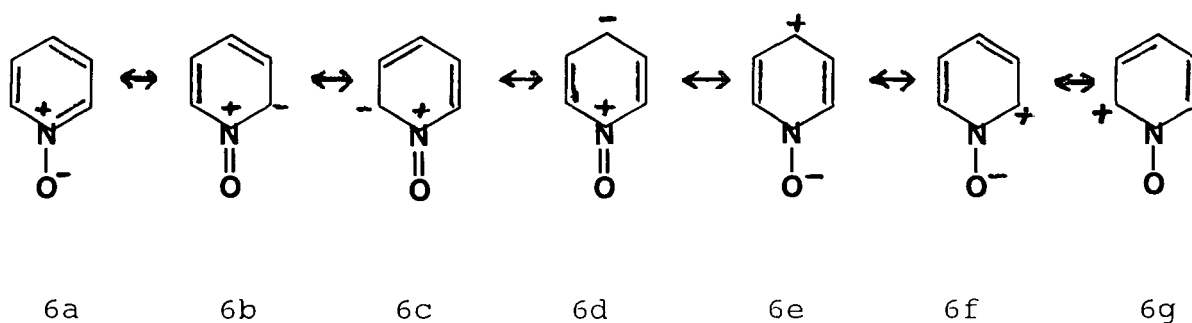


Heteroaromatic amines such as pyridine and quinoline are converted to their N-oxides in a similar manner. The properties of the heteroaromatic-N-oxides, for example quinoline-N-oxide (5) and pyridine-N-oxide (6), differ considerably from those of the tertiary amine oxides due to the availability of the aromatic pi-system in the former which permits extensive delocalisation of the oxygen lone pairs.



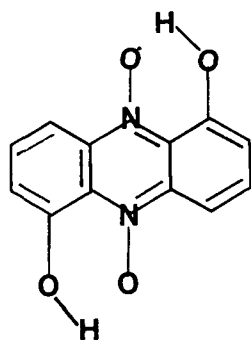
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Pyridine-1-oxide (6) was first prepared by Meisenheimer¹ by perbenzoic acid oxidation of pyridine. Largely due to further work by Meisenheimer² and by Bobranski³ the heteroaromatic N-oxides were a well recognised group of compounds by the end of the 1930's. In early 1940 the Japanese began their extensive study of the chemistry of heteroaromatic N-oxides. That year Linton⁴ in the USA measured the dipole moment of pyridine-N-oxide and found that it was markedly smaller than the value calculated from the moments of pyridine and the N-oxide group. He pointed out the contribution of the canonical forms (6a-6g) to the resonance hybrid of pyridine-N-oxide:

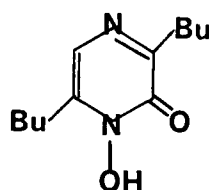


Ochiai⁵ in 1943 recognised the difference between aliphatic and aromatic N-oxides, the difference being comparable to that between the hydroxyl groups in alcohols and phenols, or between the amino group in alkylamines and anilines. He therefore proposed that amine oxides should be

classified into aliphatic and aromatic N-oxides. Abstracts of Ochiai's papers started to appear in Chemical Abstracts after the end of World War 2. den Hertog in the Netherlands developed similar ideas. A third early centre of N-oxide research was that of Colonna and his group in Italy which emphasized the analogy between heterocyclic N-oxides and nitrones. The discovery that the antibiotics iodinin (7) and aspergillic acid (8) were N-oxides gave further impetus to the study of the general chemistry of N-oxides.

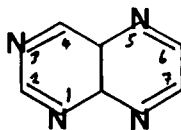


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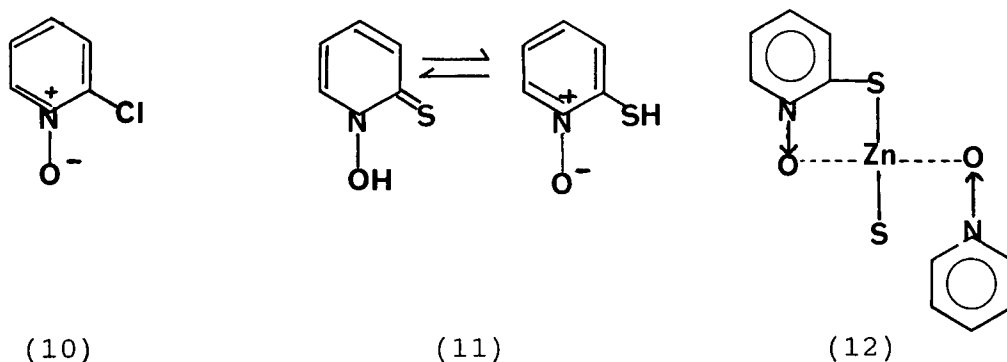
Added interest was provided by claims that the conversion of certain alkaloids [e.g. the vitamin folic acid, containing derivatives of the pteridine structure (9)] into their N-oxides led to a reduced toxicity without a parallel decrease in beneficial biological activity.



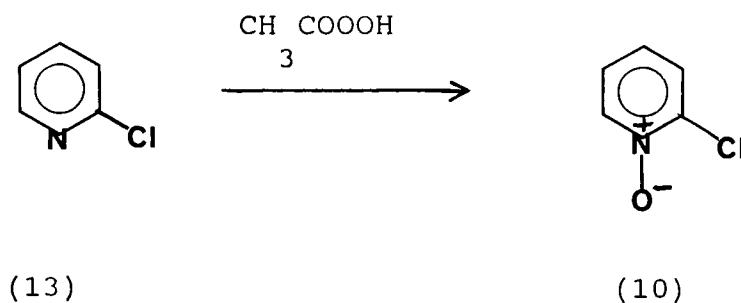
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2-Mercaptopyridine-N-oxide (11) and some of its derivatives

are effective pesticides, fungicides and bacteriocides for a broad spectrum of organisms.^{13,14} 2-Chloropyridine-N-oxide (10) is of major interest as it is the precursor to 2-mercaptopyridine-N-oxide (11) and its derivatives e.g. zinc-2-pyridinethiol-1-oxide (12).



2-Chloropyridine-N-oxide (10) is manufactured on an industrial scale in the USA, Ireland, West Germany and Japan. In Ireland Olin Chemicals B.V. manufacture all three compounds (10), (11) and (12) in large quantities. The starting material for all three is 2-chloropyridine (13) which is commercially available in large volumes at reasonable cost. 2-Chloropyridine is converted to its N-oxide by peracetic acid:



Peracetic acid is the most common reagent for the

N-oxidation of heterocyclic compounds. However its transportation and the recovery of peracetic acid and acetic acid on an industrial scale are problems which adversely affect process economics. Hydrogen peroxide, acetic acid and sulphuric acid are also used together industrially in an "in situ" process, but recovery of the acetic acid is uneconomic. In addition acetic acid places a large loading on biological effluent treatment plants, increases process costs and may cause pollution of the aquatic environment. More recently interest in organic N-oxidising reagents continues as with the hydrogen peroxide/urea/phthalic anhydride system of Kaczmarek¹⁵ et al. Potent inorganic catalysts (the peroxides of the oxyacids of Group VI elements such as tungstic and molybdic acids^{16,17,18}), have been used for N-oxidation and to epoxidize olefins²⁰ but little information appears in the literature. However an inorganic catalyst would have to be removed from an organic/aqueous stream and this may also cause problems.

From the point of view of Olin Chemicals it is desirable to develop an alternative process for the N-oxidation of 2-chloro- pyridine which does not have the disadvantages of peracetic acid and which will at the same time give high yields of the N-oxide with a minimum of side reactions. A survey of the literature indicates that many methods are available for the N-oxidation of nitrogen heterocycles.

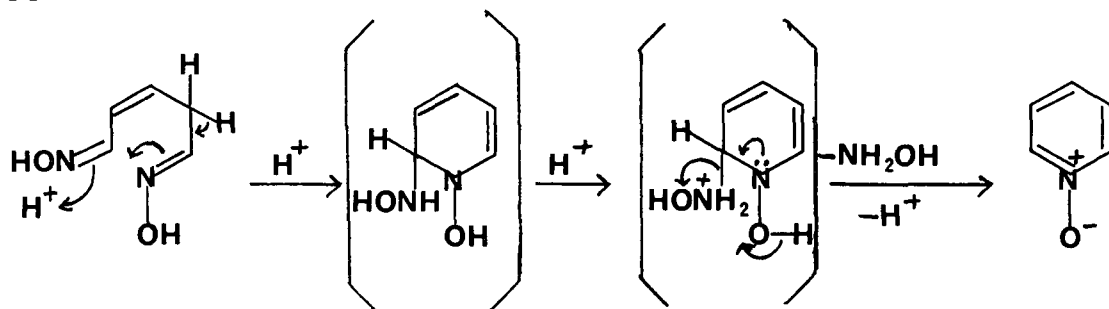
ASPECTS OF HETEROCYCLIC N-OXIDE FORMATION.

Practically all known methods for the preparation of heterocyclic N-oxides may be classified into one of three major groups :

- (a) direct N-oxidation of the corresponding heterocycle,
- (b) formation of the ring carrying the N-oxide group by a cyclisation reaction,
- (c) chemical modification of an existing cyclic N-oxide with preservation of the N-oxide function.

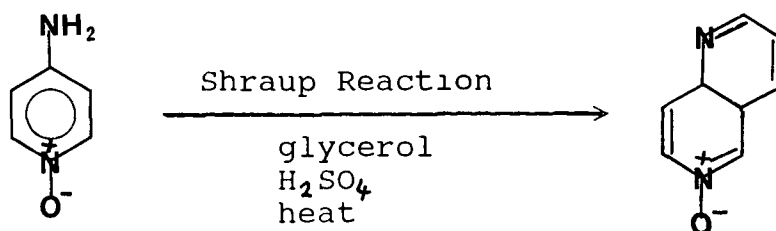
Only method (a) is relevant here since 2-chloropyridine is the starting material we wish to convert to its N-oxide.

A good example of (b) is that of Baumgarten and his²¹ co-workers who showed that when glutaconic aldehyde and hydroxylamine are heated in methanol in an acid medium, the dioxime formed as an intermediate undergoes cyclisation with liberation of one mole of hydroxylamine, and pyridine-N-oxide is formed:

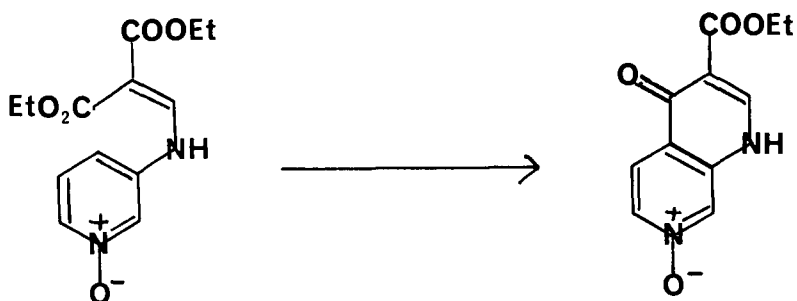


An example of (c) is ring closure onto an N-oxide ring,

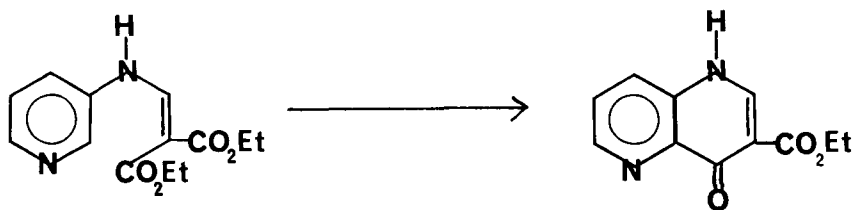
though relatively few examples are known. In such reactions, ring positions "gamma" to the N-oxide group are generally preferentially substituted. Kato et al²² have demonstrated that 4-aminopyridine-N-oxide undergoes the Skraup reaction to give 1,6-naphthyridine-6-oxide:



The pyridine-N-oxide derivative (14) cyclizes at the 4-position analogously. The corresponding free amine (15)²⁰ also cyclizes, but in contrast substitution occurs at the 2-position to yield (16).



(14)

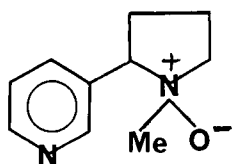


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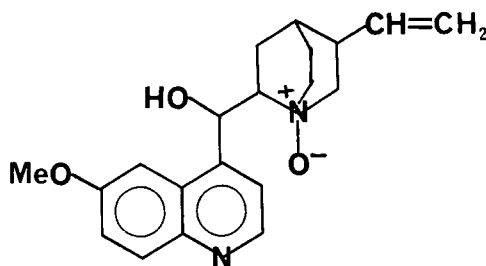
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Hydrogen Peroxide.

Hydrogen peroxide alone does not normally react with nitrogen-containing heteraromatic compounds, although it does smoothly convert saturated tertiary amines to the corresponding N-oxides. Thus the alkaloids nicotine^{24,25} and quinine,²⁶ each of which contains both a hetero-aromatic and a tertiary amino-nitrogen, are converted into mono-N-oxides (cf. 17 and 18 respectively) by hydrogen peroxide, but give di-N-oxides on treatment with peracetic acid.²⁷



(17)



(18)

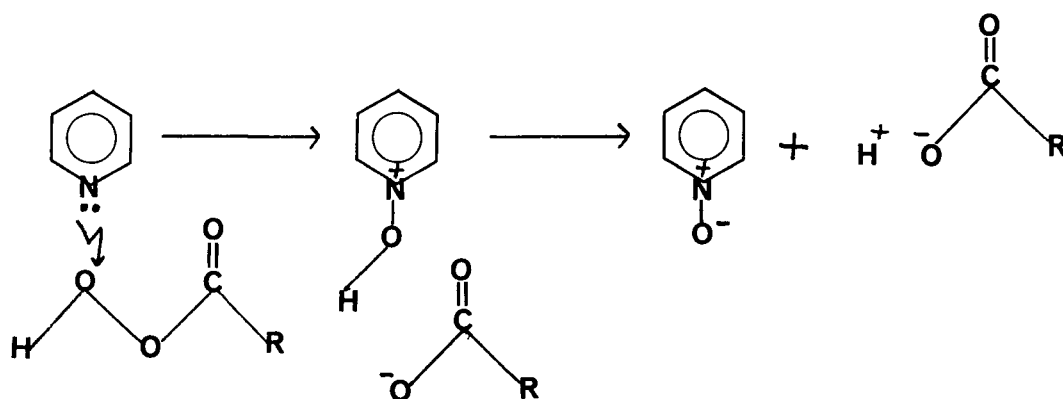
A literature search indicated that all of the important oxidising agents are percarboxylic acids, of which a variety have been used.²⁸ A kinetic study has shown that the reaction of pyridine with perbenzoic acid in aqueous dioxane is of second order and involves reaction of the pyridine free base with the unionised peracid. The rate falls off at low pH values due to formation of pyridinium cation and a corresponding rate drop at high pH values is due to formation of peracid anion. Electron donating alkyl

groups on the pyridine ring enhance the reaction rate, illustrated in Table 1 by the second order rate constants measured under standard conditions at 25 °C. These correlate with pKa values of pyridines as bases.

Substituted pyridine	$k \times 10^3$ (sec ⁻¹ mole ⁻¹ litre ⁻¹)	pKa
---	4.80	5.15
4-Me	7.25	6.02
2,4-diMe	10.2	6.79
2,4,6-triMe	10.2	7.50

Table 1.

These findings are in accord with a mechanism of the following type:

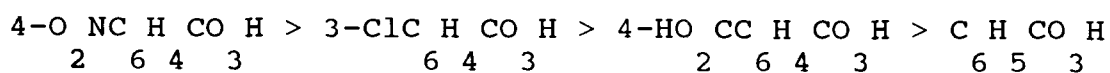


Steric effects are reflected in the lower than expected rate found for 2,4,6-trimethylpyridine.

The kinetics of perbenzoic acid N-oxidation have been extended to cover a wider variety of alkyipyridines and also to mono-chloropyridines.²⁹ Linear relationships were found between the second order rate constants and the

Hammett sigma constants for the mono-substituted compounds. Rho for the reaction has, as expected, a large negative value of -2.35. For all the compounds studied, a satisfactory linear relationship was found between the second order rate constants and the pKa values, except for the 2,6-disubstituted derivatives where steric hindrance obviously interferes with N-oxidations.

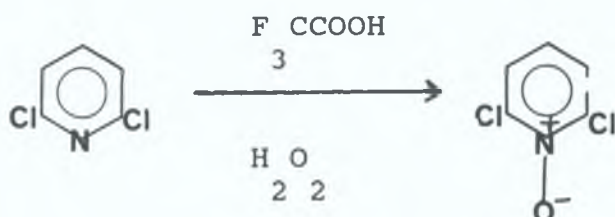
N-Oxidation with a percarboxylic acid or hydrogen peroxide in glacial acetic acid is the result of bond formation between the lone pair electrons of a nucleophilic nitrogen and an electron deficient hydroxyl group acting as an electrophile. The progress of the reaction should depend on the basicity of the nitrogen and on the ability of the oxidizing agent to polarise in such a way that the -OH function is electron deficient. Consequently the activity of a dicarboxylic acid such as monoperphthalic acid would be anticipated to be greater than that of the monocarboxylic acid perbenzoic acid because of the electron withdrawing power of the second carboxyl group. Other acids containing powerful electron withdrawing groups should also be more active. A series in order of decreasing reactivity can be suggested:



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Evans et al. found that while 2,6-dichloropyridine, whose basicity is low due to steric hindrance and the inductive effect of two ortho halogens, resists N-oxidation

with perbenzoic and peracetic acids, it forms the N-oxide in 70-75% yield if warmed with 30% hydrogen peroxide in trifluoroacetic acid. The fluorine of trifluoroacetic is powerfully electron withdrawing and polarizes the -OH function.



Therefore, for a smooth N-oxidation to proceed, electron withdrawing groups are desirable in the percarboxylic acid while electron donating groups are advantageous in the heterocyclic base. 2-Chloropyridine is somewhat deactivated because of its electron withdrawing chlorine so we must therefore look to design a percarboxylic acid with enhanced reactivity. Before going on to discuss percarboxylic acid resins the use of some well known percarboxylic acids and some associated side reactions will be briefly considered.

ALIPHATIC PERCARBOXYLIC ACIDS.

Peracetic Acid is the most utilized reagent for the conversion of nitrogen heterocycles to their N-oxides.
¹⁰
 Katritzky takes 22 pages of text to list its applications. To effect N-oxidation the heterocyclic

compound, glacial acetic acid and excess of 30% aqueous hydrogen peroxide are usually heated at a temperature between 20 °C and 90 °C for 3-24 hours; a temperature of 70 °C is frequently selected and reactions are commonly allowed to proceed overnight. For 2-halogenopyridines yields of 70-80% are reported.¹⁰ The N-oxide is obtained as an aqueous solution after neutralisation of the acetic acid and removal of the excess halogenopyridine by distillation.

Pertrifluoroacetic Acid is a strong oxidizing agent and has been used in a number of cases where peracetic acid fails or gives poor yields of the N-oxide. It is often the reagent of choice for the laboratory preparation of 2-halogenopyridine-N-oxides. Pentachloropyridine has been converted to its N-oxide with pertrifluoroacetic acid although care is needed, since prolonged heating causes deoxygenation.

Permaleic Acid is advantageous for the N-oxidation of some compounds which are otherwise difficult to oxidize. 2-Chloropyridine, 2-halogenoquinolines, chloropyrimidines and chloropyrazines have been converted to the corresponding N-oxides in good yields with this reagent.

AROMATIC PERCARBOXYLIC ACIDS.

N-oxidations with aromatic percarboxylic acids are generally carried out in nonpolar solvents at room temperature, conditions that are considerably less severe

than those for peracetic acid oxidation and are suitable for sensitive substrates.

Perbenzoic Acid is the second most frequently used reagent for the conversion of nitrogenous bases into their N-oxides. Reactions are commonly conducted in chloroform solution and there are fewer side reactions than with peracetic acid. For 2-, 3-, and 4-halogenopyridines Katritzky et al.¹⁰ reports a yield of ca 60%. The reaction is usually effected by adding the base to a chloroform solution of perbenzoic acid and allowing the mixture to stand for several days at room temperature.

m-Chloroperbenzoic Acid, which is crystalline, stable and commercially available, is a convenient alternative to perbenzoic acid for effecting N-oxidation. Because of its electron-withdrawing chlorine, the rate of N-oxidation is several times that of perbenzoic acid.

p-Nitroperbenzoic Acid. The p-nitro group is a more effective electron-withdrawing group than the m-chloro group and for epoxidation of olefins at least it is 5-20 times more reactive than perbenzoic acid whereas m-chloroperbenzoic acid is only slightly more effective.³¹ It has been suggested as an alternative to³² perbenzoic acid for N-oxidations.

