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SYNTHESIS AND USES OF SOME AZAPARACYCLOPHANE DERIVATIVES

A Thesis presented by

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To My Family

ABSTRACT

Complexation between phane type hosts and neutral guests is reviewed. The synthesis and some properties of catecholate siderophores are also discussed. Attempts to make 2N,2ON′-dimethyl-2,11,20,29-tetra-aza[3.3.3.3]paracyclophane are described. Approaches to make N-(4,4′-dimethoxybenzhydryl)-N′-methyl-1,4-xylylenediamine, a possible precursor to the required paracyclophane, failed. A process of selective acylation using 4-toluenesulphonic acid and the macrocyclic polyether 18-crown-6 has been further developed but could not be applied successfully to the synthesis of the paracyclophane. Attempts to bridge two of the nitrogens in 2,11,20,29-tetra-aza[3.3.3.3]paracyclophane using isophthaloyl dichloride are described.

The synthesis of 2,20-di-aza[3.3.3.3]paracyclophane from 1,3-diphenylpropane has been successfully completed. The protection of 1,2-dihydroxybenzene (catechol) moieties and their attachment to amines have been examined, culminating in the linking of a catechol to the di-azaparacylophane. The synthesis of several model catecholamides are also described.

The use of these catecholic systems together with iron(III) and hydrogen peroxide in the catalytic hydroxylation of benzene (the Hamilton oxidation) has been studied. The paracyclophane - dicatechol species has been shown to be a catalyst, but the presence of a molecular cavity in the system appeared to produce no great benefit.

The whole catalysis process does not appear to have any real practical use. Crystallographic and ^{1}H nmr studies of N,N'-dimethyl-2,20-di-aza[3.3.3.3]paracyclophane indicate a lack of binding ability in this particular macrocycle. Some approaches to the synthesis of a new, more rigid, paracyclophane are described.

Some reactions with diphenylphosphinoacetaldehyde, a potentially useful synthon in an iterative Wittig reaction procedure are discussed.

ACKNOWLEDGEMENTS

I would like to thank Dr. A.G.M. Barrett for his most helpful guidance throughout the course of this work, and Dr. S.J. Abbott (I.C.I. New Science Group) for most useful discussions. I owe thanks also to all my colleagues past and present within the research group for providing an interesting and stimulating working environment. Special mention must be made of Drs. Greg Simpson, Jim Irving, Ray Duffin, and Steve Barker, and Messrs. Martin Wythes, Robin Attrill, and Howard Broughton for all their help and most useful suggestions at all times, but most especially during the writing of this thesis. Finally, I am greatly indebted to Mrs. Kate Duffin for deciphering my handwriting and typing this work.

CONTENTS

CHAPTER 1

HOST COMPLEXATION WITH NEUTRAL GUESTS

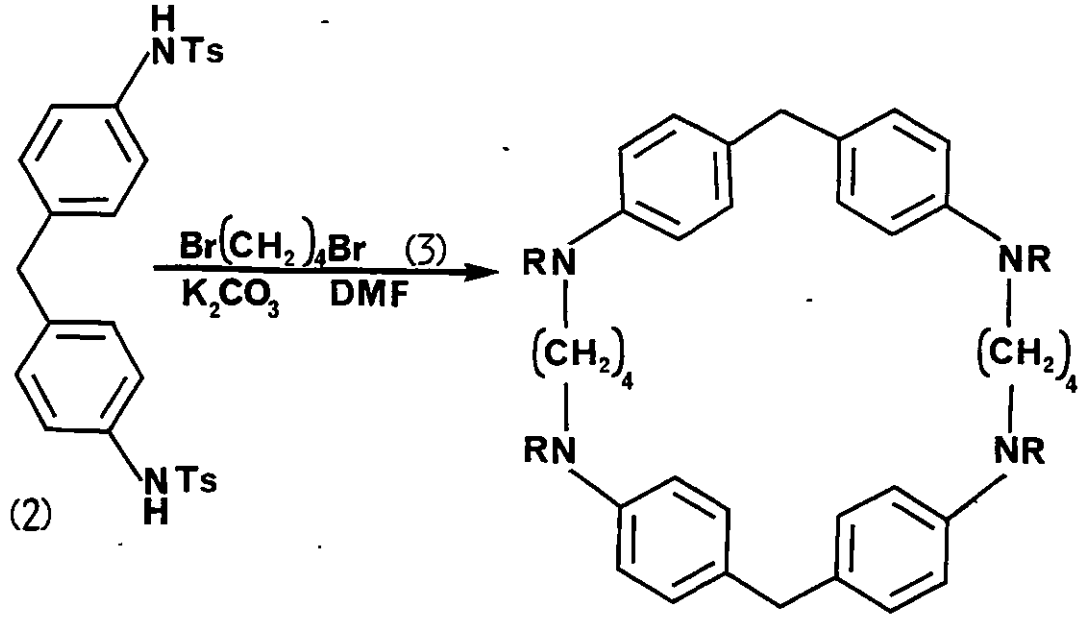
Host-guest interactions are a much studied field in organic chemistry.

The more specific area of host complexation with uncharged guests has received scarcely less attention, mainly due to its relevance in biochemical systems, for example enzyme-substrate pairing or in interactions at drug receptor sites.

Many classes of host molecules have been synthesised in the last fifteen to twenty years and it is far beyond the scope of this summary to describe all of these. Many reviews and books have been written on crown ethers[1,2,3] the last of these especially covering the known literature on interactions with uncharged guests. Therefore this field will not be pursued. Cyclodextrins have also attracted long and thorough surveys[4,5,6,7] and again will not be considered here. Clathrate chemistry, where uncharged guests are trapped in intermolecular cavities, is extensively reviewed[8,9] and will only be mentioned below where the situation warrants it.

Azaparacyclophanes and other macrocyclic molecules have been found to contain hydrophobic pockets or clefts within which small and often uncharged molecules can reside, and it is with this ever developing field that the bulk of this report concerns itself. This survey will begin by the examination of host compounds where some definite evidence exists for intramolecular binding with uncharged guest molecules.

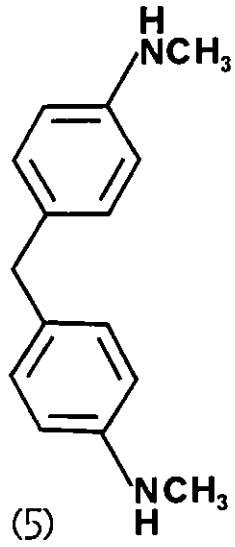
In 1980 Koga's group published evidence for intramolecular complexation between a newly synthesised tetra-aza[6.1.6.1]-paracyclophane (CP 44) (1) and several hydrophobic guests in solutions of aqueous acid[10,11]. CP 44 (1) was made by the cyclisation of N,N'-(ditoluene-4-sulphonyl)-4,4'-diaminodiphenylmethane (2) and 1,4-dibromobutane (3) in N,N-dimethylformamide containing potassium carbonate, followed by detoluene-4-sulphonylation, in 17% yield. The paracyclophane (1) was shown by ^{1}H nmr to cause large upfield shifts in the position of aromatic protons of several aromatic alcohols notably 2,7-dihydroxynaphthalene. The positions of some of the protons, in DCl-D_2O solution (pD 1.2), of 2,7-dihydroxynaphthalene were shifted towards tetramethylsilane by almost 2 ppm. The acyclic analogue (5) of CP 44 (1) was shown to produce only a minimal perturbation of the ^{1}H nmr peak positions. Of more interest perhaps was that CP 44 (1) formed crystalline complexes from aqueous solution with a variety of substrates including naphthalene, 1,4-xylene, 1,3-dihydroxynaphthalene, and durene (6). The latter complex was subjected to X-ray crystallography and the structure was successfully elucidated as the tetrahydrochloride. It showed the durene (6) molecule positioned exactly in the middle of the host. CP 44 (1) had adopted a conformation whereby opposite benzene rings were in parallel planes to each other. The cavity formed had rectangularly shaped open ends ($\sim$3.5 x 7.9Å) and a depth of 6.5Å. Since the complex was obtained from an aqueous medium and durene (6) itself is non-polar, it is clear that hydrophobic interaction plays a key role in the association and that polar interactions do not participate. The CP 44 could be considered as a very simple model for a binding site in many biologically important systems.

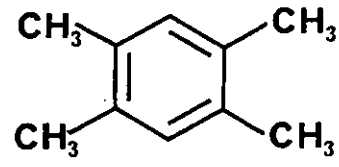


(1) R = H

(4) R = Ts

(7) R = $C(=O)(CH_2)_5NH_2$





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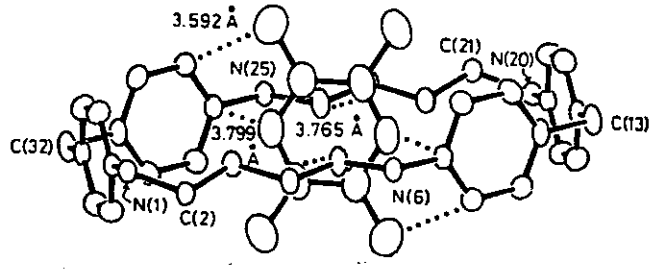


Complex Between

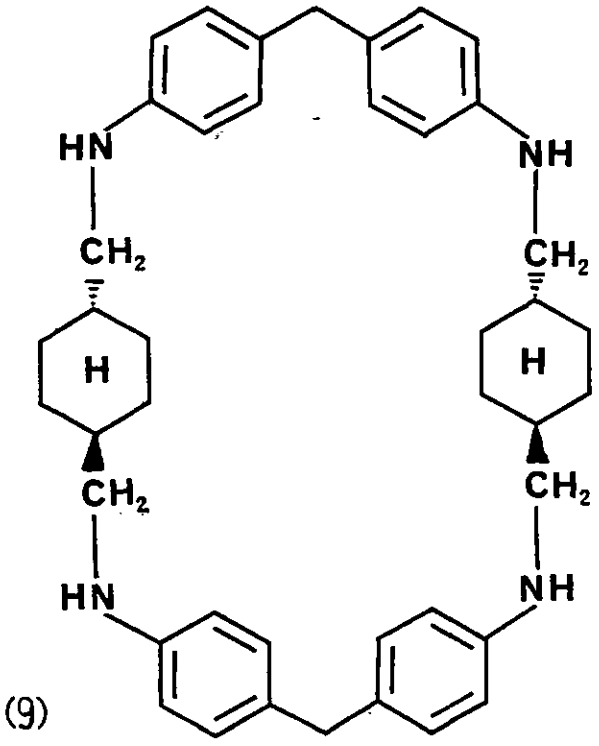
(1) and (6)

SCHEME 1

This X-ray structure proved to be a landmark in this aspect of host-guest chemistry. At last unequivocal evidence existed that intramolecular complexation did occur with uncharged molecules, and several groups are now working to design new hosts and to obtain similar positive proof.