Perphthalic Acid is a popular reagent for the synthesis of N-oxides because of its ease of formation from phthalic

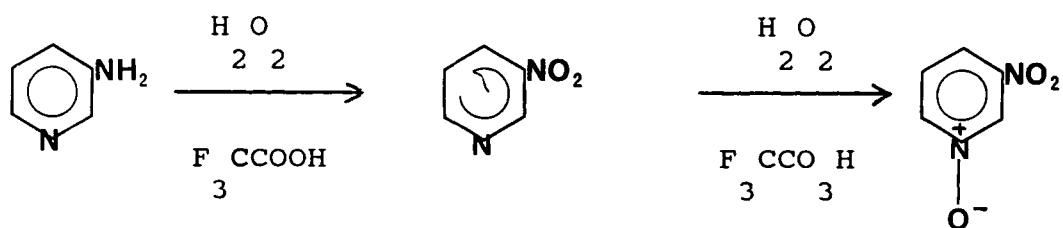
anhydride and hydrogen peroxide, and its relative stability. It is used under very mild conditions. Typically the base is allowed to react with an ethereal solution of perphthalic acid at a temperature between -20°C and $+20^{\circ}\text{C}$ from a few hours to a few days or longer.

SIDE REACTIONS

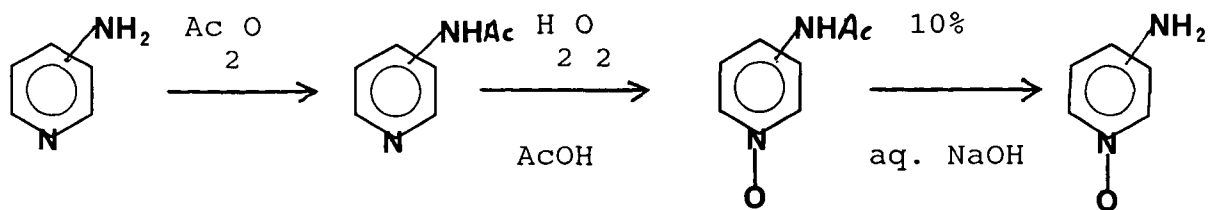
Percarboxylic acids and hydrogen peroxide can act as nucleophilic reagents and the N-oxidation reaction may be accompanied by substitution of the ring with hydroxyl, by cleavage of the ring, or by other reactions.

(a) Oxidation Of Other Substitutents:

A primary amino group can be oxidized to a nitro group by treatment with a peracid:

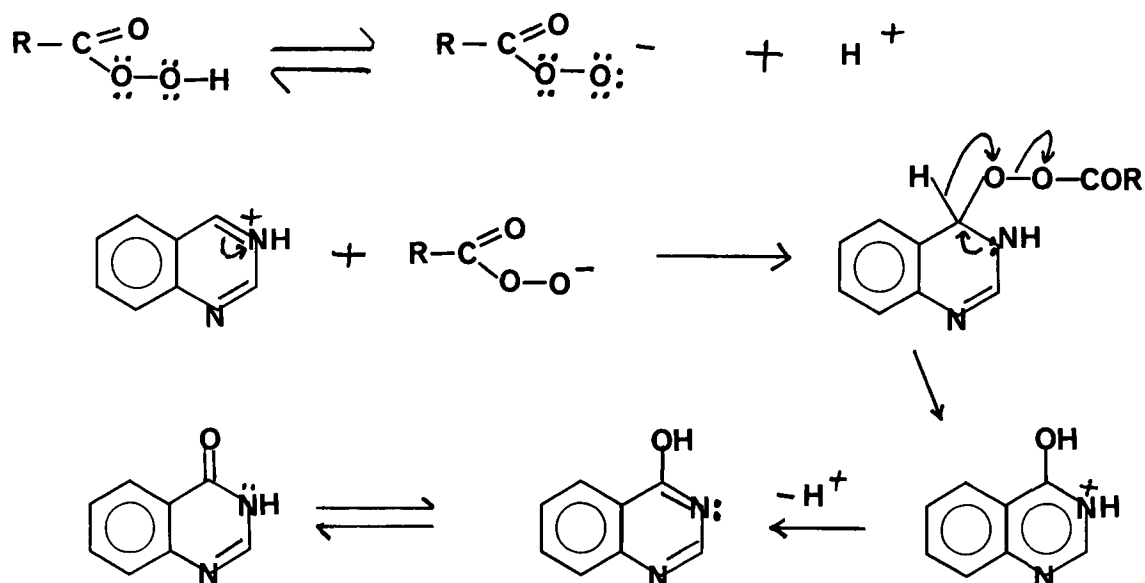


In such a case, it is usual to initially protect the primary amino group by acylation and to release it by hydrolysis following N-oxidation:



(b) Replacement by Hydroxyl Group.

The percarboxylic acid used as a reagent for direct oxidation may also act as a nucleophile:



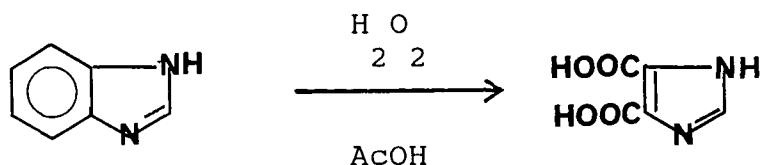
This reaction is more liable to occur in alkaline medium, but it also occurs in acid medium if the aromatic heterocycle has a position highly susceptible to nucleophilic attack as shown in the above example.¹²

(c) Oxidative Cleavage Of The Ring.

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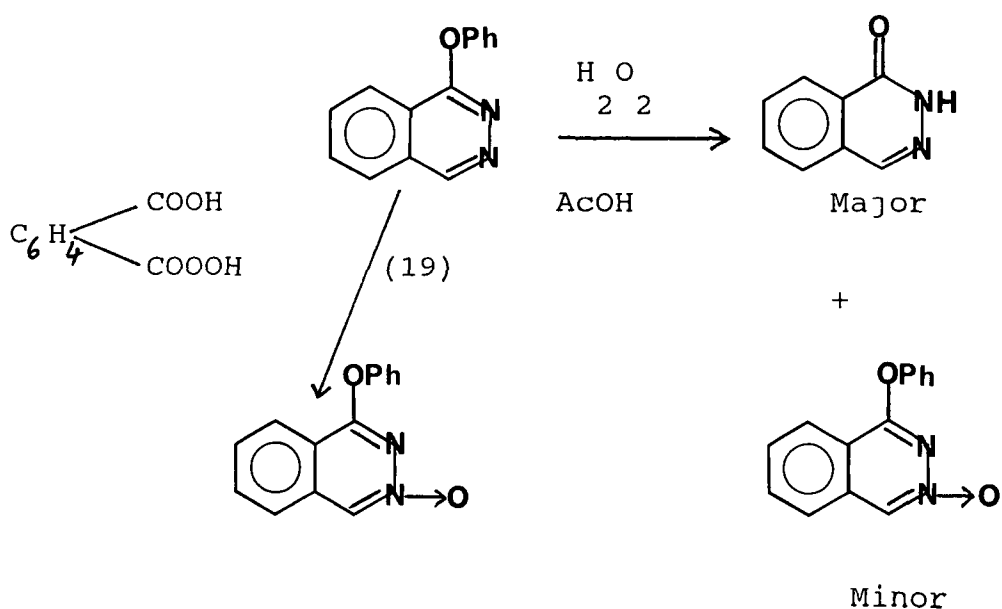
Von Euler found that the imidazole ring in benzimidazole was resistant to N-oxidation with hydrogen peroxide and

glacial acetic acid, and the reaction resulted in cleavage of the benzene portion, forming imidazole-4,5-dicarboxylic acid:



(d) Hydrolysis When Acetic Acid And Hydrogen Peroxide Are Heated Over Extended Periods.

1-Phenoxyphthalazine (19) easily forms its 3-oxide by the application of monoperphthalic acid. On the other hand, the use of hydrogen peroxide and glacial acetic acid for the oxidation mainly results in displacement of the phenoxy group and the yield of the 3-oxide decreases:³⁵



(e) Deoxygenation:

Many N-oxides are converted into parent bases if they are heated strongly, either alone or in the presence of various solid catalysts. Thus simply heating pyridine N-oxide at 220 °C gives some pyridine; the decomposition is catalysed by copper or zinc powder. Oxidative deoxygenations have been reported, i.e. deoxygenation reactions which occur on treatment of an N-oxide with an oxidizing agent. For example peracetic acid causes loss of the N-oxide function from 2-hydroxy-quinoline-1-oxide.

All of the percarboxylic acids discussed so far, with the exceptions of peracetic and pertrifluoroacetic acid, can be recovered from solution, after decomposing the peracid to its carboxylic analogue, and precipitating the carboxylic acid by acidification. On an industrial scale where large quantities of these acids would be used, this would entail an additional filtration step, probably using a plate type filter press. This could result in a significant yield loss by entrapment of the N-oxide in the crystalline mass. For N-oxides (such as 2-chloropyridine-N-oxide) which form a hydrochloride, yield loss by coprecipitation could be very significant. Some of the N-oxide could be recovered on rework and purification but these additional steps would adversely affect process economics. These problems are much less important on a lab bench scale where these peracids can be readily used for N-oxidations.

As one approach to avoiding these problems on a plant scale

consideration has been given to immobilization of the percarboxylic acid on an inert support. The functionalized support could then be suspended in a solution of the amine (for example 2-chloropyridine) and the N-oxidation carried out. The N-oxide would then be recovered following simple filtration and the support recycled. An alternative method would be to pack the functionalized support in a tubular reactor and to pump the amine solution through it. On exhaustion the supported percarboxylic acid groups could then be regenerated.

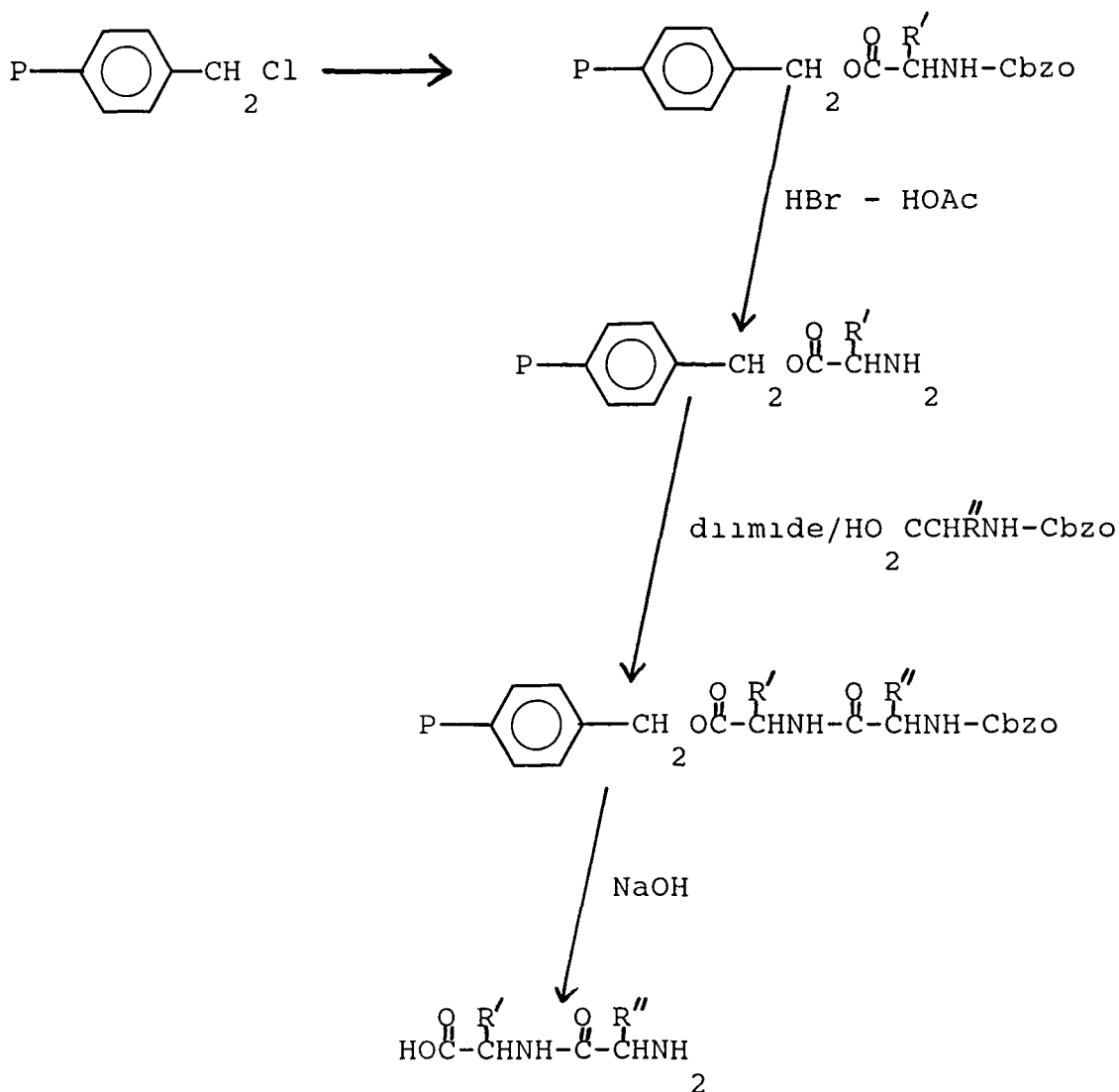
IMMOBLIZED CATALYSTS.

The use of immobilized catalysts in organic chemistry is well documented in the literature.³⁶⁻⁷² It is not intended to carry out a comprehensive review of this increasingly important field of chemistry but the following examples attempt to demonstrate the wide applicability of insoluble polymer supports in chemical synthesis.

(A) Solid Phase Peptide Synthesis.

This involved the stepwise addition of protected amino acids to a growing peptide chain which was bound to a solid resin particle. This provided a procedure whereby reagents and byproducts were removed by filtration and recrystallization of intermediates was eliminated. The advantages are speed, simplicity of operation and the possibility of automation. The feasibility was first demonstrated by the

synthesis of the tetrapeptide L-leucyl-L-alanyl-glycyl-L-valine. The idea is illustrated in the following scheme:

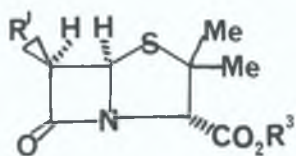


Merrifield's work has had widespread consequences. Since he first introduced the technique of "solid-phase" peptide synthesis in 1963 there has been considerable interest in the reactions of species attached to polymers. The following example demonstrates one possible application.

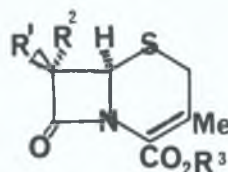
(B) Oxidation Of Some Penicillins And Other Sulphides By
Use Of Polymer - Supported Percarboxylic Acids.

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When penicillins (20) or cephalosporins (21) were treated with polymeric percarboxylic acids in DMF, THF or acetone at 20°C they were oxidized selectively to give the S-oxides in high yield (78-100%). Oxidation of penicillins to S-oxides is of interest because the S-oxides can be converted into commercially important cephalosporin derivatives.



(20)



(21)

The oxidations of 6,6-dibromopenicillanic acid (20: R = Br, R = H) and methyl 6-chloropenicillanate (20: R = H, R = Cl, R = Me) are of particular interest because mixtures of the epimeric sulfoxides were produced. The former gave the R- and S-epimers in the ratio 87:13. This ratio is comparable to that 91:9 found when m-chloroperbenzoic acid was used under similar reaction conditions. The 6-chloro compound gave the R- and S-epimers in the ratio 5:95, compared to 12:88 with the monomeric percarboxylic acid. The fact that the percarboxylic acid residues were attached to the phenyl rings of polystyrene therefore makes little or no difference to the stereo-selectivity of the reagent. The resin was recoverable and could be regenerated and reused several times.

Percarboxylic acid resins are used in many other important applications, most notably epoxidations of olefins. Further consideration of these resins will be taken up in a later section.

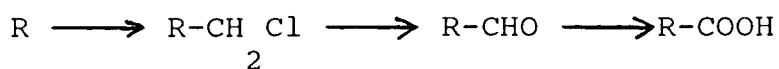
In summary the above examples illustrate the use of immobilized reagents. Some advantages of using such reagents are ease of use, recovery and regeneration for recycling. Many of these systems are suitable for automation, e.g. automatic or automated instrument systems⁷³ are now available for peptide synthesis. In addition some immobilized catalysts are more active or more selective³⁷ than their monomeric analogues, e.g. rhodium hydrogenation catalysts. Chemical modification of supported structures e.g. steroids⁴² may be achieved and the reagents washed away yielding a fairly pure product after cleavage. Certain complexes are more easily synthesized on a support eg crown ethers.⁴⁴ Supported anion systems can react in non aqueous solvents and may be used in place of phase transfer catalysts⁴⁵ eg cyanide and thiocyanate anion exchange resins.

The use of an immobilized catalyst for the N-oxidation of 2-chloropyridine has not been reported. The work reported in this thesis has been concerned with the synthesis and use of an immobilized catalyst for this purpose.

OUTLINE OF POSSIBLE ROUTES TO CARBOXYLATED RESIN.

A survey of the literature yielded eight routes which have been utilized for introduction of a carboxyl group to the phenyls of a polystyrene. A discussion of each follows.

Route (A).



(22)

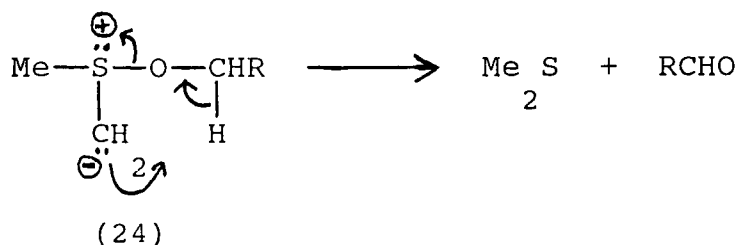
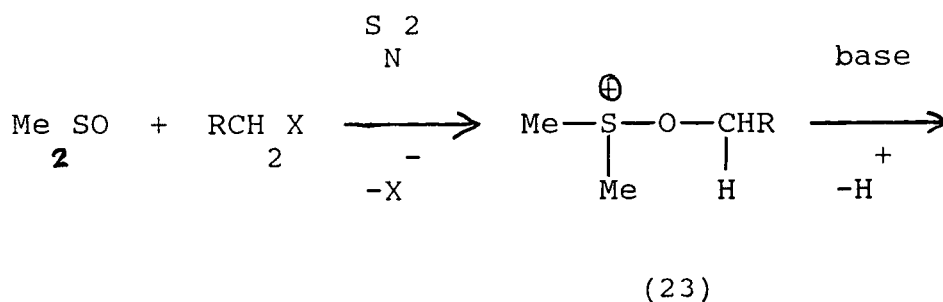
Chloromethylated resin (22), known as Merrifield Resin, is available commercially as a laboratory reagent, with 2 % divinylbenzene (DVB) crosslinking, from Aldrich Chemical Company and Koch-Light Ltd. These resins, with 2% divinylbenzene (DVB) crosslinking, are supplied with a loading of 1.0 mmole/g and 1.25 mmole/g of chlorine respectively, by the above two companies. The chlorine loadings correspond to 11.0% and 14.5% respectively of the phenyl rings substituted by chloromethyl groups in a 2 % DVB resin.

A literature search yielded a number of methods for introducing a chloromethyl group into an aromatic ring. One method⁷⁴ is to treat the aromatic compound with formaldehyde and hydrochloric acid:



Once a chloromethylated resin is available it can be formylated by oxidation using dimethylsulphoxide (DMSO) and sodium bicarbonate.^{75,76}

The mechanism involves S_N2 attack^{77,78} on the halide to form an alkoxysulfonium salt, followed by base abstraction of a proton to yield an ylide which rearranges to form dimethylsulphide and the aldehyde.

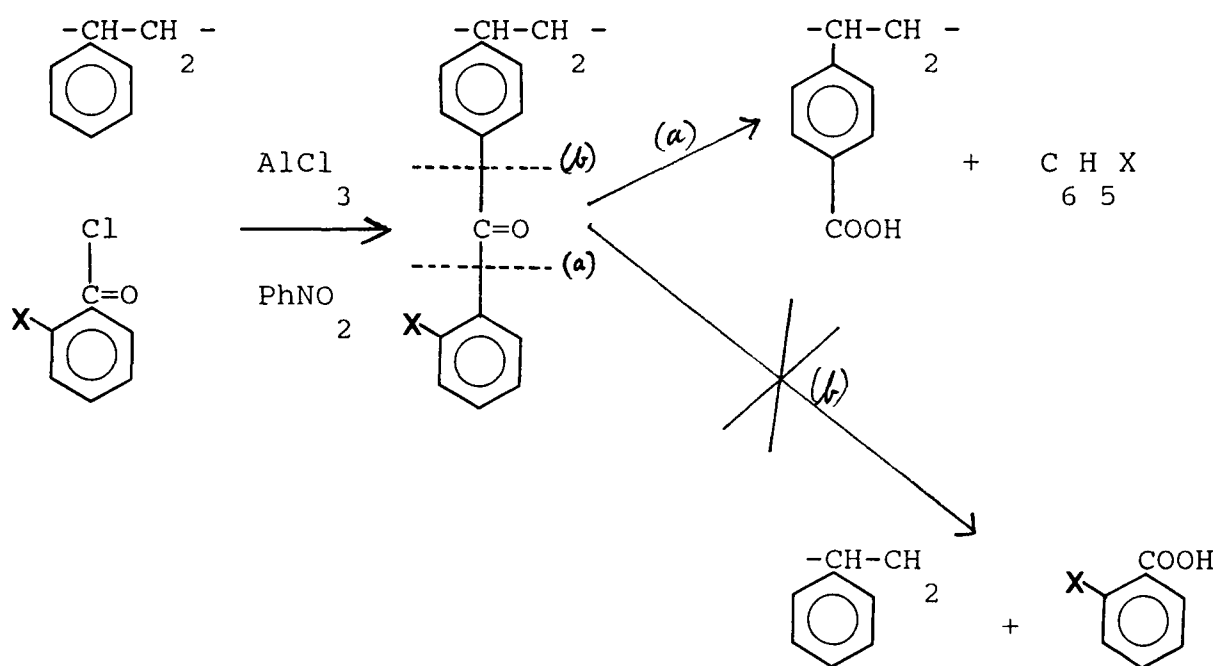


Though the mechanism of dimethyl sulphoxide oxidation is probably S_N2 in some cases the base abstracts a proton directly from the carbon being oxidized in which case the ylide (24) is not an intermediate. Alkoxysulphonium salts (23) have been isolated. This mechanism predicts that secondary compounds should be oxidisable to ketones and this is the case.

The final step, oxidation of the formyl resin, is achieved by oxidizing with methanesulphonic acid and peracetic acid^{75,76} in acetic acid.

Route (B).

The first step is a Friedel Crafts acylation with anhydrous aluminium trichloride and 2-chlorobenzoyl chloride in nitrobenzene. Selective cleavage of the 2-chlorobenzoylated resin using potassium tert-butoxide and water (mole ratio 10:3) in 1,2-dimethoxyethane under reflux has given an essentially quantitative yield of the acid ⁷⁶ for a 24 % substituted resin as in path (a):

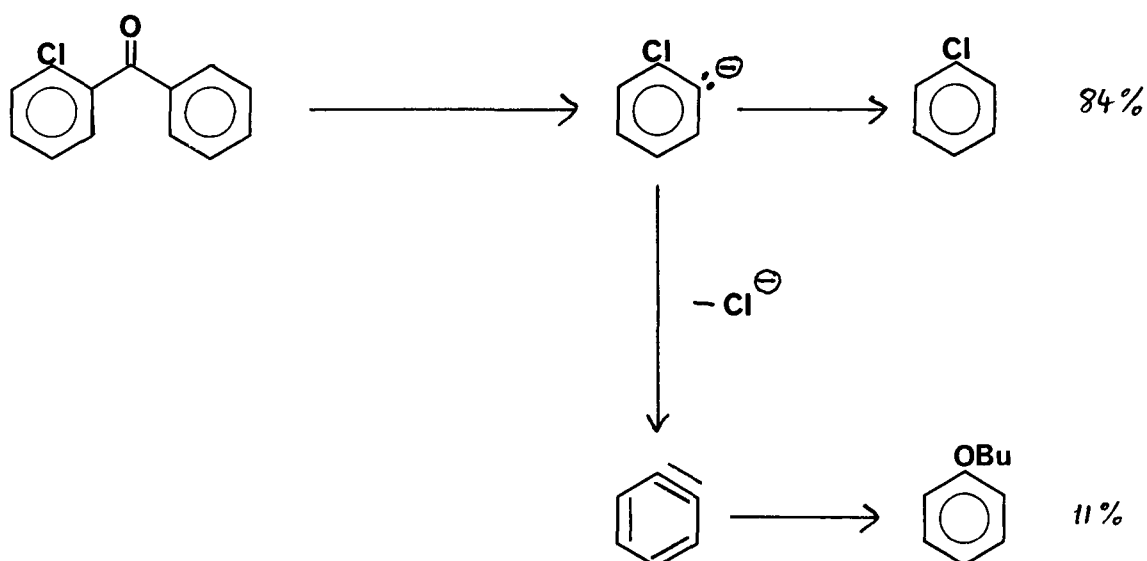


For this method to be successful the substituent X must be such that cleavage occurs almost entirely at bond (a). ⁷⁹

An ortho chloro substituent appears to be particularly suitable for this purpose.

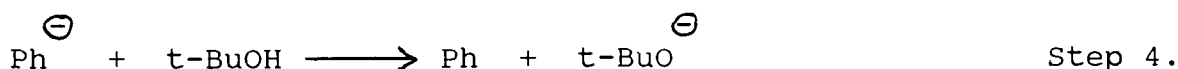
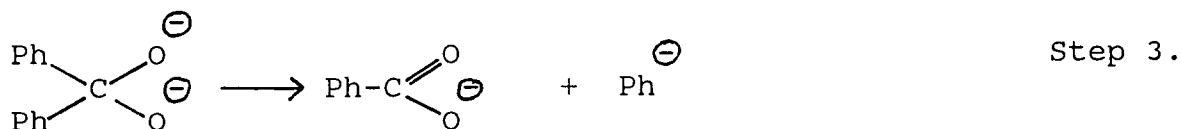
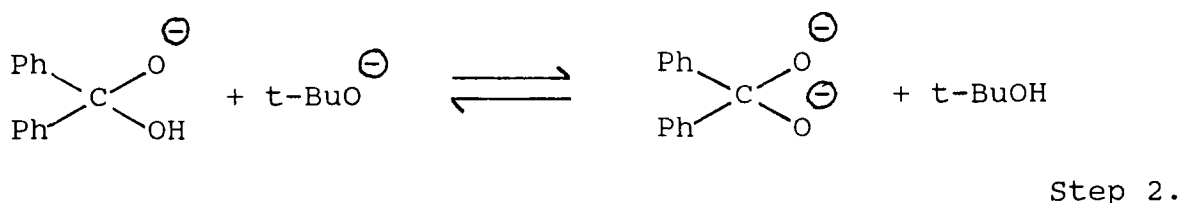
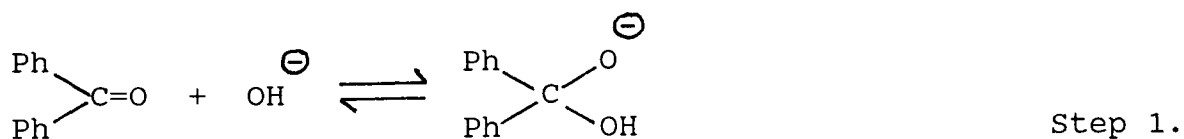
80

Previous work had shown that 2-chlorobenzophenone not only cleaved to give an acid fraction that was >99% benzoic acid, but it cleaved more easily than did benzophenone itself. In addition chlorobenzene was obtained in 84% yield. Phenyl t-butyl ether was formed in 11% yield, presumably by reaction of benzyne with the t-butyl alcohol or potassium t-butoxide present in the reaction mixture. A possible route to the latter two products is illustrated:



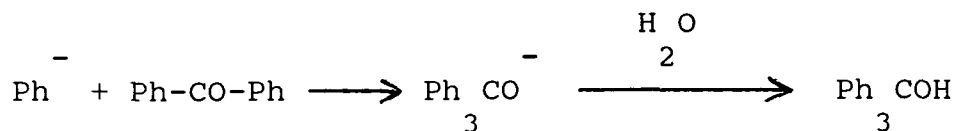
When a solution of potassium t-butoxide in ether is treated with water, a heterogeneous mixture is formed. The solid material present is almost certainly potassium hydroxide. The efficiency with which this mixture cleaves non-enonisable ketones such as benzophenone varies considerably with the relative proportions of water and t-butoxide used to prepare it. The best yields were obtained when the water to t-butoxide ratio was 3 : 10. Such a mixture probably contains potassium hydroxide,

potassium t-butoxide and t-butyl alcohol in the approximate ⁸⁰ ratio 3 : 7 : 3. It has been shown that the ⁸² initial attack on the substrate is by hydroxide ion. The observations are most easily rationalized in terms of a mechanism of the type outlined:



The first step at least probably occurs on the surface of the solid potassium hydroxide. The most likely explanation for the beneficial effect of the butoxide is that it facilitates cleavage (step 3) by removing the proton (step 2) from the initially formed adduct (step 1). It is able to do this more effectively than hydroxide because it is a stronger base and is more soluble in the reaction medium.

There is evidence that phenyl carbanions are intermediates in the cleavage, since triarylmethanols (9% yield from benzophenone) are also formed:



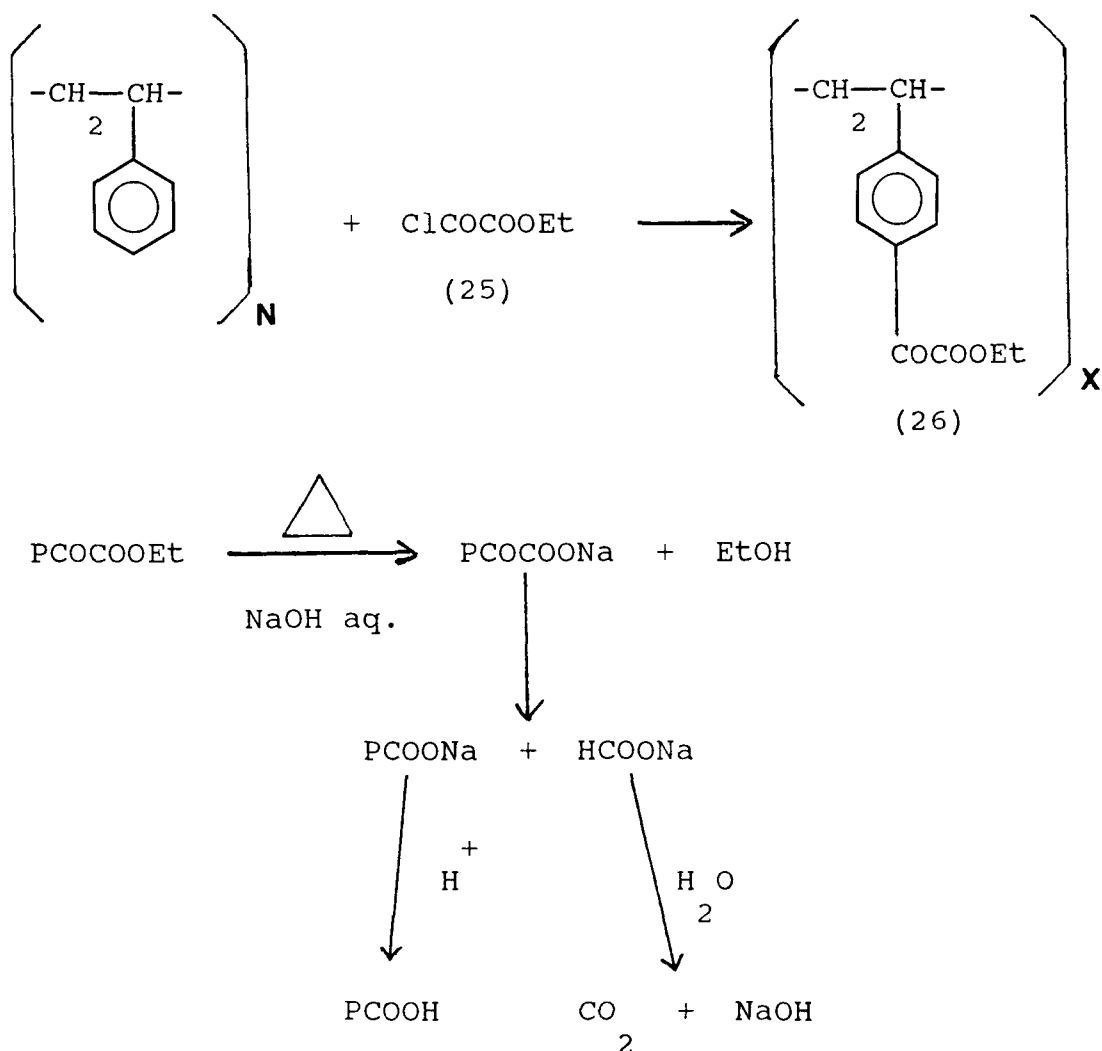
For substituents in the 2-position there is, in addition to the electronic effects, a steric effect. This favours cleavage of the bond to the ring bearing the substituent since this relieves steric strain. In the cleavage of 2-methylbenzophenone where the steric and electronic effects are in opposition, the steric effect must be more important since the major acid product is benzoic acid. In the cleavage of 2-chloro- and 2-methoxy-benzophenones where there is a strong electron withdrawing inductive effect as well as the steric effect favouring cleavage at the bond nearer the substituent, the acid products were essentially pure (>99%) benzoic acid.⁸⁰

This method of introducing carboxyl groups into a resin seems attractive for the following reasons:

- (i) it is only a two step process,
- (ii) the reagents are readily available, relatively cheap, and non-toxic,
- (iii) it should be relatively easy to monitor reaction progress by:
 - (a) weight changes,
 - (b) infra-red spectroscopy,
 - (c) chlorine elemental analysis.

Route (C).

This consists of a mild Friedel-Crafts acylation⁸³ of polystyrene with ethyl oxalyl chloride (25) followed by saponification of the resulting α -keto ester (26) and then gentle acidification to yield polystyrene containing⁸⁴ carboxylic acid groups. Argyropoulos applied this method to monodisperse polystyrene with success:

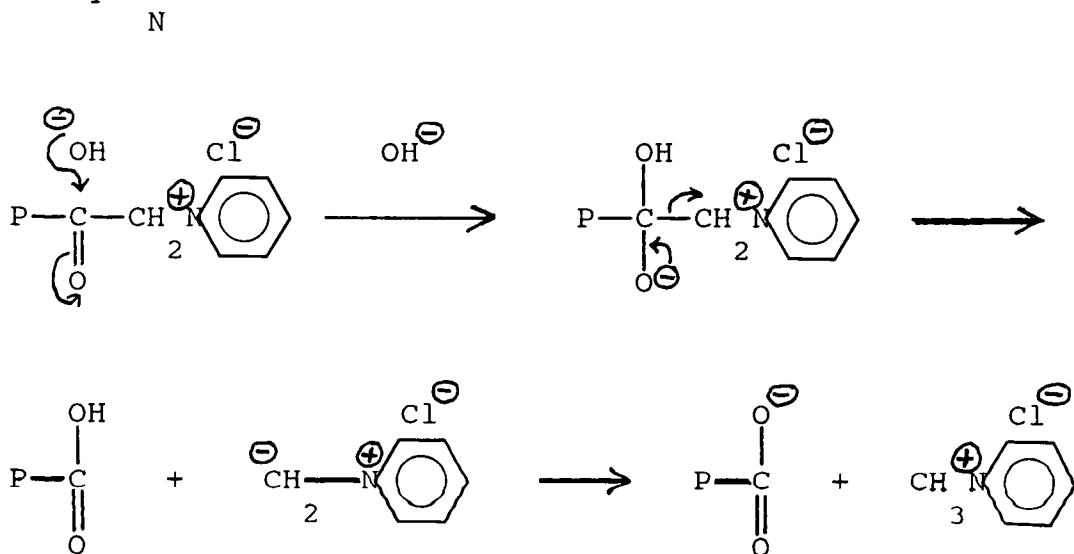


In this case there is no chlorine for microanalysis monitoring but instead two useful infra - red signatures are present. The two carbonyl groups give rise to two distinct sharp absorption bands at 1682 and 1735 cm^{-1} respectively, the latter arising from the α -keto carbonyl.

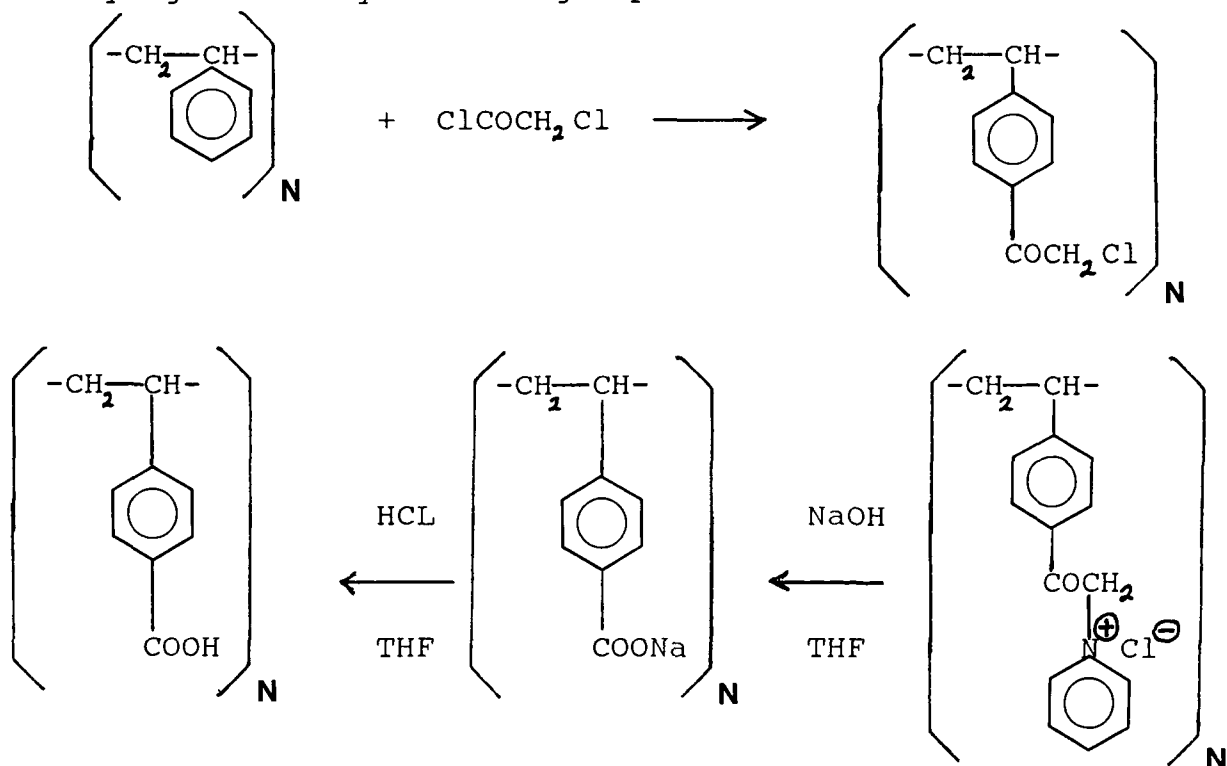
Route (D).

Treatment of crosslinked polystyrene, suspended in dichloromethane or nitrobenzene, with chloroacetyl chloride^{85,86} and anhydrous aluminium trichloride gave a phenacyl resin which was ca. 65 % substituted. Suspension of this resin in refluxing pyridine afforded the corresponding phenacyl pyridinium chloride derivative in high yield. The substituted methylene group was cleaved with aqueous sodium hydroxide-tetrahydrofuran.

The cleavage products^{87,88} are the corresponding polymeric carboxylate and methylpyridinium chloride. The cleavage of phenylpyridinium halides is entirely analogous to other well known types of cleavage of carbonyl compounds by alkalis. In particular the remarkable ease with which the chain fission occurs bespeaks a close relationship between this cleavage and that involved in the haloform⁸⁹ reaction (two alpha hydrogens). The mechanism is probably S₂.