Since their initial success, the Koga group have worked on modifying the nature and size of the cavity of CP 44 (1)[12,13,14]. They have varied the length of the chains joining the two diphenylmethane units, they have included cyclohexyl and benzene rings in the chains[12] and they have put new substituents on the nitrogens of CP 44 (1)[13]. The cavity of each of these new compounds was probed using fluorescence spectroscopy. The fluorescence spectrum of 1-anilinonaphthalene-8-sulphonate (ANS) (8) has been found to be dramatically enhanced when it is in a relatively hydrophobic environment[4,15] and this technique has been used to test the cavities of other synthetic host molecules[16,17]. It should however be remembered that the ANS is a charged species and at the low pH at which most of these determinations were carried out, the azaparacyclophanes were also protonated. Consequently some electrostatic interactions must be occurring.

Koga's study shows that one particular tetra-azaparacyclophane (9) binds to ANS 80 times more strongly than CP 44 (1). He has also observed some useful substrate selectivities[14] between CP 44 (1), CP 56 (10) and the paracyclophane (9), their binding with a series of naphthalene mono- and disulphonates being examined. The differences were probably due to the different cavity sizes leading to different inclusion geometries within those cavities. ^{1}H nmr studies[11] suggest that pseudoaxial inclusion is adopted by CP 44 (1), and this conformation



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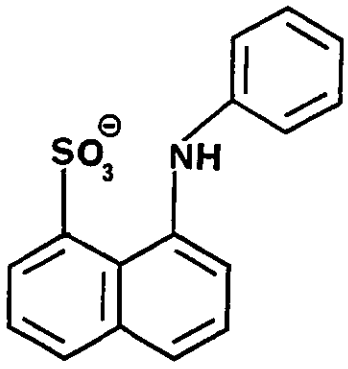

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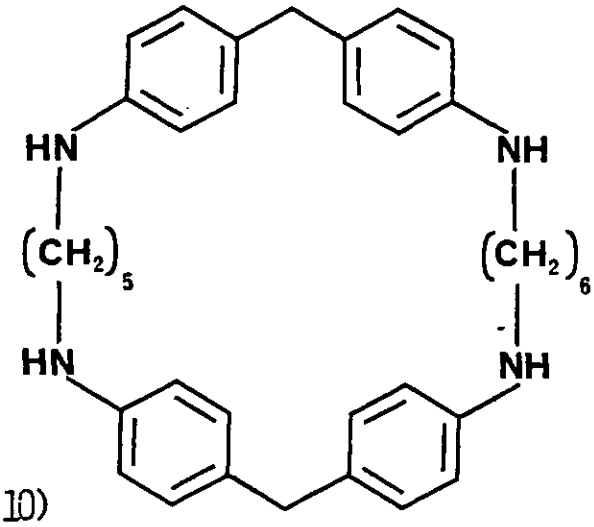

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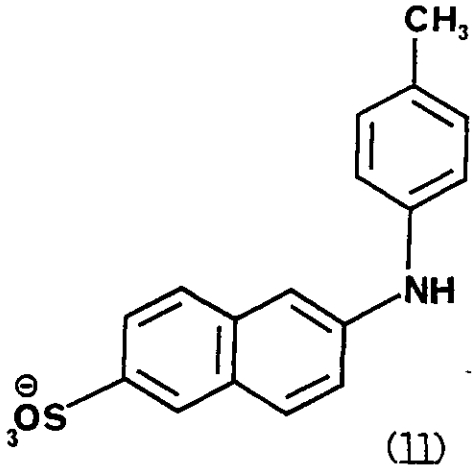

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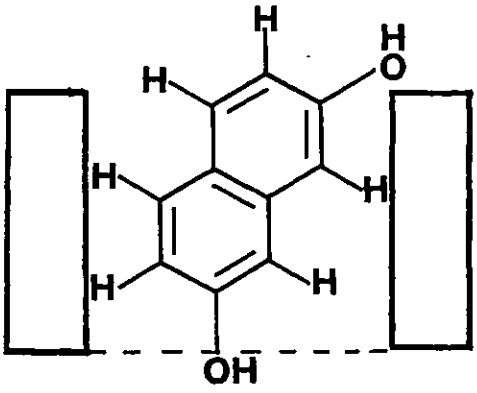
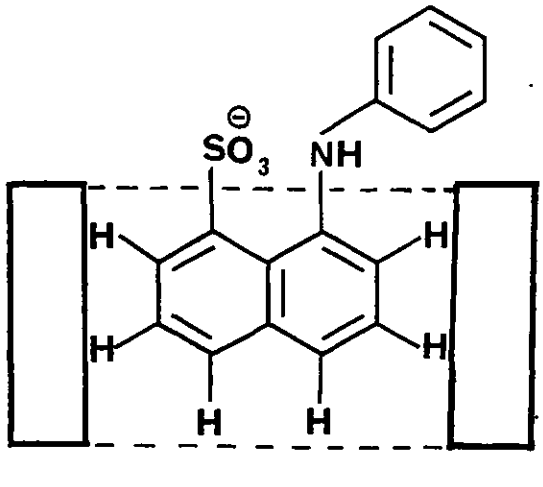


"Pseudoaxial" Inclusion by (1)



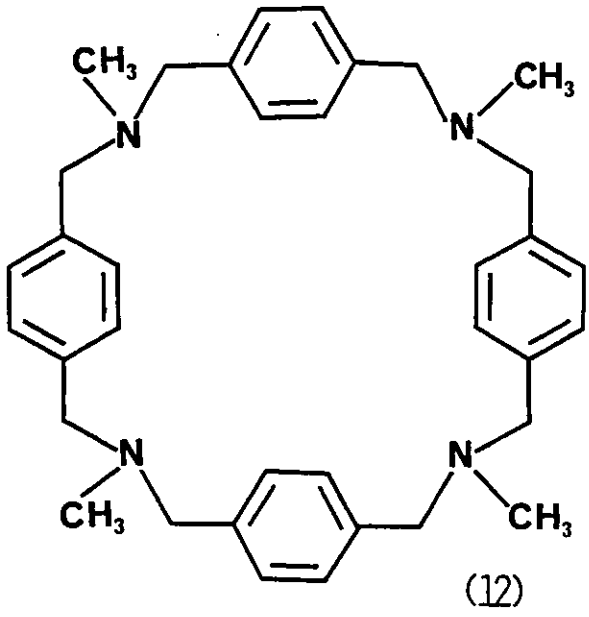
"Equatorial" Inclusion by (9) or (10)

would favour complexation with β-substituted naphthalenes, whereas the equatorial inclusion expected in the larger cavities of CP 56 (10) and compound (9) would clearly favour α-substitution in the included naphthalene moiety.

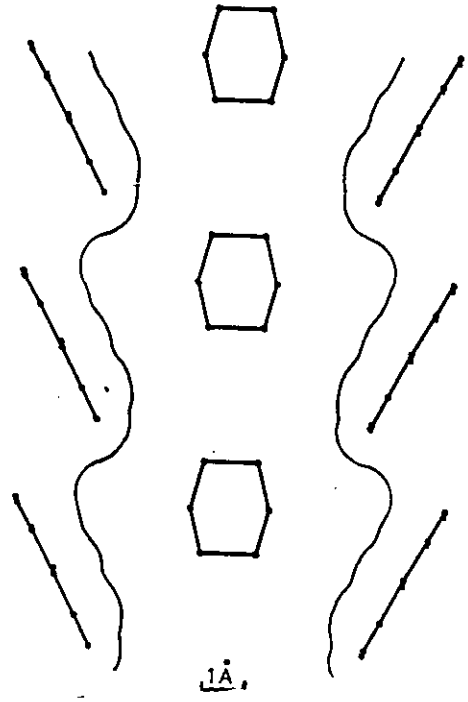
Putting potentially charged side chains on to CP 44 (1)[14] resulted in the formation of a series of compounds for example compound (7) that bound with 2-toluidinonaphthalene-6-sulphonate (TNS) (11) rather weakly, but these molecules did have the very useful property of being water-soluble at neutral pH.

This systematic study has produced some interesting results, the most valuable findings involving substrate selectivity where small changes in cavity dimension can produce major changes in substrate binding. However none of these compounds have yet been used as successfully as CP 44 (1) in complexation with a neutral non-polar guest molecule.