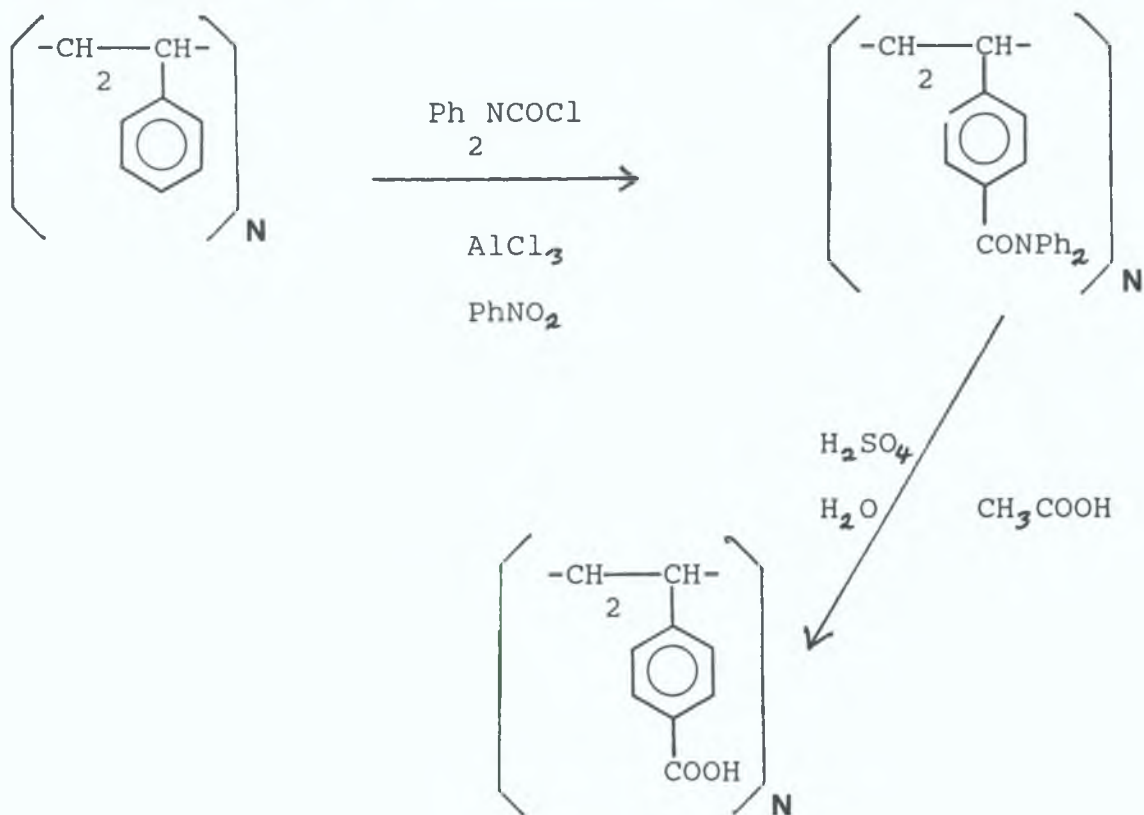


Finally treatment of the polymeric carboxylate with dilute aqueous hydrochloric acid and tetrahydrofuran yielded a poly-p-vinylbenzoic acid with ca. 60 % of the phenyl rings carrying a carboxylic acid group:



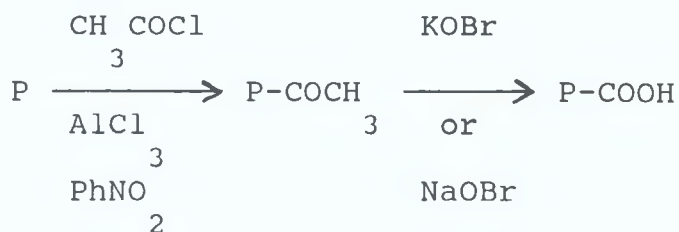
Route (E).

Treatment of crosslinked polystyrene with diphenylcarbamoyl chloride^{48,90} in nitrobenzene yielded the carboxamido polymer which on hydrolysis with a mixture of acetic acid, sulphuric acid and water yielded the carboxylated resin:



Route (F).

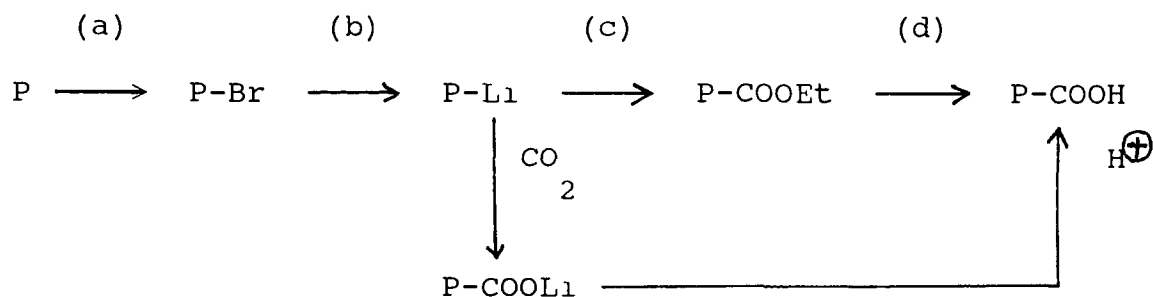
Acylation with acetyl chloride⁹⁰ is similar to that with chloroacetyl chloride above. The methyl group is not such a good leaving group but can be oxidized with potassium hypobromite:



Experimentally, introduction of carboxylate by this route⁴⁸ has led to low levels of substitution, for example 0.74 mmol/g versus a calculated value of the order of 7.6 mmol/g for 90 % substitution for a 0.5 % DVB resin. This figure would be expected to be lower for a 4 % DVB resin. Another disadvantage is the fact that large quantities of bromine are required in the oxidation step.

Route (G).

When polystyrene was brominated and then reacted with n-butyllithium the product was p-styryl-lithium. Reaction of poly-p-styryl-lithium with ethyl chlorocarbonate followed by basic hydrolysis and acidification afforded a carboxylated resin.⁸⁵ Carbon dioxide followed by acidification^{91,92} was also used in place of chlorocarbonate. However this lithiation route gave only low loadings of the desired carboxylate groupings.



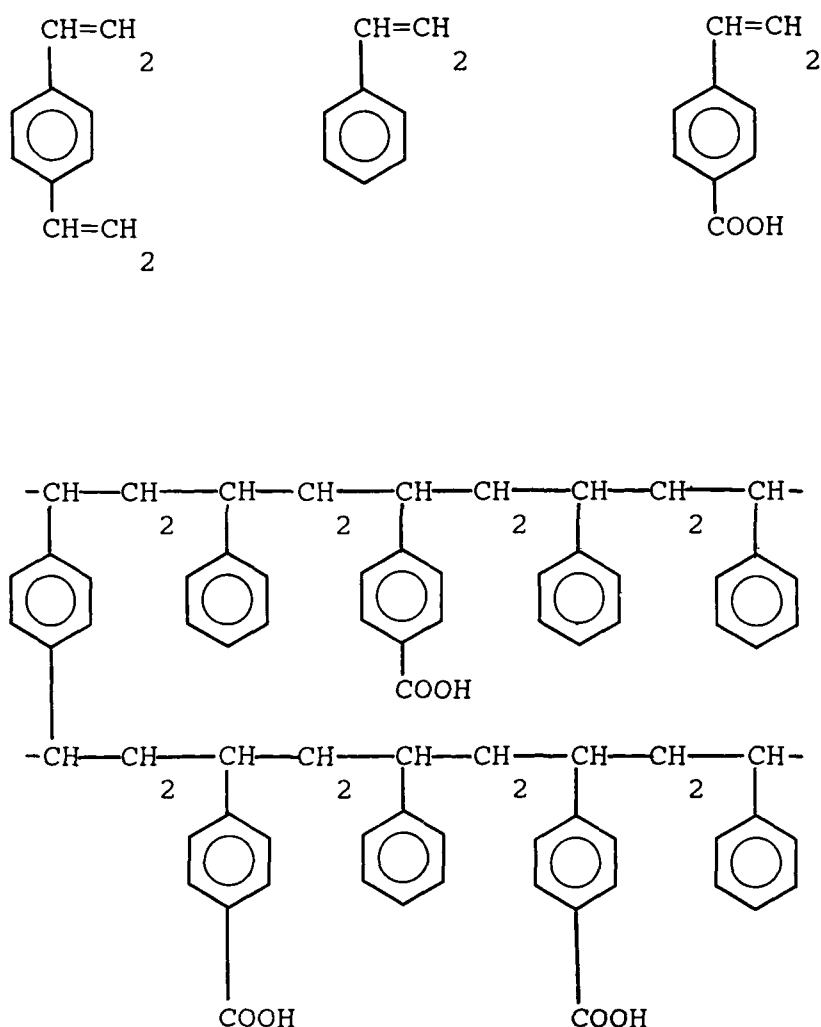
(a) $\frac{Br}{2} / \frac{CCl_4}{4} / \frac{Ti(OAc)_3}{3}$
 (c) EtOCOC₂H₅.

(b) BuLi/PhMe

(d) (1) KOH/MeOH, (11) H

Route (H).

It has been found that carboxylated ⁴⁸ polystyrene resin ⁹³ can be prepared by co-polymerisation of the monomers styrene, divinylbenzene and p-vinylbenzoic acid (or methyl p-vinyl-benzoate followed by hydrolysis):



This process is suited to industrial scale production but considerable skill and experience is required to produce resin beads of a constant bead and pore size distribution from batch to batch.

Chapter 2

CARBOXYLATED RESIN PREPARATION

RESULTS AND DISCUSSION SECTION.

This discussion is divided into three main parts. In the first part the criteria for a useful precursor resin and how it might be used are explained. The second part deals with the application of commercially-obtained Merrifield resins. The third part examines three alternative routes to a carboxylated resin under the headings:

- (a) preparation via 2-chlorobenzoylation and subsequent cleavage, and discussion of microanalysis results,
- (b) preparation via ethyl oxalyl chloride,
- (c) preparation via chloroacetyl chloride,
- (d) calculation of the percentage substitution and cleavage.

Only route (c) produced the desired high levels of functionalisation with carboxylate groups.

SECTION 1: CRITERIA FOR A USEFUL RESIN.

The intention was to explore the development of a peracid resin which might be useful for the N-oxidation of 2-chloropyridine, preferably on an industrial scale. Requirements for such a resin would include:

- (a) availability of a suitable precursor resin at

reasonable cost, in large quantities and in suitable physical form, (b) safety in handling, (c) stability under the given reaction conditions, (d) lack of undesirable side reactions. In addition it must be porous in both organic and aqueous phases so reactants have access to the active sites both before and after modification.

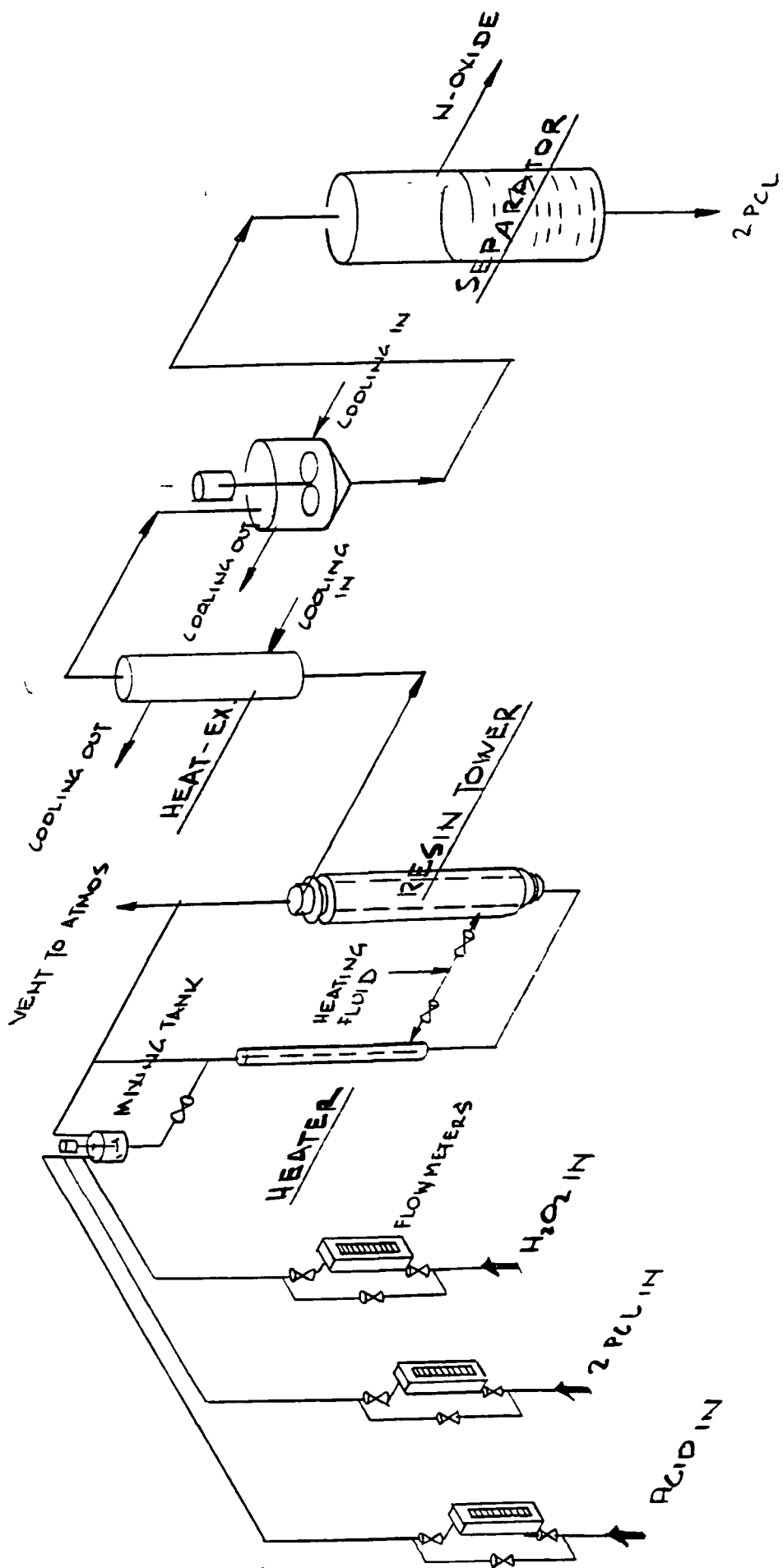
Approximately twenty companies worldwide were contacted and asked if they could supply a porous polystyrene-divinylbenzene crosslinked resin functionalized with carboxylic acid groups i.e. aromatic weak acidic cation exchangers. No company could supply such a resin. Only aliphatic weak acidic cation exchangers such as IRC-50 (methacrylic acid-DVB) and IRC-72 (acrylic acid-DVB) from Rohm & Haas and Dowex MWC-1 (acrylic acid-DVB) from Dow Chemical Company were available. Peracid resin has been previously prepared from this type of aliphatic resin.⁹⁷ Takagi et al. for example have prepared an aliphatic peracid resin from XE-89 (methacrylic acid-DVB, ion exchange capacity 11.8 meq/g dry) of oxidation capacity 5.88 meq/g dry resin.^{98,75} However two reports indicate that these aliphatic peracid resins explode very readily on impact. This fact renders them useless in an industrial environment. On the other hand aromatic peracid resins⁹⁸ could not be made to explode on impact,⁷⁵ and were found to be quite stable.

Henceforth the search focussed on finding a suitably porous polystyrene resin or another material, and methods

for functionalizing it with percarboxylic acid groups. In all the literature examples^{75,76,85,97-100} the carboxyl function was first introduced and subsequently converted to the peracid using methanesulphonic acid and hydrogen peroxide. The resin was then filtered off, purified and dried before use. This would not be very practical on an industrial scale requiring a batch process.

However it might be possible to develop an "in situ" process, in which the resin is placed in a stirred reactor or a packed column and a mixture of 2-chloropyridine, hydrogen peroxide, methanesulphonic acid, or even sulphuric acid added or passed through. The peracid would be generated "in situ" and then be used to form the N-oxide. A packed system might be expected to be more efficient as product formed would be flushed out of the resin by fresh incoming reactants. The product would not then obstruct active sites on the resin and would also be subjected to high temperatures and low pHs for a shorter time as it could be cooled and neutralized as it flowed away from the resin. Fig.1 (see page 37) schematically illustrates such a system.³¹ It would in principle be suitable for computer-controlled continuous automatic operation, and more than one resin tower could be used in series or in parallel.

The work reported in this thesis was carried out in a batch-type stirred reactor because it was simple to investigate and was designed to test the feasibility of the concept of using resins in this process.



There is very little mention in the literature of⁹⁹ N-oxidation with a resin, though Hirao et. al. have reported quantitative conversion of nicotinic acid to its N-oxide.

A number of potentially suitable polystyrene-divinylbenzene crosslinked resins were supplied by Rohm and Haas for experimentation. Their physical properties are summarised in Table 2, this data being compiled from product data sheets supplied by Rohm and Haas.

Resin Type	Surface Area	Particle Size	Av.Pore Diameter	%DVB
XE-305	50-60m ² /g	0.35-0.45mm	140 nm	4%
XAD-2	300m ² /g	0.4mm	9 nm	> 20%
XAD-4	800m ² /g	0.35-0.45mm	4-6 nm	> 20%
XAD-1180	650m ² /g	0.2-1.0mm	-----	> 20%

Table 2.

These are macroreticular resins. A single bead consists of an agglomeration of a large number of very small microspheres. The porous structure is of an open cell variety so that fluid can readily penetrate the pores. The resins have a continuous gel phase and a continuous pore phase (Fig 2).

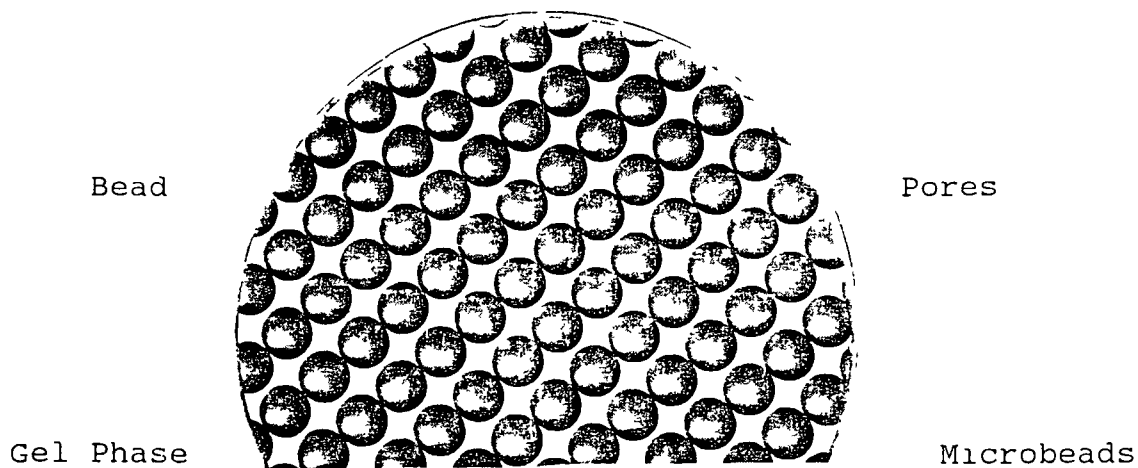


Fig 2.

Macroreticular resins offer a number of advantages over conventional gel-type resins. The large discrete pores mean that high molecular weight molecules can be more completely eluted from the resin on regeneration than would be the case with other materials. When used in ion-exchange applications, the open structure of the macroreticular resin permits the use of tough copolymers which would be too dense to effectively act as ion-exchange resins if they were used in a strictly gel type resin. Although of somewhat lower capacity than gel-type resins, this is often offset by longer operating life of the macroreticular resins or the fact that they will effect removals not possible by gel-type resins.

XE-305 resin was chosen for these experiments because of its large pore size and also because the percentage DVB was low at 4%. The percentage terminal ethyl groups was also known to be 4% from the manufacturer. A relatively low DVB

content leaves more phenyl groups exposed for substitution and may favour a higher -COOH loading. DVB crosslinked polystyrene was preferred to non-crosslinked resin because it was insoluble in 2-chloropyridine, could be recovered by simple filtration and was available as well defined macroreticular beads.

SECTION 2: MODIFICATION OF MERRIFIELD RESINS.

Route A (see experimental section).

Because of the low levels of functionalisation (1.25 mmole Cl/g, Koch-Light; 1.0 mmole Cl/g Aldrich) of the two Merrifield resins investigated, the weight changes in going from one step to the next in Route A were only minimal. Therefore accurate monitoring of the percentage modification by weight change was not possible.

Infrared spectra used to monitor changes in the resins were of poor quality but nevertheless definite changes were noted on going from one step to the next. Therefore i.r. was only used as a guide to follow changes in the 1700cm^{-1} region and hence functional group changes. Unless otherwise stated all ir spectra were run in KBr discs on a Perkin-Elmer 197 Infrared Spectrometer. Microanalysis was not carried out on these resins.

Four batches of carboxylated/percarboxylated resin were prepared from Merrifield resins. The chloromethylated Merrifield resin was heated with sodium bicarbonate in dimethylsulphoxide to effect conversion of the chloromethyl substituents to formyl groups. The formylated resin was then oxidized using hydrogen peroxide (70%) in the presence of methanesulphonic acid and acetic acid. Details are included in the experimental section. The appearance of a band at 1700cm^{-1} on formylation and the emergence of two bands at 1690cm^{-1} and 1730cm^{-1} respectively on

oxidation suggested that the desired functional group changes had been achieved. Supported by the infrared evidence it was assumed, based on the work of Greig et al.⁷⁵ and Harrison et al.⁷⁶, that quantitative group interconversion was achieved in the synthetic steps from Merrifield resin to carboxylated product. The resins prepared were subsequently investigated for the N-oxidations of 2-chloropyridine (Chapter 3).

SECTION 3: THE PREPARATION OF HIGHLY CARBOXYLATED RESINS.

(a) CARBOXYLATION OF POLYSTYRENE RESIN VIA

2-CHLOROBENZOYLATION: Route B (see exp. section).

2-Chlorobenzoylation of XE-305 resin (4% DVB crosslinking) was carried out under more forcing conditions than described⁷⁶ for Biobeads SX 2 (2% DVB crosslinking). The unit average molar ratios of resin : 2-chlorobenzoyl chloride : aluminium chloride were altered from (1:1.2:2) to (1:2:4), some additional solvent (nitrobenzene) was used, and reaction times were extended from 24 to 42 hours. In calculating the values for the resin the "molecular weight" was taken to be the unit average formula weight [see section(d)]].

The apparently high level of 2-chlorobenzoylation achieved (see experimental section chapter 4 pages (4 & 5), 105% substitution in one reaction and 109% substitution in another) can almost certainly be accounted for by reagents and solvent having been retained within the resin matrix. The product was difficult to dry and tended to increase in weight when exposed to the atmosphere for a few minutes.

The resin showed a band in the i.r. at 1660cm⁻¹
(lit: 76,79⁻¹ 1670cm⁻¹). The higher than expected level of chlorine found (Found: 16.61%; expected for 100% chlorobenzoylation: 13.98%) was supported by the greater than expected weight increase. Entrapped chlorine

containing residues, particularly if in the form of aluminium trichloride, would also have depressed the observed value for carbon (Found: 68.45%; calculated: 75.01%) as was found here.

Cleavage.

The 2-chlorobenzoylated resin was treated⁷⁶ with potassium t-butoxide/water in dimethoxyethane/dimethyl sulphoxide under reflux. In the first trial reaction quantitative cleavage appeared to have been achieved. However the polymer beads disintegrated during the lengthy process. The i.r. spectrum was of very poor quality though a broad band centred around 1680 cm^{-1} was observed. Weight loss suggested that 99% cleavage had been achieved whereas microanalysis indicated reagent entrapment and/or partial retention of chlorobenzoyl groups as the following results show: found C 68.67%, H 5.34%, Cl 1.93%, and S 0.99% versus calculated values: C 74.30%, H 5.62%, Cl 0.00%, and S 0.00%.

On repeating the cleavage with a further portion of 2-chloro- benzoylated resin it was found that the beads had not disintegrated to any great extent after 62 hours of cleavage at 70-73 $^{\circ}\text{C}$. However under these conditions they tended to stick together and little cleavage had occurred as a small weight gain was recorded.

Further attempts to clearly cleave the 2-chlorobenzoylated

resins were unsuccessful. A wide variety of reaction conditions was investigated, including different solvent systems (dimethoxyethane, dimethylsulphoxide, pyridine and 1,4-dioxan). None of these variants resulted in reproducible cleavage of the 2-chlorobenzoylated resins and this route to carboxylated polystyrenes was abandoned.

Resins With Lower Loadings.

It was noticed that the substituted resins, while bulkier, tended to swell much less than the XE-305 resin in a given solvent. Also the greater than expected weight increase recorded on substitution due to retained reagents and solvent suggested that it might be worth investigating less heavily substituted resins. Therefore two resins with lower levels of substitution (77% and 56% by weight increase) were synthesized and the cleavage procedure carried out on them. The solvent used for these 2-chlorobenzoylations was dichloromethane as it appeared to be better at swelling the XE-305 resin than nitrobenzene.

The two resins were then treated with the cleavage reagent as detailed in the experimental section. The 77% substituted resin underwent 51% cleavage. The 56% substituted resin in contrast underwent 80% cleavage. The resin obtained however, with only 44% of the phenyl groups substituted, was much less heavily substituted than had been initially intended for use in subsequent N-oxidation experiments.

Attempted Cleavage Of A Disrupted Resin.

One sample of the highly 2-chlorobenzoylated resin was ground to a fine powder before cleavage to disrupt the bead structure and expose functionalised sites to the cleavage reagents. However only 30% cleavage appeared to have occurred. This route was lengthy and troublesome and did not appear susceptible to ready production of the required carboxylated resins.

Reliability Of Calculations For 2-Chlorobenzoylation and Cleavage.

The figures of 105% and 109% substitution respectively for 2-chlorobenzoylation (as calculated by weight change) could be due to small quantities of reagents being trapped within the resin matrix. As a cross check elemental analyses were carried out. Harrison et al.⁷⁶ had found excellent correlation between % Cl present and weight change (g/g).

Some microanalytical results are given in Table 3 below. The measured chlorine content (16.61%) can best be understood in terms of the presence of residual chlorine-containing species (reagents, solvent) trapped in the resins.

Evidence has been found in the literature that aluminium chloride can be trapped in the type of resin used in these experiments. Indeed such polymer-bound aluminium trichloride reagents have found application in synthetic chemistry.^{94,95} Blossey et al.⁹⁵ urged caution in the use of polymer-bound aluminium chloride as it was very difficult to remove completely and reported that it could be detected by the presence of a band at 1650cm^{-1} . Greig et al.⁹⁶ and Harrison et al.⁷⁶ reported a band at 1670cm^{-1} for their 2-chlorobenzoylated resins. In the present work a broad band at 1660cm^{-1} was observed, perhaps an overlapping of the above two bands. In the literature reports resins containing <2% DVB were used. It seems possible that the higher DVB content of the resins

used in the present work may have contributed to the greater entrapment of reagents and solvent. It had also been previously noted in the literature that when DMSO was used with polystyrene resins, they were subsequently found to contain 1-3% sulphur.^{75,76}

Analysis	XE-305	Resin A	Resin B	Resin C
% C Calc.	92.24%	75.01%	74.30%	74.72%
% C Found	91.66%	68.45%	68.67%	71.50%
% H Calc.	7.76%	4.71%	5.62%	5.08%
% H Found	8.15%	4.65%	5.34%	4.99%
% Cl Calc.	0.00%	13.98%	0.00%	8.30%
% Cl Found	0.88%	16.61%	1.93%	11.19%
% S Calc.	0.00%	0.00%	0.00%	0.00%
% S Found	0.00%	0.20%	0.99%	0.04%
% O Calc.	0.00%	6.30%	20.08%	11.90%
% O by Diff.	0.18%	10.09%	23.07%	11.92%

Table 3.

Resin A = 2-Chlorobenzoylated (105%) by weight gain.

Resin B = Fully cleaved and degraded resin from Resin 1.

Resin C = Partially cleaved resin from Resin 1 (52%) by weight loss.

(b) ACYLATION OF XE-305 WITH ETHYL OXALYL CHLORIDE.

Route C (see experimental section).

Argyropoulos^{83,84} developed a method for randomly carboxylating monodisperse polystyrene to various levels. It consisted of a mild Friedel-Crafts acylation of polystyrene with ethyl oxalyl chloride followed by saponification of the resulting α -keto ester - Route C. The resin used by Argyropoulos did not contain any DVB crosslinking but nevertheless it was considered worthwhile to attempt this route with the XE-305 resin. The conditions and results for the monodisperse polystyrene⁸³ are given in Table 4.

Solvent	R:Acyl Chloride:AlCl ₃	Rxn. Time	Temp	% Sub.
CS ₂	1 : 1.17 : 1.29	24 hrs.	R.T.	39-41%
C ₆ H ₅ NO ₂	1 : 0.33 : 0.40	1 hr.	40 °C	14-15%

Table 4.

Argyropoulos found that nitrobenzene gave cleaner products than carbon disulphide, possibly because of the formation of thiocarboxylic acids of the structure R-CS₂H in the latter solvent. Two distinct sharp absorption bands (C=O Str.) were found at 1682cm⁻¹ and 1735cm⁻¹ respectively, the latter was due to the α -keto group. The saponified resin exhibited⁸³ broad bands, one centred at 2920cm⁻¹, the other at 1700cm⁻¹ (thin film on NaCl plate).

For 100% substitution of XE-305 a weight gain of 0.8668 g/g would be expected. It was anticipated that the weight gain and i.r. spectra would have allowed easy monitoring of the substitution reaction.

Attempted acylations gave poor results. No weight increase was observed when dichloromethane was used as solvent suggesting lack of reaction. Changing to nitrobenzene at 40 °C yielded a figure of 11% substitution.

In another reaction in which resin and reagent concentrations were reduced in anticipation that more dilute solutions would penetrate the resin more effectively, and in which the reaction temperature was raised to 80 °C, and the reaction time extended, an increased level of substitution was noted. However the apparent 20% substitution achieved was much lower than desired.

The i.r. spectrum of the 20% substituted resin contained the expected carbonyl bands at 1680cm^{-1} and 1740cm^{-1} . Microanalysis results supported the level of substitution estimated by weight increase if some allowance was made for entrapped reagents. However the level of chlorine found (3.20 %) clearly indicated that reagent entrapment was also occurring during preparation by the ethyl oxalyl chloride route. Further work with this route was discontinued.

(c) ACYLATION USING CHLOROACETYL CHLORIDE.

Route D (see experimental section).

Camps et al.⁸⁵ and Blanch et al.⁸⁶ achieved a carboxyl loading of 65% by this route from polystyrene but did not provide details of the experimental conditions used. Trial conditions, involving molar ratios 1 : 1.1 : 1.31 for resin : acyl chloride : aluminium trichloride were taken as the starting point in the present work. In calculating the values for the resin the "molecular weight" was taken to be the unit average formula weight [see section(d)]].

In a typical experiment XE-305 resin was reacted with chloroacetyl chloride and aluminium chloride in nitrobenzene for 23 hours at 50 C. The product was isolated and purified and found to be 94% substituted, as estimated by weight increase. The chloroacetylated resin was heated under reflux in pyridine for 8-24 hours, recovered, washed and dried to give a free flowing black resin. The pyridinium phenacyl product was immediately cleaved with potassium hydroxide in aqueous tetrahydrofuran. The product was filtered off, washed and treated with hydrochloric acid in aqueous tetrahydrofuran. The resulting resin was recovered by filtration, washed, purified and dried. On a weight loss basis 94% cleavage of the chloroacetyl substituted resin appeared to have been achieved. This (resin 1) corresponded to 88% substitution (i.e. 94%*94%) by carbonyl of the XE-305 resin. Changes in the functionalisation of the resins at the end of each step were monitored by infra red spectroscopy.

This route appeared to be relatively straightforward and efficient and was used to synthesize a number of additional batches of functionalized resin with loadings ranging from 80% to 50% chloroacylated. These resins finally gave carboxylated resins with loadings in the range 63%-43% (see experimental section). In total, six batches of carboxylated resin were prepared by the chloroacylation route. These resins were then used to study the "in-situ" N-oxidation of 2-chloropyridine.

Disappointing results were obtained where highly loaded resins were used initially in the N-oxidations (see Chapter 3). Perhaps too high a loading on the resin had a detrimental effect on N-oxidation and may be a lower loading might have been beneficial. It was with this in mind that resins with lower loadings were prepared by lowering the ratio of chloroacetyl chloride in nitrobenzene. The levels of chloroacylation achieved were 80%, 60%, and 50%. During the subsequent synthetic steps involving formation of the phenacyl pyridinium derivative and its cleavage, 100% cleavage was not achieved as measured by weight loss. This indicated that some functional groups other than carboxylate remained or that reagents were entrapped in the resin.

It had been noticed that dichloromethane caused the resin to swell much more than nitrobenzene. Hence the use of 1,2-dichloroethane as a chlorinated solvent with a higher boiling point was explored for the acylation. The level of

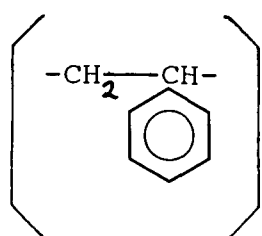
substitution achieved was only 51%. In a second such experiment more forcing conditions were used: temperature increased by 20 °C, reaction time extended by 14 hours, and the molar ratio of acyl chloride increased by 13%, yet the level of substitution attained was slightly lower at 47%. These significantly lower levels of substitution indicated that 1,2-dichloroethane was not a suitable solvent for this acylation.

When working with these resins it was noted that a small proportion of white beads carried through all the synthetic steps without apparent change. In any event the chloroacyl resin appeared the most uniform. The phenacyl pyridinium resin appeared to contain a disproportionately large number of light coloured beads which appeared not to have reacted at all. Some sample discrimination may have occurred and could account at least in part for some of the deviations from calculated values of the levels of substitution achieved.

In summary, a number of resins were prepared with different loadings. Reagent entrapment seemed to be a problem in their preparation as was reliability of functional group conversion. The best test of the activity of the functionalised resins was to use them in some N-oxidations and to determine how effective they were. The next chapter discusses these results.

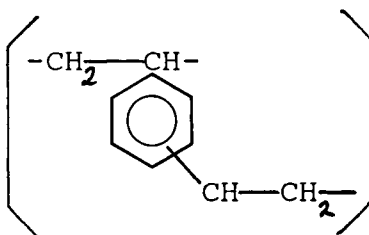
(d) CALCULATION OF THE PERCENTAGE SUBSTITUTION OF
POLYSTYRENE RESIN AND OF THE PERCENTAGE CLEAVAGE OF
FUNCTIONAL GROUPS.

Throughout the Experimental and Results and Discussion Sections, differentiation is made between unsubstituted pendant groups which are subsequently substituted and groups already substituted within the resin, and which form an integral part of the structure of the resin. The former refer to the structural unit (27), while the latter refer to the structural units (28) and (29). "TOTAL AROMATIC GROUPS" is the collective designation for all of these.



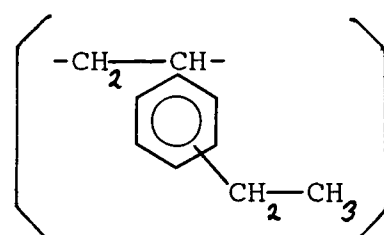
(27)

104



(28)

130



(29)

132

The formula weights of units (27), (26) and (27) are 104, 130 and 132 respectively. For the XE-305 resin the contributions of units (28) and (29) are 4% each (data supplied by Rohm & Haas). Therefore unit (27) constitutes 92 % of the polymer. From this information a "UNIT AVERAGE FORMULA WEIGHT, M" can be calculated for this polymer as:

$$M = (0.92 \times 104) + (0.04 \times 130) + (0.04 \times 132) \\ = 106.16$$

The molecular weight of the phenyl group is 77 so therefore the phenyl groups can be expressed as a percentage of M :

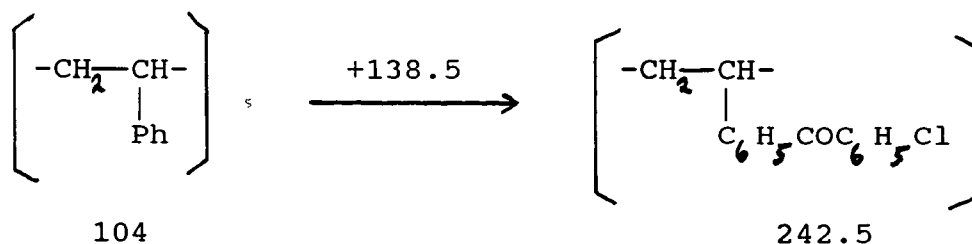
$$\% \text{ Phenyl groups} = (77 \times 100 \times 0.92) / (106.16) = 66.73 \% \text{ w/w.}$$

The factor 0.92 is to account for the 92% abundance of phenyl groups in this resin. This may then be expressed as:

$$\text{mmole phenyl/g XE-305} = (0.6673 \times 1000) / (77) = 8.6662$$

This figure can be used to calculate the percentage of phenyl groups substituted if the reasonable assumption is made that only unsubstituted phenyl groups (27) can be acylated in the Friedel Crafts reactions carried out. ^{96,104-107} For the purpose of calculating levels of substitution only monosubstitution of pendant phenyl groups was assumed.

For 2-chlorobenzoylation of an unsubstituted phenyl unit:



there is a mass increase of 138.5 a.m.u. on substitution. For reaction of 100% of the free phenyl groups in this resin:

$$\text{Weight gain per gram} = (138.5 \times F \times 8.6662) / 1000 = 1.2002 \times F$$

where F = the fraction of phenyl groups substituted.

Thus the weight gain per gram (g/g) can in principle be used to determine F in this reaction.

In a similar manner the % chlorine present by weight may also be used to provide an estimate of F, the fraction of phenyl groups substituted:

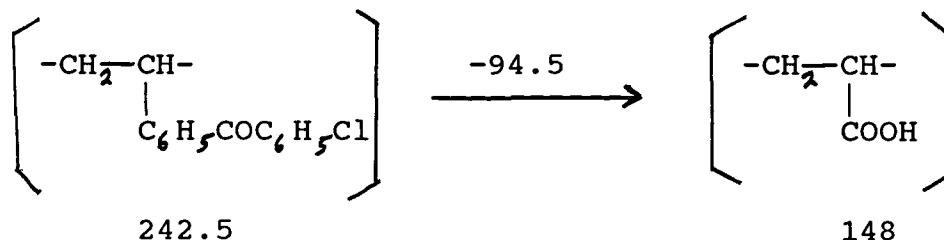
$$M = [242.5 \cdot 0.92 \cdot F] + [104 \cdot 0.92 \cdot (1-F)] + [130 \cdot 0.04] + [132 \cdot 0.04]$$

For 100 % substitution, $M = 233.58$ and:

$$\% \text{ Cl present by weight} = (35.5 \cdot 0.92 \cdot F \cdot 100) / M$$

For 100% substitution % Cl = 13.98 %

Analogous calculations can be performed for the cleavage step:



and for the other acylation reactions discussed.

Previous workers had found⁷⁶ excellent correlation between weight change g/g and % Cl. In the present work whilst some correlation was also found, factors such as residual reagents and solvent tended to introduce some ambiguity into the results. This may have been due to the greater degree of DVB cross-linking in the resins used.

Chapter 3

N-OXIDATION OF 2-CHLOROPYRIDINE.

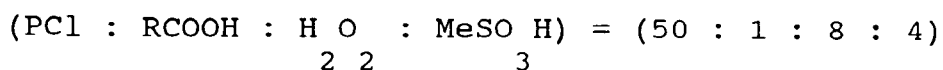
RESULTS AND DISCUSSION.

This chapter falls into four sections:

- (a) use of Merrifield derived resins with low loading,
- (b) use of highly loaded resins derived via chloroacylation,
- (c) use of a highly loaded aliphatic weak acid and an aromatic sulphonic acid resin,
- (d) studies on the decomposition of 2-chloropyridine N-oxide.

(a) N-OXIDATIONS WITH CARBOXYLATED RESIN DERIVED FROM MERRIFIELD RESIN.

The objective of these investigations was to attempt to develop a potential industrial process for the conversion of 2-chloropyridine (PCl) to its N-oxide in the presence of the resin catalyst, to optimise the reaction conditions, and to recover the catalyst for recycle. In order to compete with existing processes a yield greater than 60% would have to be achieved. No information was available on what reaction conditions would be most favourable for the N-oxidation using resin catalyst. After some preliminary experimentation to determine a reasonable reaction rate as determined by the rate of decrease of hydrogen peroxide concentration, the molar or unit average formula weight ratios (See Section (d) Chapter 2):



were chosen, where RCOOH = resin bound $-\text{COOH}$ and methane sulphonic acid provided acidity. The moles of $-\text{COOH}$ on the resin were calculated assuming 100% functional group conversion during preparation from the starting Merrifield resins. The optimum temperature for these reactions was determined to have been 75 °C.

If the reaction mixture containing the 2-chloropyridine could be recycled through a resin tower the effective ratio of $\text{PCl} : \text{R-COOH}$ would be increased many times.

THE OXIDATIONS.

Four small scale and three larger scale oxidations were run. Carboxylated resins derived from two sources were used Koch-Light and Aldrich Chemical Company (see Chapter 2). The small scale experiments were run in two pairs, each pair using resin from the two suppliers to test whether there was a significant difference between the two sources. Reaction time for the experiments using the Aldrich derived resin was extended by two hours to compensate for the lower loading. The concentrations of N-oxide were measured in extracts and washings by HPLC and were used to calculate the percentage yield of product. In the first pair of experiments hydrogen peroxide was the limiting reagent. The yields were similar at 5%.

Effect Of Increased Hydrogen Peroxide.

In another pair of experiments the quantity of hydrogen peroxide was quadrupled and the reaction time extended a

further two hours for both experiments. The yields were 14% and 13%. The results indicated that increasing the hydrogen peroxide four-fold improved the yield by a factor of 2.5. This series also indicated that both resin systems had similar efficacies.

Effect Of Increased Resin And Hydrogen Peroxide On Yield After Scale-Up.

Further experiments were scaled up in larger reaction flasks (see Experimental Section). After adjusting the scaling to prevent the resin absorbing all the PCl the ratios $\text{PCl} : \text{RCOOH} : \text{H}_2\text{O}_2 : \text{MeSO}_3\text{H} = 31 : 1 : 64 : 4$ were arrived at. Effectively the $\text{PCl} : \text{resin}$ ratio was decreased from (50 : 1) to (32 : 1) ie there was more resin per unit of PCl . Here the 2-chloropyridine had become the limiting reagent (ratio of $\text{PCl} : \text{H}_2\text{O}_2 = 1 : 2$). The yield obtained from the first scaled-up experiment was 16%. Relative to the previous pair of experiments (ratio $\text{PCl} : \text{H}_2\text{O}_2 = 1 : 0.6$) a 3.2 fold increase in peroxide and a concurrent 1.6 fold increase in resin usage only resulted in a 1.2 fold increase in yield.