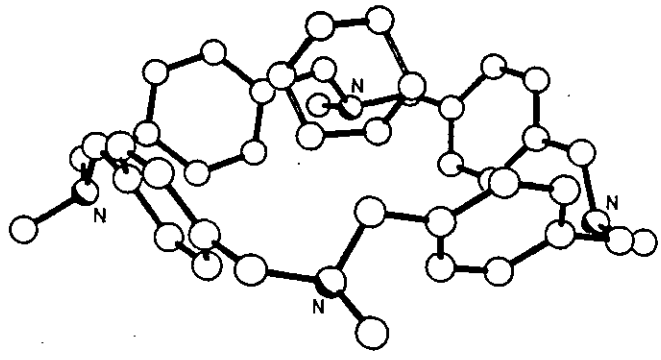
Twelve years ago Urushigawa, Inazu and Yoshino[18] synthesised three new azaparacyclophanes to compare their spectral properties, and to see whether they could form inclusion compounds. Two of the molecules di-aza compounds, showed no sign of complexation but the third, N,N',N''N''' -tetramethyl-2,11,20,29-tetra-aza[3.3.3.3]-paracyclophane (12), seemed to have some interesting properties. Complexes with 1,4-dioxan and with benzene were isolated, which by ^{1}H nmr and by elemental analysis showed a 1:1 stoichiometry. It was by no means certain however that these were intramolecular inclusion complexes. The chemical shift for the guest protons in the ^{1}H nmr



(12)



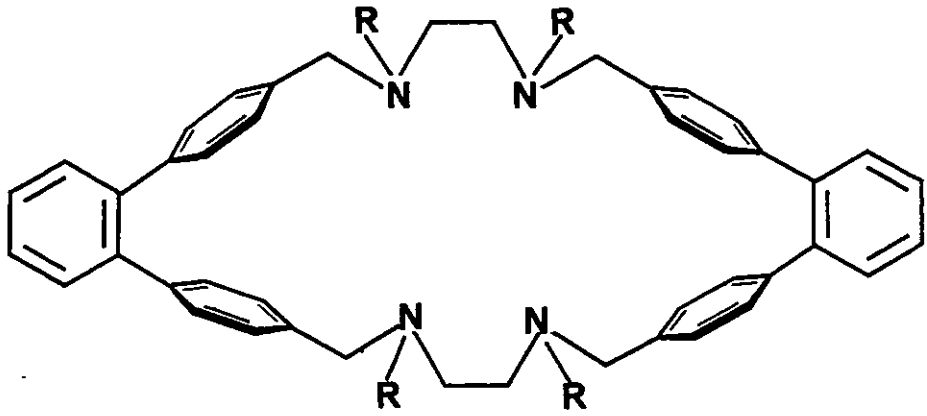
Cross-section of channel in lattice of (12) showing the "cone-in-cone" structure, the environment of the dioxan and the Van der Waals' Surface



The molecular structure of the 1:1 complex of (12) with the 1,4-dioxan

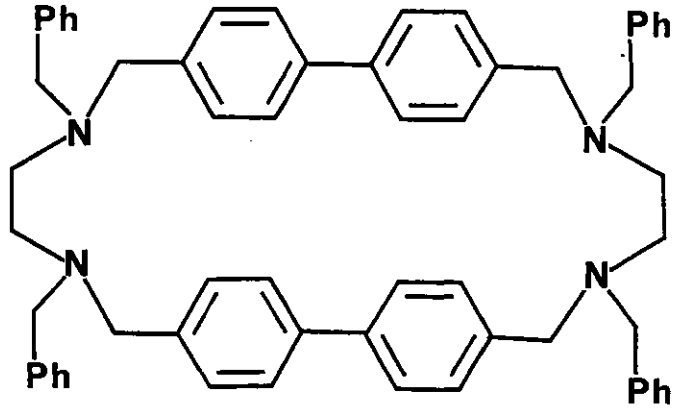
were not significantly altered from those expected in uncomplexed guests. A more recent publication[16] has demonstrated, by use of fluorescence spectroscopy, that compound (12) almost certainly contains a hydrophobic cavity, but a definite answer concerning the 1,4-dioxan complex only came in the middle of 1982 when an X-ray crystal structure of the material appeared in the literature[19]. The X-ray showed that in contrast to CP 44 (1), the paracyclophane (12) had adopted a slightly "dished" conformation with each benzene ring inclined at 28° to the vertical. This led to the cavity having an opening of 7Å at the top and 4.4Å at the bottom. Also the 1,4-dioxan molecule, although intimately connected with one particular host, did not sit buried deeply inside the cavity. Instead it protruded slightly above the plane of the cavity into a secondary cavity caused by the stacking of the cone-shaped host molecules. The diagram shows a cross-section of the crystal lattice with the hexagonal dioxan molecules sticking out slightly into intermolecular space.

Several new azaparacyclophanes have been synthesised by Vögtle[20] by straightforward high-dilution reactions between diamines and diacid chlorides. The compound (13) on recrystallisation from cyclohexane produced crystals which proved to be a 1:1 complex by ^{1}H nmr and elemental analysis. The cyclohexane was tenaciously retained as were 1,4-dioxan, tetrahydropyran, and morpholine, ever after extended drying. Conversely, molecules such as methylcyclohexane, cycloheptane, cyclooctane, decalin, benzene and toluene were not intercalated. Recrystallisation of compound (13) from a benzene-cyclohexane mixture yielded only the cyclohexane complex. This rather subtle differentiation has obviously useful implications.



(13) R=CH_2Ph

(14) R=CH_3



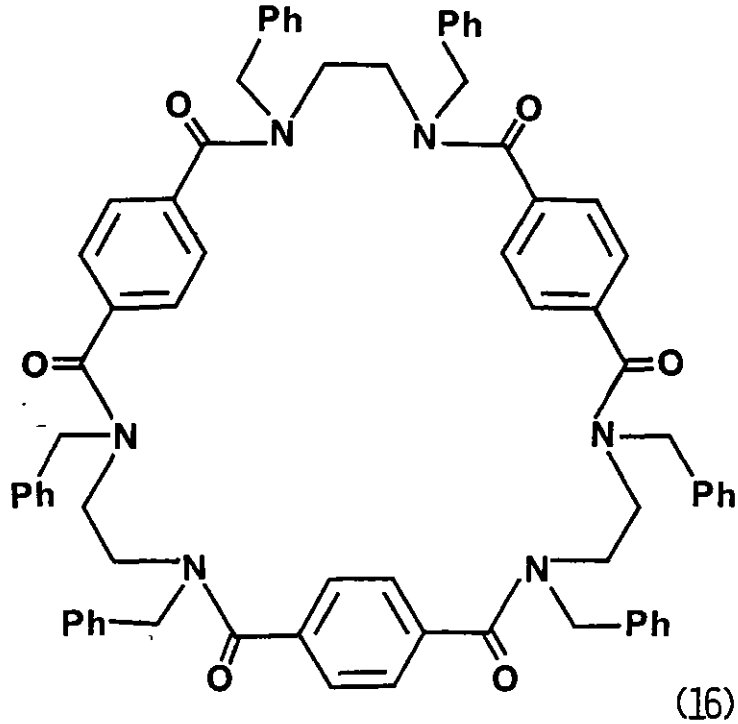
(15)

No X-ray analysis could be obtained for any of these complexes, and so it is not certain whether they represent inter- or intramolecular complexation, although the precise stoichiometry obtained and the selectivity of uptake of guests suggests to the author that the latter

type of inclusion is involved. Alteration of the N-benzyl group to an N-methyl group led to the inactive compound (14), demonstrating the importance of the side chain in influencing the host-guest interaction. Finally compound (15) containing biphenyl units was able to bind with penta- and hexafluorobenzene but not with several slightly smaller guests. Thus again we can see that relatively small alterations to cavity dimensions lead to large changes in substrate selectivity. This implies that hosts may be designed for very specific purposes.

Recently the same group has published[21] an X-ray crystal structure of a complex of a hexa-aza[6.6.6]paracyclophane hexaamide (16) with chloroform. The paracyclophane was made from terephthaloyl dichloride and N,N'-dibenzylethylenediamine and the included chloroform survived prolonged drying under vacuum and recrystallisation from ethyl acetate.

The X-ray structure shows that the chloroform guest is oriented and fixed in the cavity with the hydrogen atom pointing into the niche along the trigonal axis of the host. The size of the chlorine atoms prevents the guest from burying itself too deeply into the host. The aromatic rings surrounding the cavity are inclined at an angle of 17° to the C3 axis. Similar chlorinated guests do not complex with paracyclophane (16) again showing the discriminating abilities of this type of cavity. It is interesting to note that this host complexes only as the hexaamide derivative. Reduction with diborane to the hexaamine (17)[20] modified the properties of the compound sufficiently to stop any association with uncharged guests.