Effect Of Increased Methanesulphonic Acid (MSA).

Doubling the relative amount of MSA, while all other variables were kept constant resulted in a significant yield increase to 24%. For every mole of PCl (113.5g) used, 12g of MSA or 10.5% by weight was required and this would have high costs disadvantages on a plant scale. The quantity of resin used could not be increased as it would

have absorbed all the PCl and the reaction mixture would have essentially solidified. Alternative approaches might be to substitute a cheaper acid for MSA or to dramatically increase the loading of -COOH on the resin so that smaller quantities of resin might be more effective.

Effect Of Mixed Catalyzing Acids.

Rerunning the first larger scale experiment with MSA with an additional equimolar quantity of the cheaper inorganic phosphoric acid resulted in a yield of 16%. The phosphoric acid was therefore of no benefit.

Summary.

In summary it was demonstrated by this series of experiments that resins with a low functional group loading could not be expected to achieve the stated objective of better than 60% yield of product N-oxide and that further effort was best directed towards investigation of more highly loaded resins.

(b) N-OXIDATION OF 2-CHLOROPYRIDINE WITH CARBOXYLATED RESIN
PREPARED VIA 2-CHLOROACYLATION.

Resins prepared via the 2-chloroacylation route (see Chap.2 page 51) are identified by the level of carboxylation achieved and are referred to by number, see table below.

RESIN No.	% 2-CHLOROACYLATION	% CLEAVAGE	CARBOXYLATION
1	94	94	88
2	51	100	51
3	60	78	47
4	50	84	42
RESIN M	MERRIFIELD DERIVED	**	10-11

Table 5.

These experiments were carried out on a scale of 1.15 moles of 2-chloropyridine and 1.5 - 2.5 moles hydrogen peroxide, generally at 75 °C. Methanesulphonic acid and sulphuric acid were studied. Product was extracted and analysed by HPLC in order to calculate yield.

THE N-OXIDATIONS.

USE OF A HIGHLY LOADED RESIN - RESIN 1.

Resin 1, 88% carboxylated was used in a series of experiments. Two of these were repeats to see if the potency of the resin decreased on usage. The yields were 27% and 23% respectively. This may suggest that the potency decreased

but more likely reflects the magnitude of the experimental error. The $\text{PCl} : \text{COOH}$ (resin bound) ratio was ~100% more favourable at 21 : 1 than for resin M at 40 : 1, yet only a modest increase (from 16% to 25%) was obtained with the more highly substituted resin.

Effect Of Increased Methanesulphonic Acid On Resin 1.

Increasing the methanesulphonic acid by 53% resulted in a yield of 24% i.e. no improvement. The only advantage of the highly loaded resin was that only about one third the amount of resin 1 was required to achieve a 24% yield when compared to resin M with lower loading. However longer reaction times had to be used for resin 1 (twenty two hours).

EFFECT OF REDUCED FUNCTIONAL GROUP LOADING OF THE RESIN.

RESIN 2.

Was it possible that hydrogen bonding within the resin beads was occurring and preventing ingress of N-oxidizing reagents and substrate? It seemed reasonable that this bonding might be more extensive throughout a highly loaded resin than in a less highly loaded resin. To test this hypothesis a series of experiments was carried out using 51% carboxylated resin 2. About the same weight of this resin was taken as was used in the experiments with resin 1. This effectively increased the $\text{PCl} : -\text{COOH}$ ratio by about 45% relative to that used for resin 1. Using the same quantity of methane sulphonic acid as was used with the

first resin 1 experiment a yield of 14% was obtained. This seemed to indicate that this resin was less effective than its more highly loaded counterpart where yields of 27% and 23% respectively were obtained.

Effect Of Increased Methanesulphonic Acid On Resin 2.

In a further experiment the quantity of catalysing acid was increased by 56%. The yield increased to 25%, was similar to that obtained with resin 1 and resin M, and indicated that there was no significant difference in the N-oxidising ability of the two resins. However resin 1 was insensitive to increased MSA while resin 2 and Resin M responded positively.

N-Oxidation With 88% & 51% Carboxylated Resin				
RESIN	% COOH	BEST YIELD %	REACTION TIME	EFFECT OF INCREASED MSA ON YIELD
Resin 1	88	25% mean	22 Hrs.	INSENSITIVE
Resin 2	51	24%	22 Hrs.	POSITIVE
Resin M	10-11	24%	11 Hrs.	POSITIVE

Table 6.

Noting the reaction times from the table it is seen that the less highly substituted resin gave the same yield in half the reaction time. However three times as much resin was required. This seemed to support the hypothesis that hydrogen bonding was reducing accessibility of reagents and

perhaps effective pore size of the more highly substituted resin under the prevailing experimental conditions.

Effect Of Changing The Catalysing Acid To Sulphuric Acid.

Under similar conditions to the MSA experiment, resin 2 with sulphuric acid at the same level, gave the same yield of 25% but with a reduction in reaction time of 3 hours to 19 hours. This indicated that for the more highly substituted resin, sulphuric acid was at least as good as MSA. This contrasted with the results obtained earlier when phosphoric acid was used with resin M.

Effect Of Reduced Temperature.

In an attempt to reduce possible decomposition reactions a number of experiments utilizing resin 2 were conducted at lower temperatures. Sulphuric acid was tested at 50-60 °C. Reaction time increased dramatically to 49 hours but the yield remained much the same at 24%.

Effect Of Phosphoric Acid At Reduced Temperature.

Under similar reaction conditions when phosphoric acid (85%) was substituted, reaction time increased even more dramatically to 74 hours while yield fell considerably to 16%.

Effect Of Increasing Resin Mass - RESIN 3.

Further experiments utilized resin 3 (47% carboxylated) which was initially 60% chloroacylated and subsequently 78% cleaved. This meant that 22% of the chloroacylated groups

introduced remained or possibly they occurred as some unidentified complex. When calculating the mmoles COOH/g loading on the resin, it was assumed that the residual groups were chloroacetyl. Effectively this meant that there were fewer COOH groups per gram of this resin than were on the 51% chloroacylated resin where 100% cleavage had been achieved (3.2044 mmole/g vs. 3.700 mmole/g). These residual groups may have affected the potency of the resin i.e. enhanced or diminished its activity. Three times the weight of resin used in the previous set of experiments was used here. The acid catalyst used in this set of experiments was sulphuric acid. A yield of 19% was obtained.

In a second experiment using this resin the weight of sulphuric acid used was increased by 29% and the temperature by 5 °C to 65 °C. Again 19% yield was achieved but reaction times were significantly less at 27 and 19 hours respectively vs 49 hours for resin 2. Either of two explanations would seem to account for these differences. The peroxide may have been decomposing at an enhanced rate or the product itself may have been decomposing during these rather long reaction times. The most obvious factor to consider here was the residual groups retained on the resin as these could be contributing to either or both decomposition processes.

Resins after use in all three sets of experiments were purified and dried. No significant changes in weight or in i.r. spectra were observed. After the first use in an

oxidation the colour of the resin became considerably lighter but thereafter remained unchanged. The fall-off in yield with increased resin mass might suggest that something pertaining to the resin had caused decomposition of either the N-oxide or the hydrogen peroxide and this needed to be looked at more closely. Because of the possible interference from the residual chloroacetyl groups no further experiments using this resin were run at elevated temperatures.

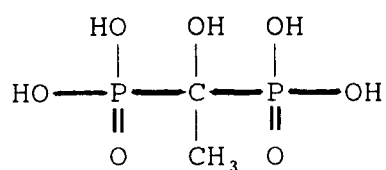
ATTEMPTS TO INCREASE YIELD.

Increasing The Ratio Of Resin - Resin 4.

Resin 4 was 42% carboxylated somewhat lower than resin 2 at 51%. Using 2.2 times as much resin 4 as resin 2 and reducing the reaction temperature 10°C to 65°C to minimise possible decomposition, the same yield of 25% was obtained.

Use Of A Peroxide Stabilizer.

So far the objective of >60% yield had not been achieved. One possibility was that much of the peroxide was decomposing rather than reacting to form the N-oxide. A commercial stabilizer for peroxides:- Dequest 2010,¹⁰¹ (1-hydroxyethylidene-1,1-diphosphoric acid) or HEDPA, was made available for some experimental work. It was supplied as a 60% active solution. A U.S. Patent¹⁰² claims it stabilizes peroxides at the 0.5 - 3.0% level. Its structure (30) is as shown.



(30)

HEDPA was used in some experiments to determine whether it improved the yields. Since lowering the reaction temperature in some earlier experiments had failed to increase yield by reducing possible product decomposition the next set of experiments were run at about 75 C. As a dramatic yield improvement of the order of 100-200% was required to achieve the objective of >60% yield, a wide range of reaction conditions was explored including changes in the reactant ratios and the use of HEDPA.

The best result achieved (33% yield, reaction time of 26 hours) involved increasing the weight of resin by 27%, and the hydrogen peroxide by 68%, as well as addition of HEDPA to the peroxide, which was then added slowly over a prolonged period. This yield however was well short of the objective. Two liquid phases were observed towards the end of the reaction when using increased amounts of hydrogen peroxide while only one liquid phase was present when less hydrogen peroxide was used.

Attempt To Reduce Phase Effects.

In attempts to minimise the phase separation problem, propan-1-ol was added to the reaction mixture. In addition

it was anticipated that the propanol would help the polar peroxide penetrate the organic resin more effectively. At the work-up stage two distinct layers were observed, so it had not solved the phase separation problem. The propanol did not enhance oxidation, the yield remaining essentially the same (30%).

Use Of HEDPA Alone In An Oxidation.

103

Another U.S. Patent claims that HEDPA can be converted to its peroxide derivative by reacting its alkali salt with hydrogen peroxide. Apart from stabilizing peroxide, HEDPA in its acidic form may form a peracid and oxidize PCl to its N-oxide. Using the same molar quantity of HEDPA as MSA used earlier and under similar conditions, but with no MSA or sulphuric acid present, a yield of 27% was obtained, only marginally lower than the best previous yield (33%). The reaction time was however substantially increased (43 hours). It therefore appeared beneficial to include HEDPA in the N-oxidations in the presence of MSA or sulphuric acid.

Effect Of Equal Weights Of HEDPA And Sulphuric Acid On Two Types Of Resin.

Resin 1, 88% Carboxylated.

In the last series of experiments the weight of resin used was about 25% that of the 2-chloropyridine. When scaled-up to an industrial scale it would require very large

quantities of resin and a large plant reactor to contain it, thereby increasing costs. The resin used had only 42% of its phenyl groups substituted by carboxylate. It therefore seemed reasonable to rerun an experiment using resin with a higher carboxylate loading, using less resin and an increased quantity of HEDPA. Resin 1, 88%, carboxylated was used with equal weights of HEDPA and sulphuric acid at 75 C. The weight of resin was only about 10% that of the PCl₅. The yield (33%) was similar to the best achieved by resin 4 using a small amount of HEDPA. Reaction time was 3 hours less.

Resin 4, 42% Carboxylated.

Using resin 4 but this time with equal weights of sulphuric acid and HEDPA and temperature a little higher at 83 C, again gave a yield of 32%. This was far short of the stated objective but a reduction in reaction time to 14 hours had taken place.

Summary.

All results so far had indicated that there was an upper limit to the yield achievable with the resins studied. The reactions were very inefficient with respect to hydrogen peroxide. The oxidations all had prolonged reaction times and required large quantities of strong acids to achieve relatively low yields of (30%-35%) compared to those targetted (>60%).

Investigation Of Mass Balance In Some Oxidations.

In order to investigate further what might have been happening during the oxidations, consumption and recovery of PCl was examined more closely. All extracts and washes were, analysed by HPLC for both N-oxide and PCl content. The results are presented below.

Resin	Mole% PCl as NOX	Mole% PCl as PCl	Mole% PCl Total	Mole% PCl Missing
1	33%	49%	82%	18%
4	32%	44%	76%	24%

Table 7 - showing % PCl recovered as N-oxide and PCl.

Mass balance indicated that 18% and 24% respectively of the initial PCl was unaccounted for at the end of the oxidations. A separate study (see section d later) confirmed that the N-oxide (NOX) product was unstable under conditions prevailing in the oxidations whereas 2-chloropyridine was stable.

For resin 4 the reaction time had decreased considerably but this was probably due to the higher temperature and increased quantity of resin causing increased decomposition. Fourteen hours was still a relatively long reaction time for a thermally labile product to have been subjected to elevated temperatures.

This would explain why experiments with greatly increased

quantities of resin only gave a modest increase in the amount of N-oxide recovered. It would also explain the very dark colour of many of the N-oxide filtrates on neutralization and the fact that many of these solutions had a faint smell of ammonia. However no additional peaks were observed in the HPLC chromatograms of these solutions only two peaks occurred corresponding to N-oxide and PCl. The failure to observe any other components may have been due to the high dilutions necessary, a lack of absorption at 254 nm, retention times longer than the chromatogram run time or, more likely, polymeric type byproducts being retained on the guard or analytical column. Difficulties were often encountered with some of the samples fouling the frits and the top few millimeters of the column with a brown material.

Another possibility was that N-oxide product poisoned the catalyst or occupied the active sites, preventing further conversion.

(c) N-OXIDATION USING IRC-50, A WEAKLY ACIDIC ALIPHATIC
RESIN.

Earlier comments about the instability of polymeric aliphatic percarboxylic acids and their tendency to explode, referred to the purified and dried peracid resin. In the "in-situ" type oxidations used here, the percarboxylated resin was never isolated. It was formed in transient quantities when it reacted to form N-oxide or subsequently decomposed during work up.

Rohm and Haas Company supplied a resin IRC-50, a methacrylic acid/divinylbenzene, macroreticular, weakly acidic cation resin having a high loading of carboxylate (10 mmol/g) when dry. This was a much higher loading than had been achieved with the polystyrene DVB resins, for example resin 1 (88% COOH, ~5.2 mmol/g). Two experiments using this resin were carried out. The first was run under the milder conditions of resin M with a lower level of MSA. The second utilised the more severe conditions of resin 4 with equal weights of sulphuric acid and HEDPA. Resin amount was increased by 25%, the quantity of hydrogen peroxide doubled, and the temperature was 5 °C higher than for the first. Yields were 13% and 33% with reaction times of 12 and 13 hours respectively. The corresponding mass balance data is listed in table 8 for the higher yield experiment.

Mole % PCl as N-oxide	Mole % PCl as 2-PCl	Mole % PCl Total	Mole % PCl Missing
33%	57%	90%	10%

Table 8.

The lower amount (10%) of PCl not accounted for in the experiment suggests that less N-oxide decomposition took place. A large quantity of resin was used in the experiment. However its higher carboxylate loading (PCl : COOH ratio 4:1 vs 13:1) failed to push the conversion above that of the aromatic resin 1.

N-OXIDATIONS WITH STRONGLY ACIDIC ION EXCHANGE RESIN IR-120.

The cation exchange resin IR-120 (Rohm and Haas, 4.4 meq /g -SO₃ Na dry) was also used. It contained 8% DVB by weight, so that over 80% of the total phenyl groups in the resin were substituted by sulphonic groups. DVB derived bridging groups do not generally sulphonate. If the -SO₃ H group had an ability similar to that of the -COOH group to catalyse the N-oxidation reaction, then because of the high loading it might be expected that a sulphonated resin would convert PCl to its N-oxide.

To test this hypothesis some of the salt form of IR-120 was acidified, purified and dried. IR-120 experiments were run

under conditions similar to those of the first resin M experiments. One was run without additional strong acid. In a second, phosphoric acid was used as it was expected to penetrate this ionic resin. In a third experiment the sodium form of the resin was used with no additional strong acid. The sodium form failed to oxidise the substrate. The hydrogen form gave a yield of only 3%, both with and without phosphoric acid. These yields were only about half those achieved with resin M despite a much higher loading of acid groupings of 80% vs 10-11%. No further work was carried out with these resins.

(d) RECOVERY AND DECOMPOSITION OF 2-CHLOROPYRIDINE-N-OXIDE.

In order to determine more exactly what was happening to 2-chloropyridine and its N-oxide in the oxidations, a number of experiments were run to determine their fate under different conditions. These experiments are summarized in Table 9 with relevant comments.

Exp. No.	Substance Recovered	Recovery %	Conditions
1	PCl	100.2%	Acidify/Neutralize/Extract/Assay
2	N-oxide	99.7%	Acidify/Neutralize/Extract/Assay
3	N-oxide	77.0%	N-oxide soln. heated to 80 C, 24 hrs with H ₂ SO ₄ . No resin present.
4	N-oxide	79.7%	As Exp.3 except unsubstituted resin XAD-2 present.
5	PCl	99.7%	PCl and N-oxide heated to 81 C for 22 hrs in presence of unsubstituted Resin XAD-2 and H ₂ SO ₄ .
	N-oxide	94.0%	

Table 9 - Control Experiments.

(i) Effect Of Acid On PCl and (ii) Its N-Oxide

In experiments 1 and 2 known quantities of PCl or N-oxide solution (N-oxide being initially determined by the TiCl₃ method) were placed in separating funnels and some water added, followed by concentrated sulphuric acid. The mixtures were shaken and allowed to stand and cool - two layers were obtained for experiment 1. Both mixtures were then neutralized with sodium hydroxide. The solution from

experiment 2 was diluted for analysis, while the mixture from experiment 1 was allowed to separate. The lower layer was removed and extracted a second time with 100 ml of water. The extracts were separately analysed and the PCl_3 layer removed and weighed, allowances were made for the water content. Analysis was by HPLC, and recovery of 2-chloropyridine and N-oxide was essentially quantitative. It had also been established separately that the HPLC and TiCl_3 methods¹⁰⁸ were in close agreement. This established that the workup after oxidation was not the cause of the yield loss.

(iii) Effect Of Heat & Acid On 2-Chloropyridine-N-Oxide.

In experiment 3 N-oxide solution was heated in the presence of sulphuric acid (20g) at 81 °C for 24 hours. No resin was used in this experiment. Only 77% recovery was obtained. The solution darkened considerably during heating. and teflon agitator became coated with a dark brown tar.

(iv) Effect Of Added Resin On N-Oxide Stability.

Experiment 4 was a repeat of experiment 3 except that unfunctionalized resin XAD-2 was also included to see if the resin surface had any effect. This resin had the same chemical composition as XE-305 except for increased crosslinking and a smaller pore size distribution. XAD-2 resin had a greater surface area (see Table 2 page 38) and if inherent surface activity was present it would have been expected to be amplified here. The results of experiments 3

and 4 indicate that the presence of resin had essentially no effect.

(v) Effect Of 2-Chloropyridine On N-Oxide Stability In The Presence Of Added Resin.

Experiment 5 was similar to experiment 4 except that a known quantity of PCl was also included. Recovery of PCl (99.7%) was excellent, with N-oxide (94%) marginally poorer, though significantly improved over that for the previous two experiments. The PCl appeared to have stabilized the N-oxide under these conditions. The sulphuric acid may have been neutralised by the PCl and therefore not be able to decompose the N-oxide. This contrasted with actual oxidations where decompositions of 18-24% occurred in the presence of peroxide and substituted resin. It was also a little less than that obtained with weakly acidic resin IRC-50 (10%). These results indicated that the substituted aromatic resin under oxidation conditions caused most decomposition.

This set of experiments unambiguously confirmed that it was N-oxide and not PCl which decomposed under conditions likely to be found in the oxidations. Having confirmed that substantial quantities of N-oxide decompose during the oxidations using resin in a stirred reactor, there was little hope of increasing the experimental yield for conversion of PCl to N-oxide above 30-35%.

It was noticed that some of the decomposition products, a portion of which were probably polymeric tars, tended to adhere to the resin. These decomposition products may have blocked access of substrate and oxidising reagent to active sites. Many recovered resins were dark coloured before solvent extraction, boiler solvent darkened as the resin colour lightened and tars were often later noted at the solvent/glass interface in the boiler.

REACTOR DESIGN AND CONCLUSIONS.

The challenge is to reduce decomposition of N-oxide once formed. One of the critical parameters may have been product residence time on the resin. If this could be significantly reduced by designing a reactor so that, as the N-oxide product formed, it was swept away from the resin and extracted from the 2-chloropyridine stream decomposition might be substantially reduced. The 2-chloropyridine could then be recycled. As it exists at present, a stirred reactor system using functionalized resin is not a practical option on an industrial scale.

Finally it may be concluded that aromatic macroreticular resins with 2-4% crosslinking and 50-90% of the available phenyl groups carboxylated may be used for N-oxidation of 2-chloropyridine in modest yields, in the presence of sulphuric acid, some HEDPA stabilizer and a molar excess of hydrogen peroxide.

Chapter 4

CARBOXYLATED RESIN PREPARATION.