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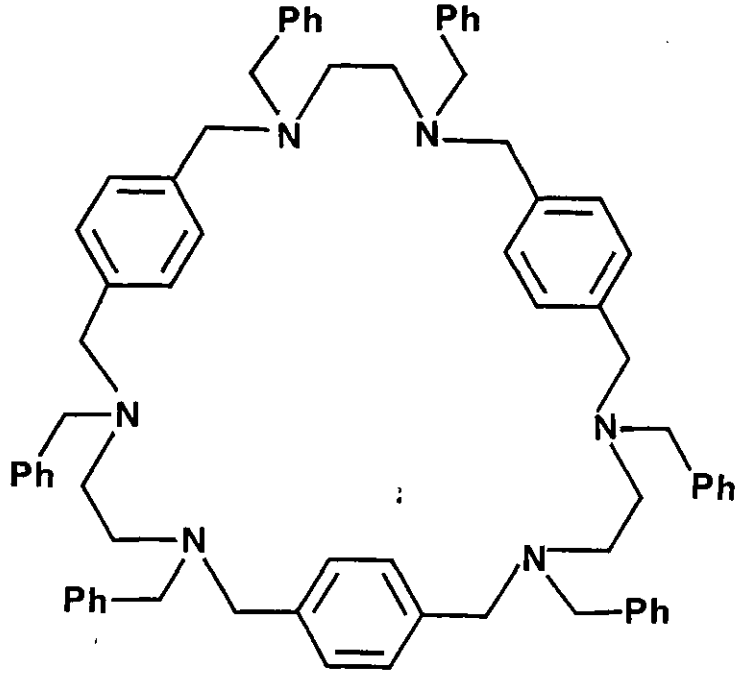


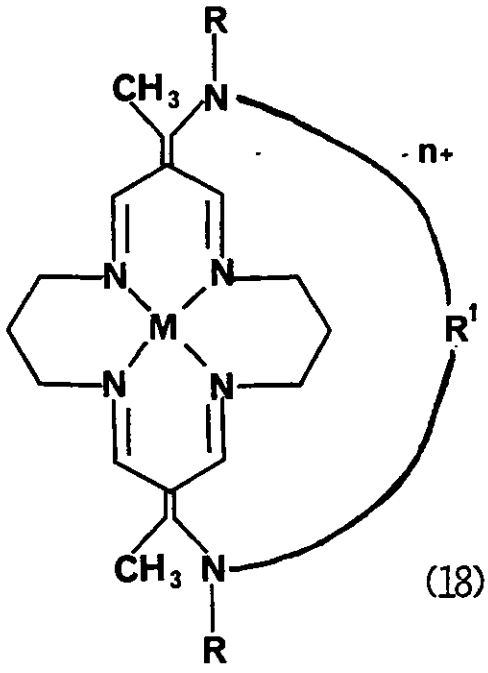
(17)

This leads to even more versatility in the design of host molecules. Both the side chains and the oxidation level obviously effect the precise dimensions and environment of the cavity.

Specific complexation alone is a very valuable achievement. However the ultimate aim of such work must be to bind uncharged substrates into a cavity and then to perform a chemical transformation on it. Thus one needs to introduce close to the binding site a unit that is capable of doing a chemical reaction. This part of the survey will concentrate on efforts to achieve this aim using macrocycles to help define the cavity.

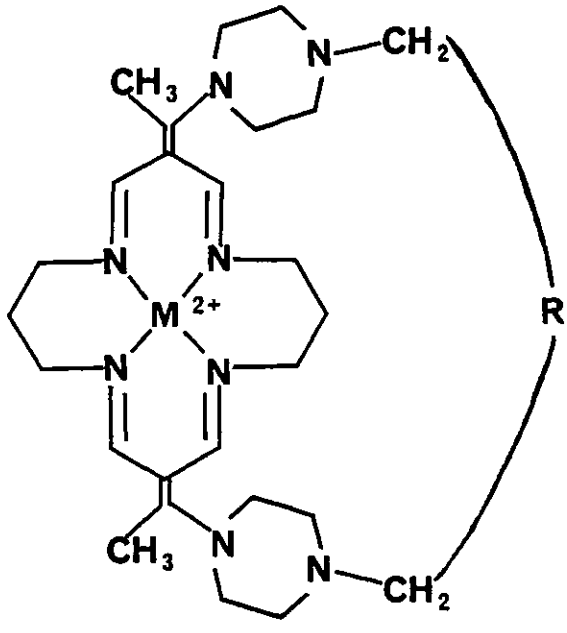
Some elegant research aimed at mimicking the cytochrome P450 enzymes has been developed over the last few years. The work started with the synthesis of a series of metal-containing macrocycles (18) which were shown[22,23] to contain a hydrophobic void or "dry cave" near the metal atom within which small ligands could shelter. The cavity of compound [18, R =Me, M = Co^{II}, R^1 = $-(CH_2)_6-$] was shown by an X-ray structure determination to be 6.65Å wide with the height varying from 4.83Å at the back to 5.60Å at the front. Oxidation of compound (18) to the cobalt(III) species led to a new compound, X-ray analysis of which demonstrated the ability of small ligands to bind to the metal centre inside the cavity. The ligand studied was the amident thiocyanate which was bonded through nitrogen. Subsequent work[23,24] established that the cobalt(II) and the iron(II) complexes of (18) could reversibly bind oxygen given a cavity of the right size obtained by a judicious choice of R and R^1. For the iron

(II) complex the best ligand used had a 1,3-xylyl group as R^1. The oxygen uptake of the ligand was observed using spectrophotometric techniques.



(18)

Having established the presence of the cavity, and the reversible oxygen binding capability of the system, the ligand was altered slightly to allow both the oxygen and an uncharged aromatic guest to co-exist in the dry cave as a ternary complex. Thus ligand (19) was designed, and binding with aromatic substrates demonstrated[25,26].

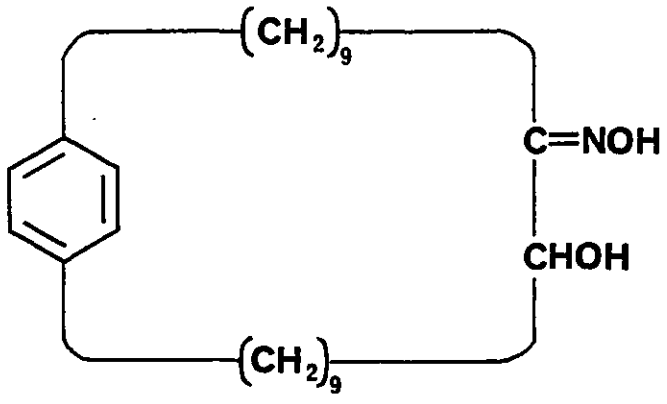


(19)

^{1}H nmr studies of compound (19, R = tetramethylxylyl, M^{2+} = copper, nickel) complexing with 1-butanol showed that an association was occurring, with the alkyl chain of the alcohol pointing into the cavity. This last finding dismissed the possibility that an actual bond was forming between the hydroxyl group and the metal. The complexation was completely due to hydrophobic effects. An X-ray crystal structure of compound (19, R = 9,10 anthracene, M^{+} = nickel) showed a definite intramolecular inclusion complex with acetonitrile, clearly establishing the mode of complexation and detailing the dimensions of this larger cavity[25]. Since nickel(II) can be removed from the centre of this type of ligand by the action of hydrogen chloride and zinc[22] the stage is now set for the formation of a ternary complex and for selective oxidations within the complex. Further developments are awaited with great interest.

Considerable attention has been focussed onto the ability of paracyclophanes to act as catalysts. Murakami, having synthesised the oxime (20)[27] found that it could be acylated by 4-nitrophenyl laurate (61) and decanoate in aqueous, alkaline acetone. Other oximes not containing large cavities were completely uneffected under similar reaction conditions. These results were explained by the following mechanism[28]. The hydrophobic interaction between the long alkyl chain of the ester and the paracyclophane cavity led to the formation of a 1:1 complex. Under the alkaline conditions of the reaction medium the oxime was deprotonated and the oximate anion attacked the ester carbonyl function. It was concluded that the substrate specificity was not exclusively due to the hydrophobicity of the long-chain ester but also to its apparent bulkiness when folded. This specificity

therefore could be altered by small changes in the paracyclophane oxime (20).



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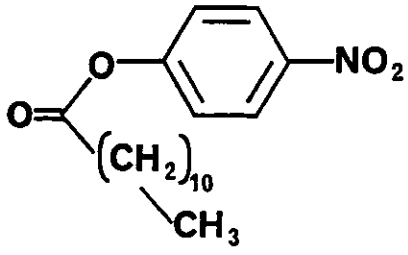

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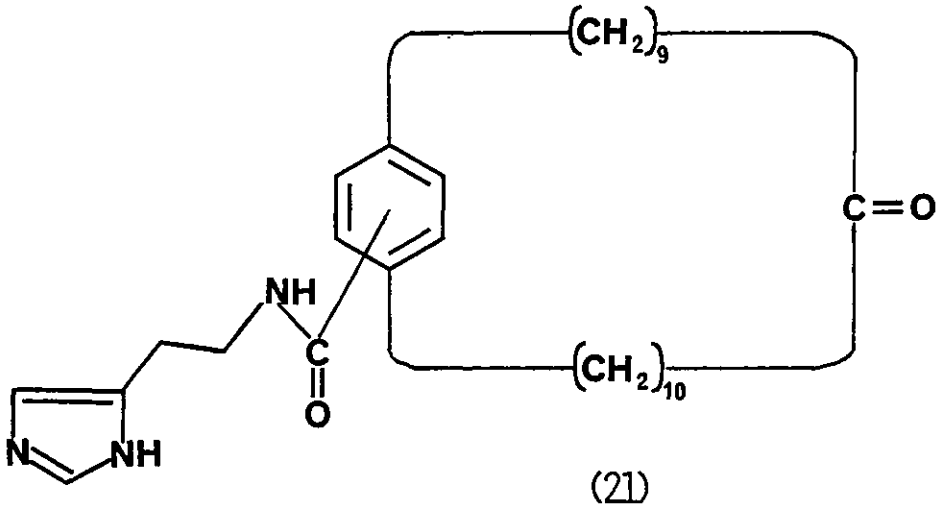
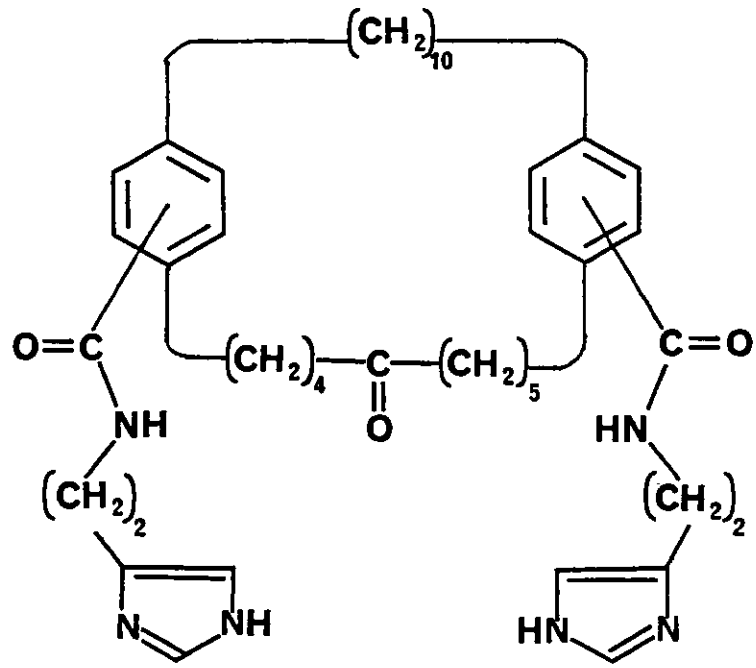


(21)

The presence of the cavity having been surmised, the group turned its attention to more elaborate systems. They attached an imidazole group to the aromatic ring near the cavity[29,30]. The resulting molecule (21) was able to significantly catalyse the deacylation of various 4-nitrophenyl carboxylates. An acceleration in the rate of deacylation of up to 240-fold was observed in those esters with long hydrophobic side chains. However the paracyclophane was of no practical use as a catalyst because the imidazole group rapidly became acylated and hence deactivated and the rate of deacylation of the imidazole was very slow in comparison to its



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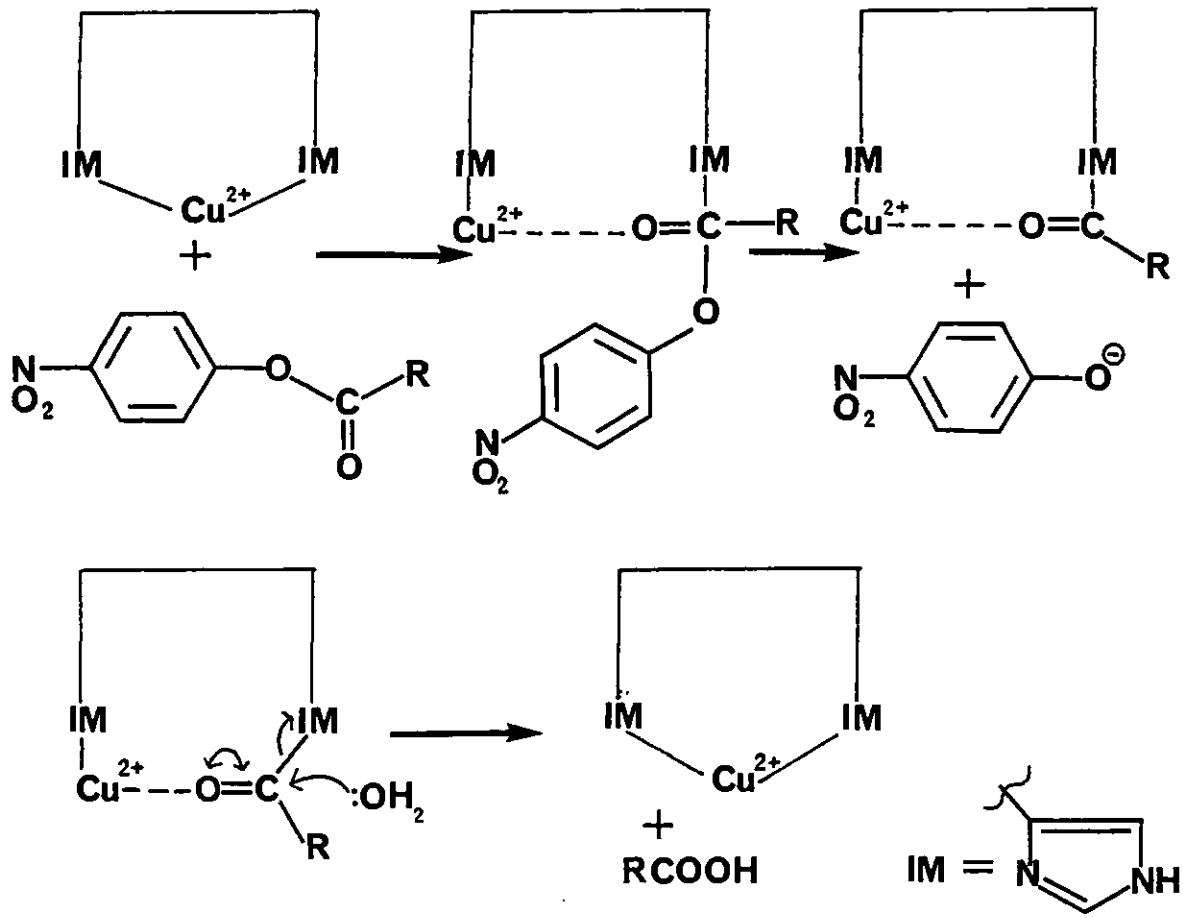


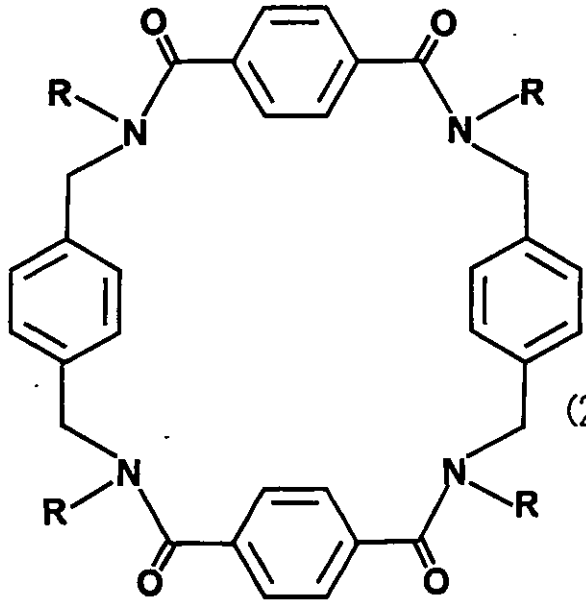
SCHEME 2

rate of acylation. Hence, only one equivalent of 4-nitrophenol was released for each molecule of "catalyst".

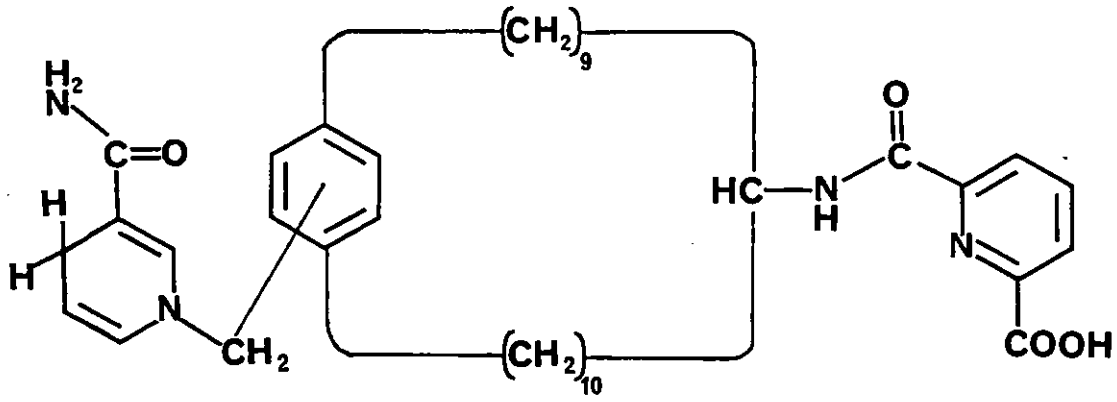
This problem of catalyst turnover was overcome by design of a new paracyclophane (22) with two aromatic rings and two imidazole moieties[31]. This compound (22) in the presence of copper(II) acts as a true catalyst for the hydrolysis procedure. The reaction is believed to still involve acylation of one imidazole, but the copper (II) complexed to the nearby second imidazole is able to conduct a rapid deacylation. Thus under steady-state conditions acylation and deacylation reactions find a balance. This is shown in Scheme 2.

Thus ideas used in cyclodextrin chemistry[4] whereby catalysis of various reactions are assisted by the presence of a cavity have been successfully exploited in paracyclophane chemistry. Further studies aimed at designing new compounds with different cavities have not yet produced very signfficant results. Murakami has made the cationic octopus azaparacyclophane[32] (23) and has studied more ester hydrolyses. He has also made a compound (24) which complexes with zinc[33,34] and should be a very useful reducing enzyme model but as yet has only used it to reduce hexachloroacetone, a substrate for which the presence of a cavity is more or less superfluous.