EXPERIMENTAL SECTION.

Section 2. Modification of Merrifield Resin.

Section 3. (a) Preparation via Chlorobenzoylation,
 (b) Preparation via Ethyl Oxalyl Chloride,
 (c) Preparation via Chloroacetyl Chloride.

Infrared Spectra.

All ir spectra reported in this thesis were run in KBr discs on a Perkin-Elmer 197 Infrared spectrometer unless otherwise stated.

Section 2.

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MODIFICATION OF MERRIFIELD RESIN.

(a) Formylation. White chloromethylated resin (Koch-Light, 1.25 mmole Cl/g) was stirred in dimethyl sulphoxide (DMSO) with sodium bicarbonate for up to 24 hours at approximately 155 °C. On cooling, the resin was collected on a sintered glass filter and washed with DMSO, hot water, a 2/1 v/v mixture of dioxan and water, dioxan, and methanol, before being extracted overnight with dichloromethane in a Soxhlet extraction apparatus. Finally the pale yellow beads of the formyl resin were dried at 30-40 °C under vacuum for 6 hours; $\nu_{\text{max}} \quad 1700 \text{ cm}^{-1}$ (KBr).

The formylation reactions were carried out in a 250 cm³ round bottomed flask (RBF) in a liquid paraffin bath heated by a hot plate with magnetic stirring. The flask was fitted

with a water-cooled reflux condenser and thermometer attached to a Fimonitor which controlled the temperature to $\pm 2^{\circ}\text{C}$. Details for the different formylated resins prepared are given in Table 10. Aldrich resin (1.00 mmole Cl/g) was used for batches 2 to 4.

Formyl Resin	Merrifield Resin		DMSO cm ³	NaHCO ₃ g	Time hrs.	Temp. °C
	Cl mmole/g	Mass g				
1	1.25	5.00	75	5.00	24	155
2	1.00	20.00	170	20.00	24	155
3	1.00	20.15	150	14.88	15	156
4	1.00	20.15	150	15.44	18	152

Table 10.

(b) OXIDATION / PEROXIDATION OF FORMYL RESIN.

This step was based on the methods of Greig et al.⁷⁵ and Harrison et al.⁷⁶. It was carried out on the four batches of formyl resin prepared above. The formyl resin was stirred with a mixture of methanesulphonic acid and glacial acetic acid at 20°C for 10 minutes to permit initial swelling. Hydrogen peroxide (70%) was added dropwise to this mixture over 30 minutes at 20 to 25°C . The mixture was then stirred at temperatures up to 72°C for 5-6 hours. The experimental set-up was similar to that used for the formylation, a small dropping funnel being used to add the peroxide.

Because the resin had a tendency to float in the dense reagent mixture, methanol was added in the case of two of the resins in order to reduce viscosity. This was at least partially successful.

At the end of the reaction period after cooling, the peroxidized resin was filtered off and washed with water, a 50:50 mixture of water and methanol, methanol, and dichloromethane and extracted overnight with dichloromethane in a Soxhlet extractor. The product was then dried in a vacuum oven for 6 hours; ν 1690cm^{-1} and 1730cm^{-1} (broad and poorly resolved). Resins 3 and 4 were peroxidised at -70°C yielding products with a very broad band at $\sim 1700\text{cm}^{-1}$. In contrast the formylated resin had a single sharp band at 1700cm^{-1} . The precursor Merrifield resins had no bands present in the 1700cm^{-1} region.

Details for the different percarboxylic acid resins prepared from the resins are given in Table 11.

Per- acid Resin	R-CHO g	MeSO ₃ H g	CH ₃ COOH cm	70% H ₂ O g	MeOH cm	Time hr.	Temp. °C
1	5.00	20.73	50	3.10	----	5	20-25
2	16.12	14.23	50	12.44	40	5	20
3	29.77	14.23	50	12.44	40	6	69
4	20.24	14.00	100	20.00	----	6	72

Table 11.

Section 3: THE PREPARATION OF HIGHLY CARBOXYLATED RESINS.

(a) CARBOXYLATION OF POLYSTYRENE RESIN VIA

2-CHLOROBENZOYLATION ROUTE B (see discussion section).

Step 1: 2-Chlorobenzoylation.

Aluminium chloride (105.0g; 0.787 mol) was added to ice-cold nitrobenzene (120cm³) and the mixture was agitated to dissolve the solids. The temperature increased and the mixture was cooled before adding the 2-chlorobenzoyl chloride (68.9g; 0.394 mol). After further cooling, the XE-305 resin beads, 4% DVB crosslinked, (21.45g; 0.202 formula units) were added and the mixture stirred at room temperature for 20 minutes. The temperature was increased and maintained at 50 °C for 42 hours. About half-way through the reaction period it was noted that little swelling of the resin had occurred. Dichloromethane (100 cm³), an effective swelling agent and frequently used Friedel Crafts acylation solvent, was added in portions. Reaction was continued at 50 °C for a total of 42 hours, the resin having swollen and darkened during this time.

After cooling, the dark tan resin was filtered off on a sintered glass filter. It was washed successively with water, acetic acid, acetic/concentrated hydrochloric acid (1:3) and then with water, followed by methanol and finally with dichloromethane. The resin was air dried, placed in portions in a Soxhlet apparatus, and extracted for 12 hour periods with dichloromethane. On removal it was air dried by vacuum suction and finally vacuum oven dried.

The pale cream resin required prolonged drying to reach a constant weight (47.57g; 105% substitution by weight increase). [Found: C 68.45%, H 4.65%, Cl 16.61%, and S 0.20%; Calculated: C 75.01%, H 4.71%, Cl 13.98%, and S 0.00%]. The i.r. spectrum exhibited a strong peak at $\nu_{\text{max}}^{1660\text{cm}^{-1}}$.

A second batch of chlorobenzoylated resin was synthesized in a manner similar to the first, except that dichloro-³methane (100cm³) was added to the nitrobenzene (100cm³) at the start. The same quantities of acylating reagents were used as before. The reaction time was reduced from 42 to 24 hours. Some data and results are given in Table 12.

Wt. of XE-305	Wt. of Product	Wt. Increase g/g	Substitution %
21.61g	49.92g	1.31	109%

Table 12.

Step 2: Cleavage.

The cleavage was based on the method described by Harrison et al.⁴⁹ In an initial trial experiment the 2-chlorobenzoylated resin (12.12g), from the first acylation, was added to a vigorously stirred mixture of potassium tert-butoxide (16.2g; 0.144 mol) (Aldrich Chem. Co.) and 1,2-dimethoxyethane (175cm³) and the mixture heated for 12 hours under reflux to allow the butoxide to diffuse into the resin. Water (0.8cm³) was then added and reflux

continued for a further 5 hours. A second portion of water (0.8cm³) was added and reflux continued for 6 hours. Some solvent vapour escaped through the stirrer gland and, in the temporary absence of further 1,2-dimethoxyethane, dimethyl sulphoxide (DMSO) (50cm³) was substituted⁵¹ and added during this period. A third portion of water (0.8cm³) was added with DMSO (50cm³) and the temperature maintained at 86 °C with a Fimonitor for 15 hours. At this stage the resin was black and did not appear to have undergone swelling.

The reaction temperature was maintained at 86 °C for two further 24 hour periods, during which two further portions (0.8cm³) of water were added. The reaction mixture was then cooled and filtered. The resin was washed with water, acetic acid, acetic/concentrated hydrochloric acid, water, methanol and finally with dichloromethane. The resulting tan resin had the texture of fine sand, the beads having apparently disintegrated. It was then extracted for 18 hours in the Soxhlet apparatus with dichloromethane, and finally dried in a vacuum oven to constant weight (7.61g; 99% yield). The i.r. spectrum had two broad bands at 1680cm⁻¹ and 1730cm⁻¹.

[Found C 68.67%, H 5.34%, Cl 1.93%, and S 0.99%;
Calculated: C 74.30%, H 5.62%, Cl 0.00%, and S 0.00%].

Cleavage was attempted on a second portion of the 2-chlorobenzoylated resin using a shorter reaction time and a lower reaction temperature.

Thus, the resin (12.14g) was added to a stirred mixture of potassium tert-butoxide (16.3g; 0.145 mol) and 1,2-dimethoxyethane (160g) and the mixture heated to 72-73 °C for two hours before adding the first portion (0.8cm³) of water. The temperature was maintained at 72 °C for 13 hours when a second portion (0.8cm³) of water was added. The beads had turned dark brown at this point. The temperature was maintained at 72-73 °C for a further 24 hours when a third portion (0.8cm³) of water was added. Reaction was continued for another 22 hours and a portion (0.8cm³) of water again added. After a further 5 hours, the reaction mixture was cooled, the resin beads recovered by filtration, washed, purified, dried and weighed as previously described. The recovered resin (13.30g) was found to have increased in weight indicating that no cleavage had taken place at the reduced temperature.

In an attempt to improve the cleavage step a number of variants were investigated, including the use of different solvent systems (dimethoxyethane/dimethyl sulphoxide, pyridine, 1,4-dioxane). None of these resulted in a successfully cleaved product.

Preparation Of Resins With Lower Loadings.

Two 2-chlorobenzoylated resins were prepared with lower loadings:-

(a) 77% Loading:

XE-305 resin (21.22g; 0.200 mol) was added to dichloromethane (200cm³) and agitated in the reaction flask. Aluminium chloride (30.9g; 0.232 mol) was then added, followed by 2-chlorobenzoyl chloride (24.51g, 0.140mol). Following the addition of dichloromethane (50cm³) and agitation for 30 minutes, the mixture was heated under reflux for 10 hours.

The reaction mixture was worked up and dried as previously described, to yield resin (40.73g) corresponding to 100% yield of 77% substituted resin on a weight gain basis.

(b) 56% Loading:

2-Chlorobenzoyl chloride (17.92g; 0.102mol) and aluminium chloride (19.54g; 0.146mol) were dissolved in dichloromethane (200cm³) to give a reddish orange solution. The XE-305 resin (21.31g; 0.201mol) was added, the mixture agitated for 1.5 hours at room temperature, heated under reflux for 6 hours and worked up as described for the 76% substituted resin to yield dry resin (35.73g), corresponding to 56% substitution.

Attempted Cleavage Of Partially Substituted Resins.

The 76% substituted resin (11.87g) was suspended in 1,2-dimethoxyethane (103g) for 12 hours. Potassium tert-butoxide (16.1g; 0.144mol) and 1,2-dimethoxyethane (90g) were then added to the resin suspension. The mixture

was heated to 86 °C for 22 hours. Water (0.8 cm³) was added after 1 and 6 hours of heating. On cooling the resin was filtered off, washed with dilute aqueous acetic acid and then with acetic acid (100 cm³). It was suspended in acetic acid and concentrated hydrochloric acid 3:1 (100 cm³) for 2 hours, filtered, washed with water (600 cm³), methanol (100 cm³), dichloromethane (50 cm³) and then dried by vacuum suction, prior to extraction in the Soxhlet apparatus, initially for 3 hours with methanol and subsequently for 14 hours with dichloromethane. After vacuum oven drying, resin (9.89g) was recovered, corresponding to 51% cleavage.

For cleavage of the 56% substituted resin, resin (12.27g) was added to 1,2-dimethoxyethane (66g), followed by potassium tert-butoxide (16.3g; 0.145 mol) and additional 1,2-dimethoxyethane (105g). The mixture was agitated for 45 minutes before heating was commenced and water (0.8 cm³) added. Reflux was maintained for 15 hours. The resin was recovered by filtration, washed as described for the previous cleavage, followed by extraction for 24 hours each with methanol and dichloromethane. After vacuum drying resin (9.61g) was recovered, corresponding to 80% cleavage on the weight loss basis.

Attempted Cleavage Of A Disrupted Resin.

In another attempt to achieve a better cleavage, resin from the second lot of highly substituted resin was ground to a fine powder with a pestle and mortar. Powdered resin

(12.80g) was suspended in dichloromethane (100cm³), filtered and the cloudy filtrate discarded. The resin was resuspended in dichloromethane in the filter funnel and the solvent sucked through to give an opaque white filtrate of tiny resin particles. The process was repeated using methanol as solvent. The two processes were repeated three times when a clear filtrate was obtained. On recovery and vacuum oven drying of the retained material, resin (12.48g) was obtained.

This resin (12.41g) was suspended in 1,2-dimethoxyethane (108g), potassium tert-butoxide (16.7g; 0.149 mol) in 1,2-dimethoxyethane (89g) was added and the mixture heated to 86-87 °C for 18 hours. Water (0.9cm³) was added after the first hour. The resin was filtered off, and washed as before, and extracted with dichloromethane for 20 hours. After vacuum oven drying resin (10.98g) was recovered, corresponding to 30% cleavage by weight loss.

(b) ACYLATION OF XE-305 WITH ETHYL OXALYL CHLORIDE.

Route C (see discussion section).

A number of acylations were attempted on the XE-305 resin. Using dichloromethane as solvent no weight increase had occurred on completion of the attempted reaction. Use of nitrobenzene as solvent gave only modest results even at elevated temperatures for an extended period.

Resin (20.15g; 0.190 formula units), ethyl oxalyl chloride (26.20g; 0.196 mole), and aluminium chloride (31.10g; 0.233 mol) were heated to 40 °C in nitrobenzene (120cm³). The reaction was maintained at 40 °C for 7 hours, then cooled to room temperature.

The black/red resin was recovered by filtration and washed as follows: dichloromethane, acetic acid, water, acetic acid, water, methanol, dichloromethane, methanol, and finally dichloromethane. It was then extracted with dichloromethane in a Soxhlet extractor for 34 hours and vacuum dried at 70 °C. Resin (22.12g) was recovered, corresponding to 11% substitution by weight increase.

A second acylation in nitrobenzene was carried out at an elevated temperature for an extended reaction period. Resin (7.27g; 0.068 mol) was added to nitrobenzene (40cm³), at 10 °C. Ethyl oxalyl chloride (9.50g; 0.070 mol) and nitrobenzene (40cm³) were then added. The reaction mixture was agitated for 5 minutes and then aluminium chloride (11.30g; 0.085 mol) and nitrobenzene (40cm³) added. The reaction

0
mixture was then heated to and maintained at 80 C for 21 hours.

The resin was recovered, washed and purified as described above. The beads were found to be tacky and were soaked for 72 hours in a mixture of (1:1:1) :-

(methanol : water : concentrated hydrochloric acid). The resin was then filtered, washed with water (800cm³) and methanol (75cm³), and dried at 60 C for 20 hours. Resin (8.52g) was recovered, corresponding to 20% substitution. [Found: C 82.53%, H 6.89%, O 7.12% and 6.49%, and Cl 3.20%; Calculated (assuming 20% phenyl substitution): C 85.73%, H 7.22%, O 7.05%, and Cl 0.00%] v_{max} 1680 and 1740cm⁻¹.

(c) ACYLATION USING CHLOROACETYL CHLORIDE.

Route D (see page 29 and discussion section).

Step 1: Chloroacetylation Of XE-305 Resin.

Chloroacetyl chloride (11.30g; 0.100 mol) was added to a round bottomed flask, fitted with stirrer and condenser, and containing XE-305 resin (10.53g; 0.097 formula units) and aluminium trichloride (15.80g; 0.118 mol) in nitrobenzene (125cm³). The reaction mixture was agitated for 30 minutes at 27-28 °C and then at 50 °C for 23 hours. On cooling and recovery by filtration, the resin was washed with dichloromethane, acetic acid, 1:3 concentrated hydrochloric acid : acetic acid, 1:4 concentrated hydrochloric acid : water, water, methanol and dichloromethane. It was extracted overnight with dichloromethane in a Soxhlet apparatus, and dried in a vacuum oven overnight at 50 °C to yield tan coloured resin (17.16g), corresponding to 94% substitution. [Found: C 65.66%, H 5.37%, O 7.88%, Cl 19.42%; Calculated: C 68.87%, H 5.28%, O 8.03%, and Cl 17.82%], ν_{max}^{-1} 1690cm⁻¹.

Step 2: Formation Of The Phenacyl Pyridinium Salt.

The chloroacetylated resin (15.05g) was suspended in pyridine (100cm³) under reflux for 8 hours. The reaction mixture was then cooled and filtered and the black resin washed with tetrahydrofuran and dried by vacuum suction. The free flowing brown/black resin was immediately used in the following step.

Step 3: Hydrolysis Of The Pyridinium Salt.

The resin from the previous step was added to a round bottomed flask, fitted with a stirrer and condenser and containing tetrahydrofuran (100cm³), potassium hydroxide (5g) and water (25cm³). The mixture was heated at 50 °C for 24 hours, cooled and filtered and the resin washed with water and tetrahydrofuran and then air dried by suction for 10 minutes, v_{max} 1690cm⁻¹ and 1640cm⁻¹.

This free flowing black resin was added to a flask containing tetrahydrofuran (60cm³), water (25cm³) and concentrated hydrochloric acid (25cm³). The reaction mixture was agitated and heated at 40 °C for 22 hours. The product resin was filtered off and washed with water, methanol and dichloromethane. It was then extracted with dichloromethane in a Soxhlet apparatus. The recovered resin was found to be tacky on removal and air drying but became free flowing on washing with methanol. The Soxhlet extraction was repeated using methanol overnight. The resin was filtered off and vacuum oven dried to constant weight (12.74g). The overall weight loss (0.15 g/g) for the combined steps 2 and 3 corresponded to a 94% cleavage of the chloroacetyl group. Overall weight changes during these transformations are consistent with a calculated 88% mono -substitution of the XE-305 polystyrene phenyls by carboxyl groups (resin 1). [Found: C 73.92%, H 6.24%, O 14.62%, Cl 2.99%, N 0.00%; Calculated : (a) assuming 6% chloroacetyl residues, C 74.66%, H 5.68%, O 18.40%, Cl 1.26%, N 0.00%; and (b) assuming 6% phenacyl pyridinium residues, C 74.69%, H 5.70%, O 17.89%,

Cl 1.23%, N 0.49%] . v ⁻¹ 1700cm⁻¹ .
max

Similar reactions were used to synthesize several more batches of functionalized resin with carboxyl loadings ranging from 42% to 63%.

It had been noted that nitrobenzene did not swell the XE-305 resin nearly so well as did the chlorinated solvent dichloromethane. 1,2-Dichloroethane with higher boiling point than dichloromethane, was examined as a potential solvent for the chloroacylation step. However poor results were obtained leading to the conclusion that nitrobenzene was the preferred chloroacylation solvent.

Infra Red Spectra.

Infra red spectra were recorded for all intermediates and products in these experiments. Better resolved spectra were obtained for resins with medium loadings relative to those with high loadings. On chloroacylation a broad band appeared at 1690cm⁻¹ , (1720cm⁻¹ reported⁸⁵ by Camps et al). On forming the pyridine complex, an additional band appeared at 1640cm⁻¹ . This disappeared on cleavage and was replaced by a broad band at 1700cm⁻¹ , (Camps et al reported⁸⁵ 1685cm⁻¹). The chloroacetyl resin also showed broad absorption centred around 3400cm⁻¹ probably due to absorbed water. It was noted that the resins rapidly increase in weight on exposure to air.

Chapter 5

N-OXIDATIONS OF 2-CHLOROPYRIDINE.

EXPERIMENTAL SECTION.

This section is divided into four main sections:

- (a) use of modified Merrifield resins in the oxidations,
- (b) use of highly loaded resins derived via
chloroacylation,
- (c) use of a highly loaded aliphatic weak acid and an
aromatic sulphonic acid resin,
- (d) studies on the decomposition of 2-chloropyridine
N-oxide.

(a) N-OXIDATION WITH CARBOXYLATED RESIN DERIVED FROM MERRIFIELD RESIN.

THE OXIDATIONS.

The experiments were divided into two main groups: small scale and larger scale experiments. In a typical small scale experiment 2-chloropyridine (34.51g, 0.3041 mol) was added to a two necked round bottom flask (150cm³), then methanesulphonic acid (2.22g, 0.0231 mol) was added, followed by Merrifield derived carboxylated resin (4.58g, 0.0057 mol as -COOH). A magnetic follower was added to the flask which was then clamped in a water bath and fitted with a thermometer and water cooled condenser. The temperature of the reaction mixture was controlled by connecting a Fisons Fimonitor to the thermometer. The Fimonitor controlled a hot plate which heated the water

bath. Hydrogen peroxide (70%; 2.77, 0.0570 mol) was added to the reaction mixture, which was then heated to 75 °C for 6 hours. A deep yellow reaction mixture was obtained which gave a positive result for peroxide when tested with starch-iodide paper. It was cooled and filtered on a sintered glass filter and the filtrate collected. The filtrate was transferred to a separating funnel and the resin and reaction flask washed with three portions (each 50 cm³) of water. These washings were added to the separating funnel which was then stoppered and shaken. After separating into two layers the lower organic layer was drawn off and the aqueous layer added to a volumetric flask and diluted to volume with water.