Tabushi[35,36] has designed the charged tetra-azaparacyclophane (25) and has shown this to be quite discriminating between various aromatic esters during hydrolysis studies. For example 4-nitrophenyl chloroacetate was hydrolysed more rapidly than α-napthyl chloroacetate. The β-naphthyl ester reacted more slowly still. That catalysis



(23) R= $-(CH_2)_{10}-\overset{\oplus}{N}Me_3\ \overset{\ominus}{Br}$



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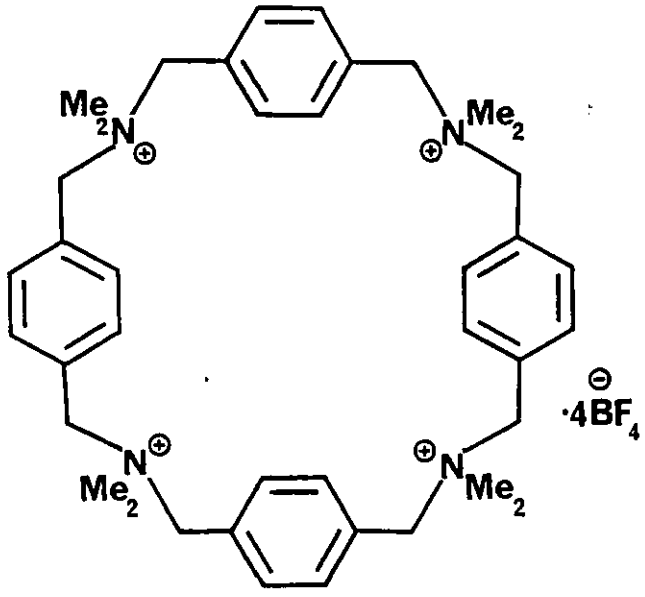
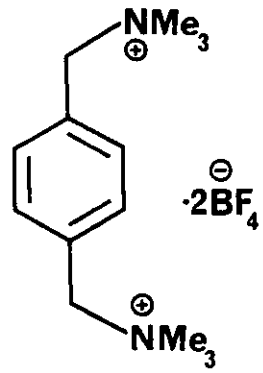


$\cdot 4BF_4^{\ominus}$

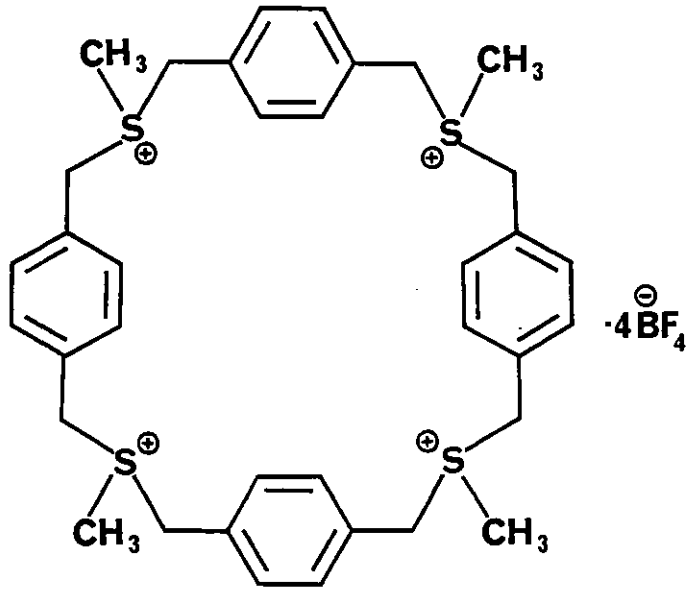


$\cdot 2BF_4^{\ominus}$

(25)

(26)

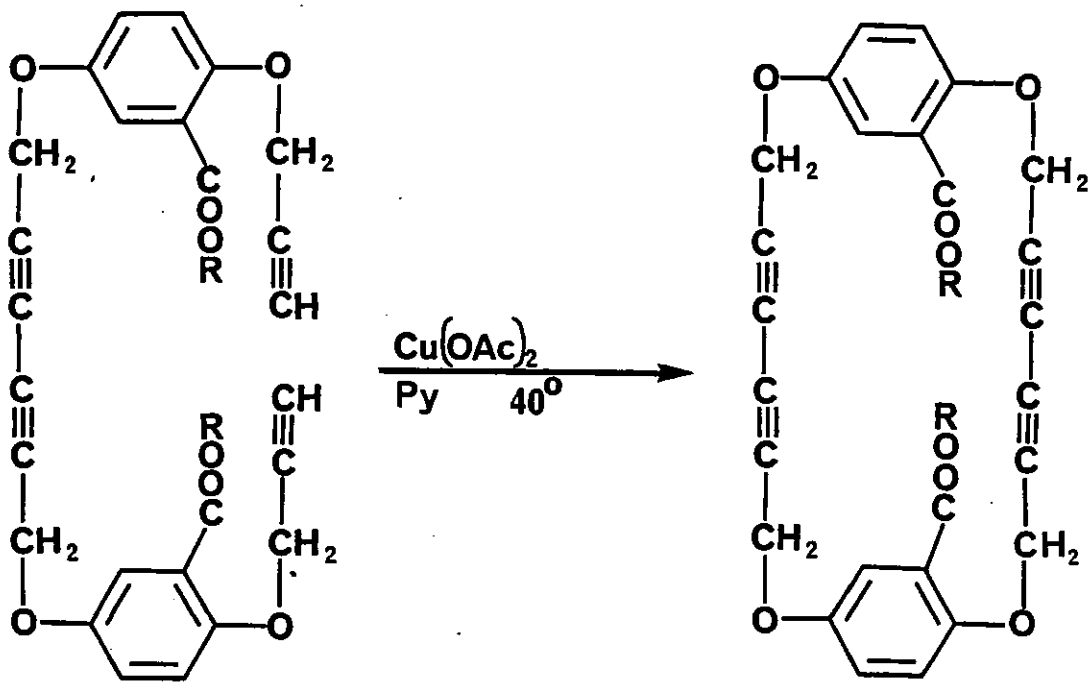
occurred, due in part to a hydrophobic interaction, was shown by the fact that the open-chain analogue (26) produced little catalytic effect. A thioparacylcophane (27) has also been made[37], but has only been studied by fluorescence techniques which have shown that this compound also possesses a suitable cavity.



(27)

The survey has so far concentrated by and large on studies where definite host-guest complexation has been observed. There are a growing number of compounds which have been designed specifically for the purpose of encapsulating a smaller guest. Although in many cases such complexations have not been thoroughly studied and encapsulation not properly observed, it is important to include these potentially important compounds.

Jarvi and Whitlock[38] wanted to synthesise molecules that were water-soluble and that possessed hydrophobic cavities with well-defined dimensions, so as to obtain a molecule showing a functional similarity to binding cavities in enzymes. They designed and made



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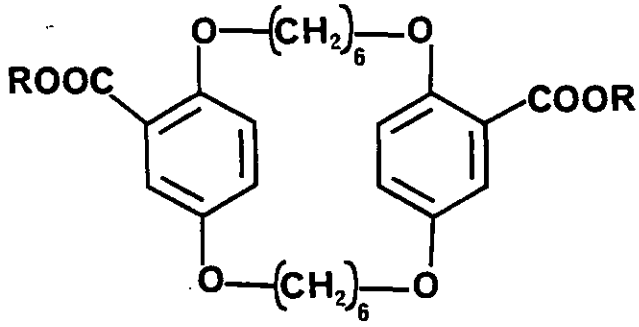

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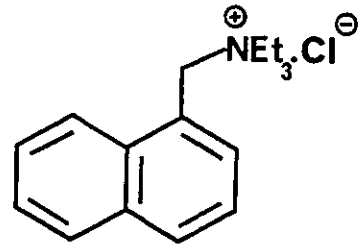

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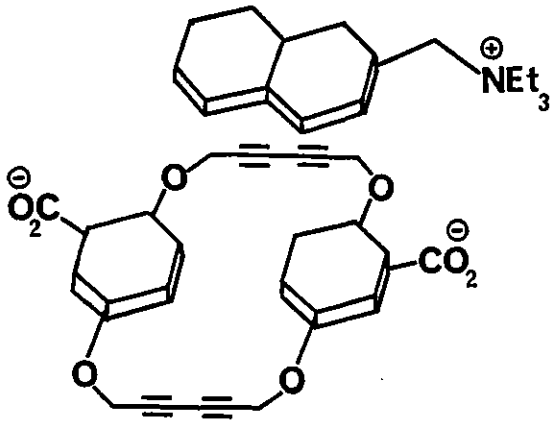
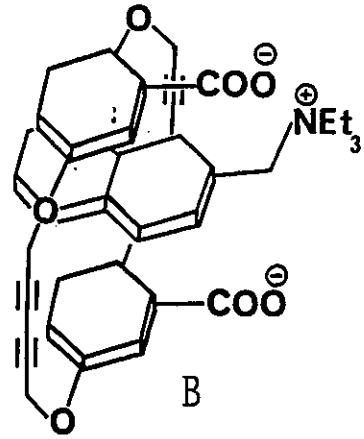


A

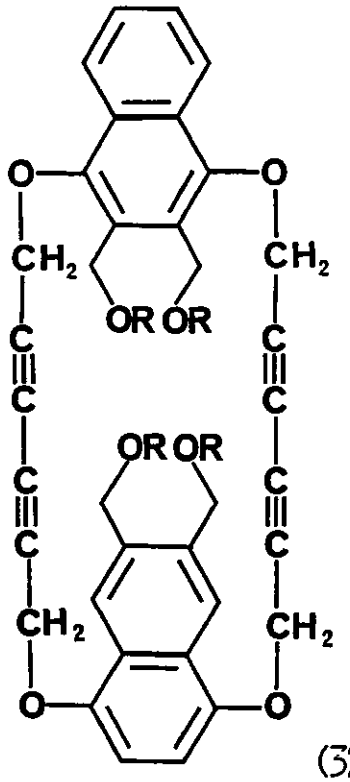


B

the tetra-oxa[8.8]paracyclophane (28). The key step in the synthesis was the intramolecular coupling of a diyne (29) in pyridine with cupric acetate at 40°C in the remarkably high yield of 67%. Hydrogenation of (28) gave the perhydro derivative (30). The potassium salt of compound (28, R = K^+) was chosen for complexation studies, this being water-soluble, and 2-naphthylmethyltriethylammonium chloride (31) was the guest. Detailed ^1H nmr studies showed that despite the fairly rigid framework of the paracyclophane (28) the stacking complex A was occurring in solution rather than the more interesting inclusion complex B. The perhydro derivative (30) was believed to exist in a collapsed form with no cavity being evident.

The group next made a series of naphthaleneophanes[39,40] again with the view to making inclusion complexes. Compound [32 R = $COCH_2N(CH_3)_2$] was used in an nmr study[39] with 2-naphthalenesulphonic acid (35) in aqueous DCl. The guest protons showed large upfield shifts and this coupled with fluorescence experiments using 1,8-anilinonaphthalene sulphonate suggested the formation of an inclusion complex.

To see whether systems (33) and (34) formed intramolecular complexes, the concept of cyclisation shift was employed[40]. This may be defined for a given proton as δ cyclophane-δ model, where the model is the half molecule corresponding to the paracyclophane before cyclisation. When the cavity of a paracyclophane is rigidly defined with the aromatic rings well separated, only a small cyclisation shift is observed as the aromatic protons from one ring do not fall inside the shielding cone of the other π cloud. In non-aromatic



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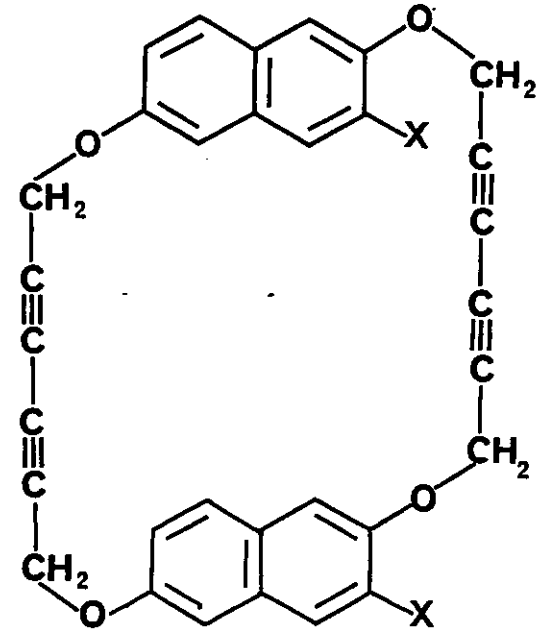

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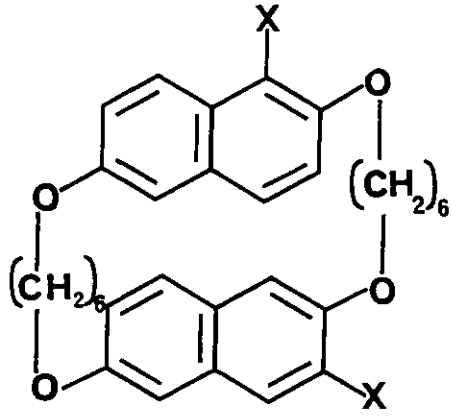

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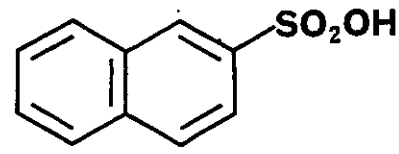

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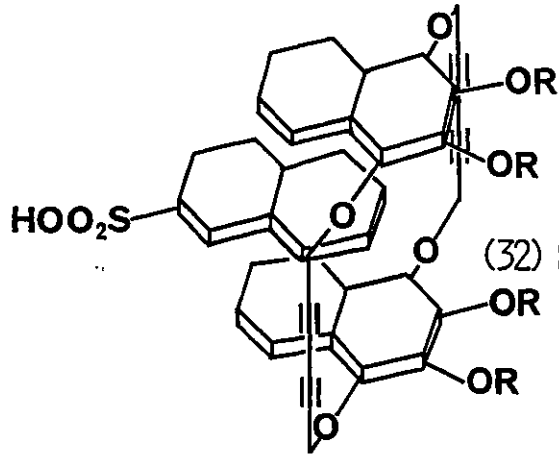
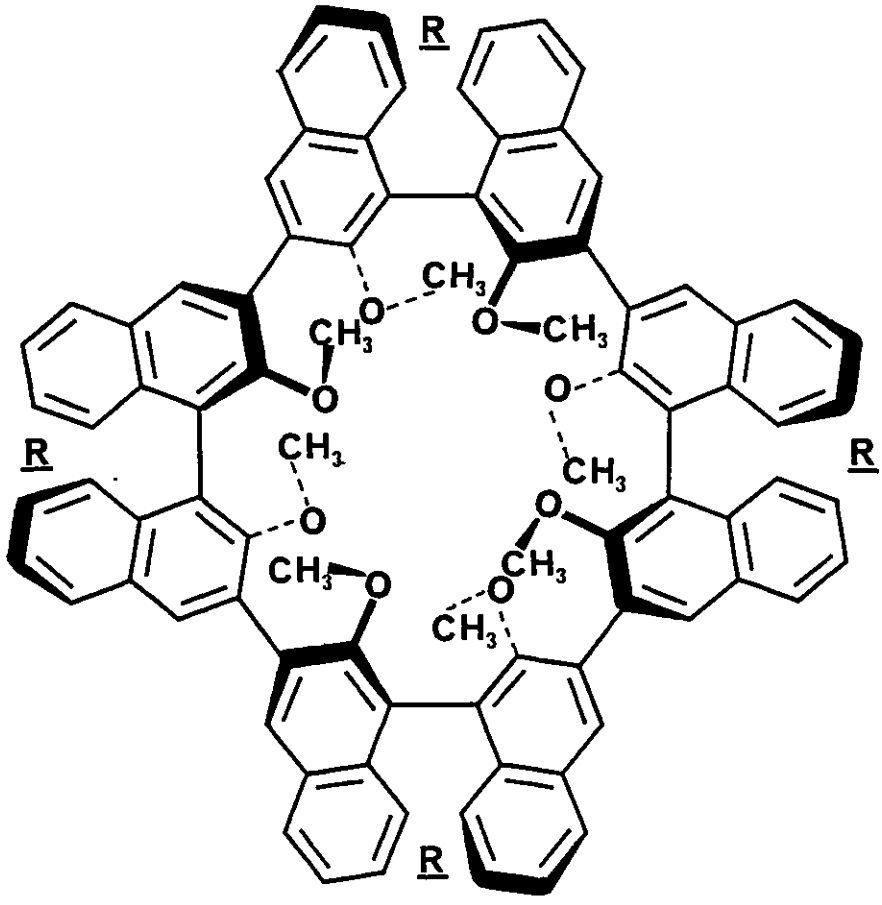


(32) R= $\overset{O}{\overset{\|}{C}}CH_2\overset{\oplus}{N}HMe_2$ AND (35) COMPLEX

solvents this cyclisation shift for the rigid system (33) was, as expected, rather small. In aromatic solvents however, a quite large upfield cyclisation shift was observed. This implied that an inclusion complex was being formed with the aromatic solvent, the new interaction being responsible for this significant increase in shielding. The floppy naphthaleneophanes (34) showed no such discrimination between solvents.

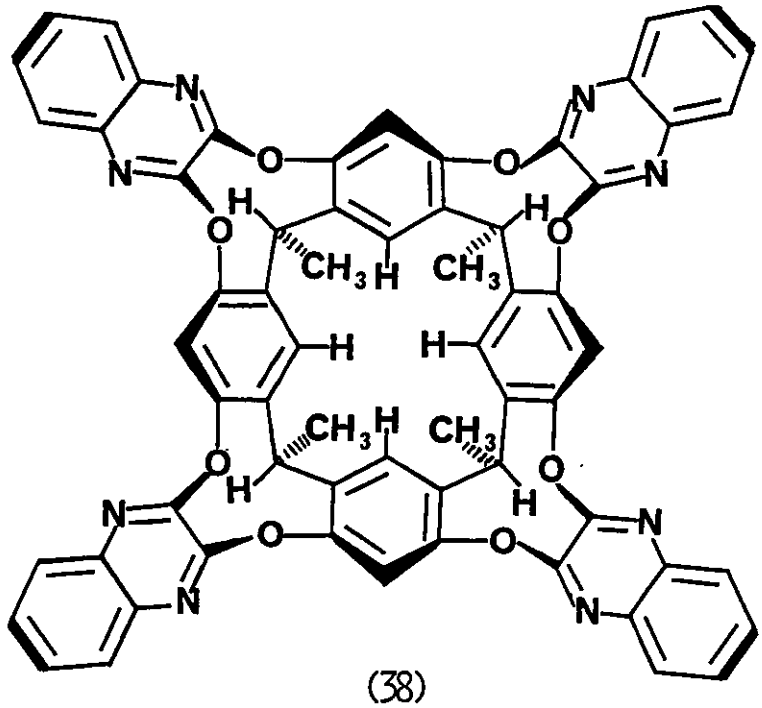
Further evidence for the complexing abilities of compounds (33) came from ultraviolet spectroscopy. 4-Cyano-1-ethylpyridinium iodide was introduced to a solution of compound (33, R = CO_2H) and a new charge transfer band was observed. This implied that the pyridinium salt was complexed to the cyclophane, the experiment being similar to one conducted by Murakami[41] who used 4-cyanopyridinium iodide to study complexation. The floppy naphthaleneophane (34, R = CO_2H) gave no new transfer band. Thus if suitable side chains can be introduced to the rigid naphthaleneophane (33) framework, this compound could be an ideal candidate for major complexation studies.

Cram has been searching for chiral macrocycles containing large, enforced cavities[42]. However, despite much excellent work, positive demonstration of binding to neutral guests has not yet been achieved. A large range of compounds have been made such as the 1,1'-binaphthyl derivative (36), which in addition to complexations with a series of charged picrates, can also be made to absorb one equivalent of cyclohexane. Molecular models show that the cavity in macrocycle (36) is cylindrically shaped with a diameter of 2.7-3.0Å and a length of about 7.7Å.



(36)

The concept of these enforced cavities, in which the conformation of the molecule cannot fold in on itself completely, is rather reminiscent of the cyclodextrins, but these wholly synthetic spherands are clearly more versatile and can have cavity sizes engineered for specific purposes.