The diluted aqueous layer was further diluted for analysis by HPLC of its 2-chloropyridine N-oxide content. The HPLC analysis was carried out on a u-Bondapak stainless steel column (30 cm by 3.9 mm) with gradient elution from 5% to 60% acetonitrile in water over 10 minutes and the gradient composition maintained at 60% acetonitrile for 2 minutes. The eluent was monitored at 254 nm. Calibration was carried out by constructing a standard curve from 2-chloropyridine N-oxide hydrochloride (Aldrich 97%). The standard was prepared by dissolving a weighed quantity of the hydrochloride in deionized water, neutralizing to pH 7.5 with sodium hydroxide solution (1M) and then diluting to volume in a volumetric flask. This solution was used as a stock solution to make further working solutions for construction of the standard curve. Allowance was made for

the assay (97%) and the hydrochloride moiety. Only one peak was obtained when the standards were run on HPLC and a linear plot was constructed. When diluted reaction mixture samples were run in the linear range, two peaks were obtained, the first due to 2-chloropyridine N-oxide and the second due to 2-chloropyridine starting material. Only the aqueous extracts were analysed for N-oxide content in the preliminary experiments because one experiment was being compared with another i.e. mass of N-oxide extractable into water (150cm³) in one versus that in another. In addition the volume of the organic layer was small (<25cm³) compared to water (150cm³) and often the organic layer was very dark possibly containing polymeric degradation byproducts which might foul the HPLC column.

The resin was washed with methanol, dichloromethane and extracted with dichloromethane in a Soxhlet apparatus and finally vacuum oven dried to constant weight. No significant weight change was noted nor were there any notable changes in the i.r. spectrum after use of the resin in the oxidation.

After measuring the concentration of the N-oxide in the diluted extract the number of moles of the N-oxide in the aqueous extract was calculated and expressed as percentage yield which, in this case was 5%.

Effect Of Increased Hydrogen Peroxide.

Quadrupling the peroxide (10.7g, 0.220 mol) and (10.96g, 0.226 mol) respectively, under similar conditions gave

yields of 14% and 13% in 8 and 10 hours respectively.

Effect Of Increased Resin And Hydrogen Peroxide On Yield

After Scale-Up.

Exploratory experiments had demonstrated that increased quantities of resin absorbed all the 2-chloropyridine. In order to overcome difficulties with absorption and high viscosity the experiments were scaled up in larger flasks, with mechanical stirrers and a greatly increased quantity of hydrogen peroxide was used.

Typically 2-chloropyridine (129.2g, 1.1383 mol) was added to a 250cm³ round bottom flask. This was followed by methanesulphonic acid (7.0g, 0.0729 mol). The flask was clamped in a heating mantle and the reaction mixture stirred gently. Then resin (29.28g, 0.0293 mol as -COOH) was added with a funnel while stirring continued. A condenser and dropping funnel containing the hydrogen peroxide (70%; 70.9g, 1.4597 mol) were fitted to the flask. A thermometer attached to a Fimonitor controller was fitted to regulate the reaction temperature by controlling the heating mantle. Initially 5cm³ of the hydrogen peroxide was added as heating was started, the temperature was brought to 75 °C and held there for 10 minutes when a second 5cm³ portion of the hydrogen peroxide was added. After another half hour the hydrogen peroxide was added dropwise over a two hour period.

After a 10 hour reaction period the reaction mixture was

cooled to room temperature, filtered on a sintered glass filter and the filtrate transferred to a 250cm³ separating funnel. The resin was washed with two (50cm³) portions of water and the washings added to the separating funnel to extract product N-oxide. The mixture in the separating funnel was shaken and allowed to separate. The lower organic layer was drawn off into a second separating funnel while the aqueous phase was transferred to a volumetric flask. The resin was washed a second time with two portions (each 50cm³) of water, the washes added to the second separating funnel and the extraction process repeated. The aqueous layer was combined with the first extract, diluted and assayed by HPLC. A yield of 16% was obtained.

Effect Of Increased Methanesulphonic Acid (MSA).

Doubling the methane sulphonic acid (13.7g, 0.703mol) and keeping all other reagent quantities and conditions constant gave a yield of 24%.

Effect Of Mixed Catalysing Acids.

Using the lower amount of methanesulphonic acid (6.9g, 0.719 mol) in conjunction with an equimolar quantity of 85% phosphoric acid (8.1g, 0.703mol), while otherwise maintaining the same reaction conditions, resulted in a fall in yield to 16%.

(b) N-OXIDATION OF 2-CHLOROPYRIDINE WITH CARBOXYLATED RESIN
PREPARED VIA 2-CHLOROACYLATION.

Resins prepared by the 2-chloroacylation route were used in a series of oxidations under various experimental conditions. The resins are identified by number, and these correspond to those used in sections 2 and 4 dealing with their preparation.

THE N-OXIDATIONS.

USE OF A HIGHLY LOADED RESIN - RESIN 1.

Typically 2-chloropyridine (132.7g, 1.169mol) was added to a round bottom flask (500cm³). Methanesulphonic acid (10.3g, 0.107mol) and resin 1 (10.21g, 0.055mol COOH) were added. A molar excess of 70% hydrogen peroxide (74.3g, 1.530mol) was added dropwise. The flask was fitted with a stirrer, condenser, thermometer, and dropping funnel. Heating was by a thermostatted heating mantle, controlled by a Fimonitor (Fisons) attached to the thermometer. The reaction mixture was heated to 75 °C and maintained at 75 °C for a period, often in excess of 24 hours, which was determined by the time it took the measured hydrogen peroxide level to fall below 2-3% in the reaction mixture. In this case reaction time was 26 hours.

Peroxide levels were monitored by extracting a small sample of the oxidation mixture and adding it to a tared flask and reweighing. Glacial acetic acid (5cm³) was then added to

dissolve the oxidation mixture, followed by water³ (50cm³). Solid potassium iodide (0.5g) was then added and the flask shaken to dissolve it, followed by ammonium molybdate (30mg) as catalyst. The liberated iodine was then titrated with standard sodium thiosulphate solution using soluble starch as the indicator. The reaction was terminated when the residual hydrogen peroxide level fell below 2-3%. Generally it was found that, if reaction was continued after this point, the reaction mixture darkened considerably. Product N-oxide was found not to interfere and a reagent blank of 0.05cm³ sodium thiosulphate was allowed for when calculating the % peroxide.

On termination of the oxidation, the reaction mixture was filtered and the filtrate placed in a separating funnel. The resin was washed with water (140cm³) and the washings added to the separating funnel, which was shaken and then allowed to separate for 12-14 hours. On separation of the two phases, the lower PCl layer was removed to a second separating funnel and further extracted with water³ (140cm³). The aqueous layers were removed, neutralised with 2M sodium hydroxide solution and diluted for analysis by HPLC.

The resin was washed a second time with water (200cm³) and the filtrate saved for analysis. A further wash with methanol³ (100cm³) was carried out and this was also saved for analysis. The resin was then extracted with methanol overnight in a Soxhlet apparatus. The boiler methanol was

also analysed for N-oxide content.

All extracts, washes, and boiler methanol were suitably diluted for analysis by HPLC for N-oxide content. All the extracts and washings were weighed and from the measured concentrations of N-oxide product in these solutions the total amount of N-oxide recovered was calculated. Typically after the first water wash and extraction 85-89% of the total N-oxide recovered was extracted, while combining the first and second water washes 95-98% of the total N-oxide recovered was accounted for. In this case the yield was 27% expressed as:

$$\text{moles N-oxide recovered} * 100 / \text{moles PCl charged}.$$

On repeating this experiment using recovered resin the yield was 23%.

Effect Of Increasing Methanesulphonic Acid On Resin 1.

Increasing the methanesulphonic acid (16.0g, 0.166mol) by 54% gave a yield of N-oxide of 24% while reaction time was reduced from 26 hrs to 22 hours.

EFFECT OF REDUCED FUNCTIONAL GROUP LOADING OF THE RESIN.

RESIN 2.

A set of experiments, utilising resin 2 (10.0g-10.5g) with a lower loading (51% carboxylated), was carried out under similar conditions to those with resin 1 (88% carboxylated). Initially, using the lower level of

methanesulphonic acid (10.3g, 0.107mol), a yield of 14% was obtained.

Effect Of Increasing Methanesulphonic Acid On Resin 2.

However increasing the methane sulphonic acid to the higher level (16.1g, 0.167mol) resulted in a yield increase to 25%.

Effect Of Changing The Catalysing Acid To Sulphuric Acid.

On substituting sulphuric acid (16.5g, 0.168mol) for methanesulphonic acid, a similar yield of 25% was achieved.

Effect Of Reduced Temperature.

Rerunning the sulphuric acid experiment in the lower temperature range 50-60 °C, gave much the same yield but reaction time increased from 19 to 49 hours

Effect Of Phosphoric Acid At Reduced Temperature.

On changing to 85% phosphoric acid (19.9g, 0.173 mol) reaction time increased further to 74 hours and the yield dropped to 16%.

Effect Of Increasing Resin Mass - RESIN 3.

Using resin 3 (47% carboxylated) (31.54g), (involving three times as much resin) with sulphuric acid (17.1g, 0.174mol) at 60 °C gave 19% yield in 27 hours. Increasing the sulphuric acid (22.1g, 0.226mol) and also increasing the reaction temperature to 65 °C gave the same yield (19%) with reaction time being reduced to 18 hours.

ATTEMPTS TO INCREASE YIELD.

Resin 4 (42% carboxylated) was used in this series of experiments. Methanesulphonic acid was used as the catalysing acid.

Increasing The Ratio Of Resin - Resin 4.

Resin 4 (23.07g) and MSA (17.1g, 0.178mol) at 65 °C gave a yield of 25% in 31 hours. This compared to Resin 2, MSA (16.1g, 0.167mol) with a yield of 25% in 22 hours.

Use Of A Peroxide Stabilizer.

2-Chloropyridine (132.2g, 1.165mol), resin 4 (29.28g), hydrogen peroxide (70%; 123.6g, 2.545mol) containing HEDPA (4cm³), and MSA (16.7g, 0.174mol) were reacted at 76 °C for 26 hours. The yield was 33%.

HEDPA = 1-Hydroxyethylidene-1,1-diphosphoric acid
or Dequest 2010 (Monosanto).

60% solution by weight. Mol. Wt. =194.016

Attempt To Reduce Phase Effects.

Repeating the above experiment but with propan-1-ol (55cm³) added in three lots during the peroxide addition to reduce phase separation, a yield of 30% was obtained in 27 hours. Two liquid phases were present at the end of the oxidation.

Use Of HEDPA Alone In An Oxidation.

Repeating the experiment but omitting the propan-1-ol and

the MSA and substituting an approximately equimolar quantity of HEDPA (58.9g, 0.182mol), resulted in a yield of 27% in 43 hours.

Effect Of Equal Weights Of HEDPA And Sulphuric Acid On Two Types Of Resin.

Resin 1, 88% Carboxylated.

Resin 1 (12.32g), PCl (131.4g, 1.158mol), hydrogen peroxide (70%, 135.8g, 2.790mol), HEDPA (20.2g, 0.062mol), and sulphuric acid (20.3g, 0.207mol) were used. Half the weight of resin 1 was premixed with HEDPA and sulphuric acid and one-eighth of the peroxide was also mixed in. Then 2-chloropyridine was added. The temperature rose to 45 °C. The remaining peroxide was added over 14 hours. The second portion of resin was added after four hours. Reaction temperature was 75 °C and reaction time 23 hours. Yield of N-oxide was 33%.

Resin 4, 42% Carboxylated.

This was similar to the previous experiment except that resin 4 (28.85g) was used. The resin was added in 4 equal lots at intervals over 8 hours and the peroxide in 8 equal lots over 10 hours. The temperature (83 °C) was run a little higher than in the previous experiment. A yield of 32% in 14 hours was achieved.

(c) N-OXIDATIONS USING IRC-50 A WEAKLY ACIDIC ALIPHATIC
RESIN.

IRC-50 resin was first subjected to a pretreatment process to clean the resin and remove fines. The IRC-50 resin (50g) was suspended in water (125cm³), which became opaque after stirring and allowing the resin to settle. The supernatant was decanted and the washing process repeated six times until the water washings became clear. The resin was then filtered off, washed with methanol (125cm³) and then extracted with dichloromethane for 22 hours in the Soxhlet apparatus. Finally it was vacuum oven dried to constant weight.

In one experiment the resin (22.95g, 0.230mol -COOH) and methanesulphonic acid (3.6g, 0.038mol) were added to 2-PCl (114.6g, 1.010mol), and hydrogen peroxide (70%; 63.4g, 1.305mol) was added slowly over the first 7 hours a few cm³ at a time. Reaction temperature was 75 °C and reaction time 12 hours. Yield of N-oxide was 13%.

In another experiment more forcing conditions were used, with sulphuric acid (20.2g, 0.206mol) and HEDPA (20.5g) present. 2-Chloropyridine (132.8g, 1.170mol) was charged to the reaction flask and resin (28.64g, 0.2864mol) was added in 4 lots and the peroxide (131.9g, 2.716mol) in 8 equal portions over a 10 hour period. In this case the temperature was 80 °C for 13 hours and a yield of N-oxide of 33% was obtained.

N-OXIDATIONS WITH A STRONGLY ACIDIC ION EXCHANGE RESIN

IR-120.

IR-120 sodium salt (4.4meq $-\text{SO}^-\text{Na}^+$ /g dry, 8% DVB, 20g) was converted to its acidic form by suspension in 2M hydrochloric acid (100 cm³). The resin was filtered off, washed with 2M hydrochloric acid and then with water. It was then suspended in methanol (100cm³), filtered off, washed with methanol (200cm³) and finally placed in a timble and extracted overnight in the Soxhlet apparatus with dichloromethane as solvent. The resin was recovered and vacuum dried at 50 C^o to constant weight. A second portion of IR-120 sodium salt was suspended in 2M sodium hydroxide solution and agitated for several hours. It was then filtered off washed with dilute sodium hydroxide followed by copious washing with water to neutral pH and then put through the purification process described above and finally dried.

These purified resins were then used in subsequent experiments. The first two utilized the acidic or hydrogen form of the resin while the third used the neutral or sodium form. Acidic resin (5.06g), 2-chloropyridine (34.4g, 0.303mol), hydrogen peroxide (70%; 2.69g, 0.076mol), and phosphoric acid (85%; 2.70g 0.023mol) were added to a two necked round bottom flask. A magnetic follower was added and the flask was fitted with a thermometer and water cooled condenser and clamped in a water bath. The water bath was heated by a hot plate which was controlled by

connecting a Fisons Fimonitor to the thermometer. The reaction mixture was heated to 75 °C for 6 hours. On cooling the resin was filtered off, the filtrate transferred to a separating funnel, and the resin washed with three portions (each 50 cm³) of water. The washings were transferred to the separating funnel, which was stoppered and shaken, allowed to separate and subsequently the lower PCl layer was drawn off. The aqueous layer was added to a volumetric flask and diluted to volume. After further dilution for HPLC analysis the yield of N-oxide was found to be 3%.

On repeating the experiment but leaving out the phosphoric acid a yield of 3% was again obtained. In a third experiment the sodium form of the resin (5.91g) was used, again the phosphoric acid was left out. The N-oxide yield was less than 0.1%.

(d) RECOVERY AND DECOMPOSITION OF 2-CHLOROPYRIDINE-N-OXIDE.

In this series of experiments samples of N-oxide and PCl were subjected to a number of procedures in an attempt to ascertain whether decomposition of either was taking place.

(1) Effect Of Acid On 2-Chloropyridine.

2-Chloropyridine (50.5g) was acidified with sulphuric acid (8.4g) by shaking in a separating funnel. Water (100cm³) was carefully added and the funnel vigorously shaken. The mixture was then neutralised with 23% sodium hydroxide solution to pH 8-9 and then allowed to separate for 12 hours. The lower 2-chloropyridine layer was removed to a second separating funnel and extracted with water (100cm³) a second time. All extracts and layers were analysed for 2-chloropyridine by HPLC after being suitably diluted. The 2-chloropyridine recovery was 100.2%.

(11) Effect Of Acid On 2-Chloropyridine-N-Oxide.

An aqueous 2-chloropyridine N-oxide solution (111.6g), supplied by Olin Chemicals and containing N-oxide (34.6g; determined by titanium trichloride analysis¹⁰⁸), was diluted with water (30cm³) and acidified with concentrated sulphuric acid (20.0g). The sample was then neutralised with sodium hydroxide solution (23%) to pH 8-9. Some white solids formed but dissolved instantly when the mixture was diluted for analysis by HPLC. The N-oxide recovery was 99.7%.

(iii) Effect Of Heat And Acid On 2-Chloropyridine-N-Oxide.

N-Oxide solution (110.2g) (34.2g N-oxide by titanium³ trichloride titration) was diluted with water (30cm³) and acidified with sulphuric acid (20.0g) in a round bottom flask fitted with a stirrer, thermometer and condenser. The mixture was heated at 80 °C for 24 hours. It was then cooled and neutralised to pH 8.2 with sodium hydroxide solution (23%). The very dark reaction mixture contained black solids which appeared to dissolve on dilution for analysis. In this case the recovery of N-oxide was only 77%.

(iv) Effect Of Added Resin On N-Oxide Stability.

Unsubstituted XAD-2 resin, another divinylbenzene crosslinked polystyrene resin similar to XE-305 but with a different DVB content, was used.

N-Oxide solution (111.6g), (34.5g by titanium trichloride analysis), XAD-2 resin (25.2g), sulphuric acid (20.0g) and water (30cm³) were heated at 80 °C for 24 hours. The reaction mixture was cooled, filtered through a sintered glass funnel and the resin washed with water (100cm³). The combined filtrate and washings were neutralised with sodium hydroxide solution and transferred to a volumetric flask. The resin was washed with additional water (300cm³) on the filter and these washings were added to the neutralised solution in the volumetric flask to make up the final volume (500cm³). The very dark brown solution smelled of ammonia and formed dense white fumes when

exposed to hydrochloric acid vapour. The teflon agitator blade in the reaction flask was covered with a black/brown tar and when wiped with tissue a purple/ red colour was noted. The resin was then washed with methanol (5*45cm³). The methanolic washes were added to a volumetric flask (250cm³) and diluted to volume with water. This solution was also black and the recovered resin gray, whereas fresh XAD-2 resin was white and very similar in appearance to the XE-305 resin used in the oxidations. The aqueous and methanolic solutions were suitably diluted for HPLC analysis of their N-oxide content. The overall N-oxide recovery was 79.7%.

(v) Effect Of 2-Chloropyridine On N-Oxide Stability In The Presence Of Added Resin.

This experiment was very similar to the last experiment except this time 2-chloropyridine (50.8g) was included as well as XAD-2 resin. The other reagent quantities were: N-oxide solution (110.0g), (34.1g by titanium trichloride analysis), water (30cm³), sulphuric acid (20.0g), and XAD-2 (20.0g). The reaction mixture was heated at 81 °C for 22 hours. After filtering off the resin, the filtrate was neutralized with the sodium hydroxide solution to pH 8-9 and then transferred to a separating funnel. Only a single layer could be detected in the separating funnel, possibly because of the very dark colour of the reaction mixture. This mixture was transferred to a volumetric flask (500cm³). Black solids (possibly sodium sulphate, precipitated from the black solution) were noted in the

separating funnel and these were washed into the volumetric flask with water. Acetonitrile (90cm³) was added to the flask to ensure homogeneity and the mixture was diluted to volume with water. Acetonitrile was added because it was used later during HPLC analysis as one of the solvents during the gradient run. This solution also smelled of ammonia. The resin was washed with water which was subsequently neutralized and diluted to volume (500cm³) in a volumetric flask. Finally the resin was washed with methanol and the methanolic washes diluted to volume (500cm³) with water. The three solutions were suitably diluted and analysed for both N-oxide and 2-chloropyridine by HPLC. Recovery of N-oxide was 94.0% and of 2-chloropyridine 99.7%.

Exp. No.	NOX Use g	PCL g	H SO g	XAD-2 g	Total Water g	Recovery NOX/PCL g	Recovery %
1	---	50.5	8.4	----	100	50.6	100.2%
2	34.6	---	20.0	----	106	34.5	99.7%
3	34.2	---	20.0	----	106	26.3	77.0%
4	34.5	---	20.0	25.1	106	27.5	79.7%
5	34.1	50.8	20.0	20.0	106	32.1 & 50.7	NOX 94.0% PCL 99.7%

Table 13.

Summary of experimental data on fate of PCL & NOX.

The N-oxide recovery is expressed in grams and was calculated from the concentrations measured in solution. Total water refers to the added water plus the amount of water in the N-oxide solution i.e. weight N-oxide solution less calculated N-oxide content in grams.

A crosscheck was made to determine the correlation between the two analytical methods i.e. the titanium trichloride and HPLC methods. 2-Chloropyridine N-oxide solution (110.0g, N-oxide content of 34.2g by titanium trichloride titration) was diluted and assayed for N-oxide by HPLC. Recovery was 98.5% which indicated good correlation between the two methods.

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