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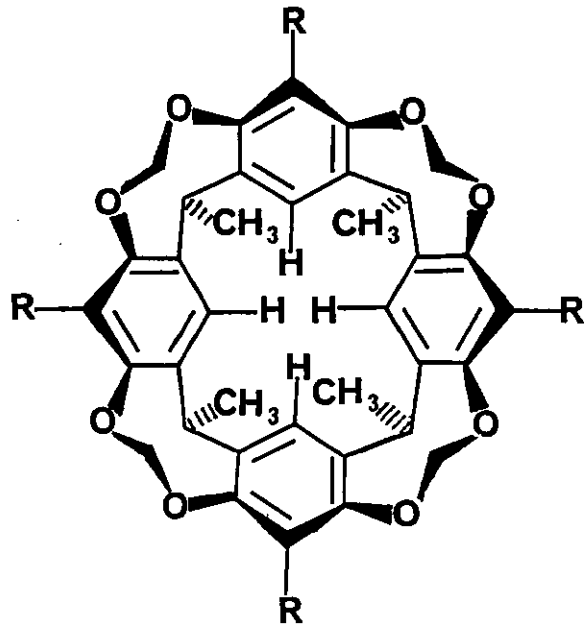
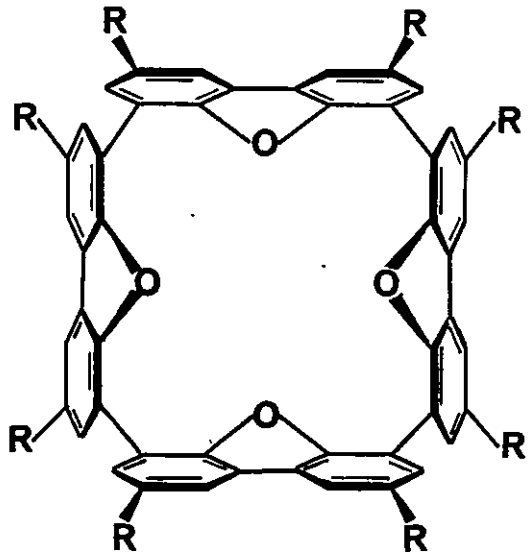


(37)

Cram next examined the systems (37) and (38), enforced cavity-containing compounds for which he coined the name cavitand[43]. Compound (37 R = H) crystallised with solvent of crystallisation as did molecule (38). Compounds (37 R = Br, CO_2Me) however, are able to fill their cavities intermolecularly and did not form solvates. Crystal structures for the solvated compounds are awaited with interest.

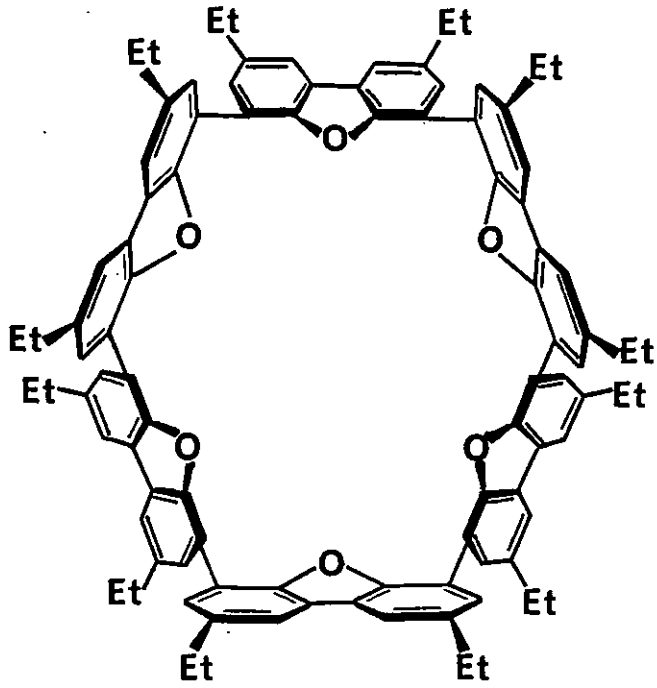
It is interesting to note that compound (38) can exist in two major conformations, the aaaa pictured in the diagram and the eeee where the di-azanaphthalene units have folded down into the plane of the paper. The $\Delta G^{\ddagger}$ for the conformational change has been estimated by ^1H nmr to be about 10 Kcal mol^{-1}. The cavity sizes in the two conformers are very different, the all eeee conformer containing a more extended surface. The eeee is also the more stable conformer in solution at low temperatures. These properties make compound (38) a very unique system in this area of chemistry.

A very recent publication[44] reports the synthesis of some new cavitands based on the dibenzofuran unit. Compound (39) turned out to be a very insoluble material, but compound (41) was a much more amenable molecule. Models of this structure show that it contains two cleft-shaped cavities approximately 12Å long, 3.4Å deep and 4.3Å wide. Some synchronised rotation about the four aryl-aryl bonds seems to be possible and at its limits, narrows the cavity to 3Å. Thus we see here another well-defined, rigid cavity, capable of embracing a molecule the size of methane. The hexabenzofuran (40) has a larger cavity than (41) the dimensions being approximately 11 x 7 x 7Å. A model of this material is capable of incorporating seven



(39) R= H

(41) R= Et



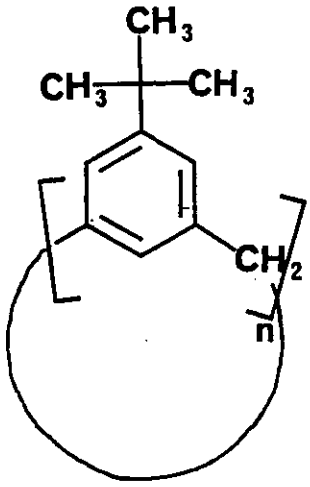
(40)

molecules of benzene. Aryl-aryl bond rotation does reduce the cavity size slightly but even at its limits, four molecules of benzene may be incorporated. The presence of the ethyl groups on (40) and (41) which are potentially functionalisable is an added bonus. Judicious choice of functionality could be used to control solubility properties, to provide binding sites for guests or to act co-operatively in catalysing the reactions of bound guests.

However, having synthesised all these elaborate molecules the next step must be to demonstrate positive binding and to then use the compounds as molecular catalysts.

A class of [1.n]metacyclophanes comprising arrays of phenolic residues attached by methylene groups at the positions ortho to the hydroxyl groups, and called calixarenes, have come into consideration as macrocyclic hosts. The methods to make them are discussed in a paper by Gütsche[45] who managed to synthesise a number of these cyclic oligomers (42). The most useful compound isolated has turned out to be an allyl calix[4]arene (43) in which the cavity has been rigidified by silylation of the phenol hydroxyl groups[46]. This molecule now possesses a rigid cone very similar to a cyclodextrin, and with easily functionalisable sites, further developments are awaited with great anticipation.

Three more potentially important hosts have been recently made[47,48]. The di-oxo[5.1.5.1]paracyclophane (44) and the di-oxo[7.1.7.1]paracyclophane (45) were made from diesters by a Dieckmann condensation[47].



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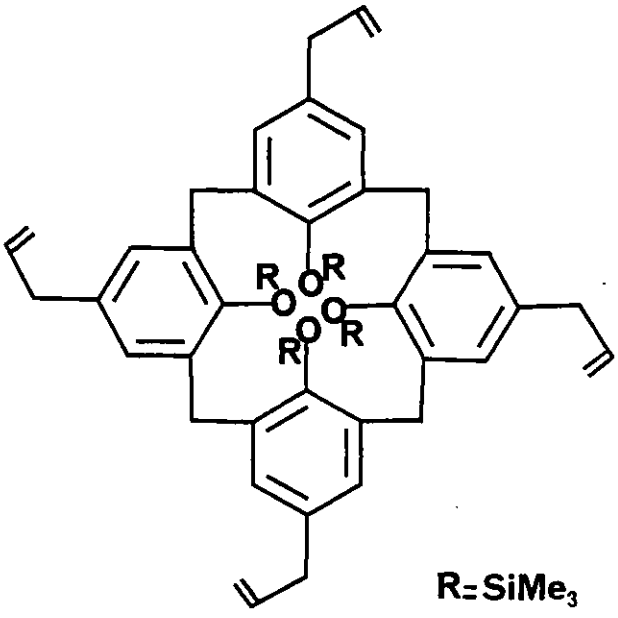

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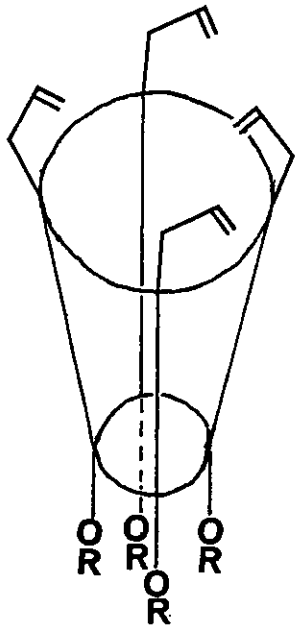
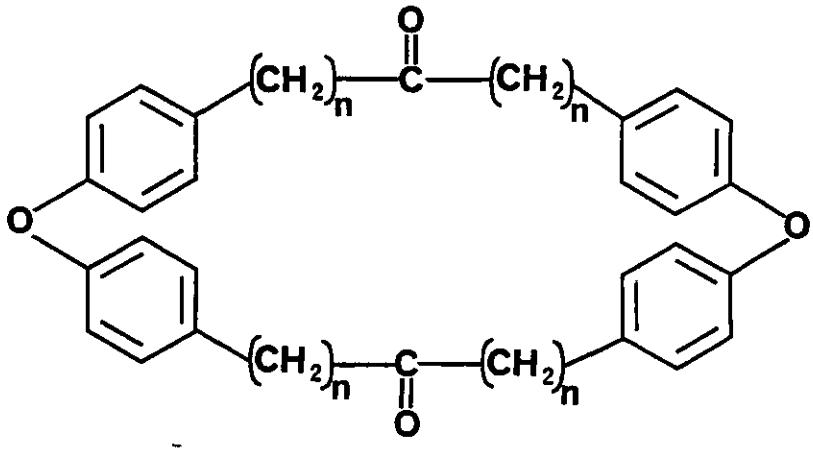


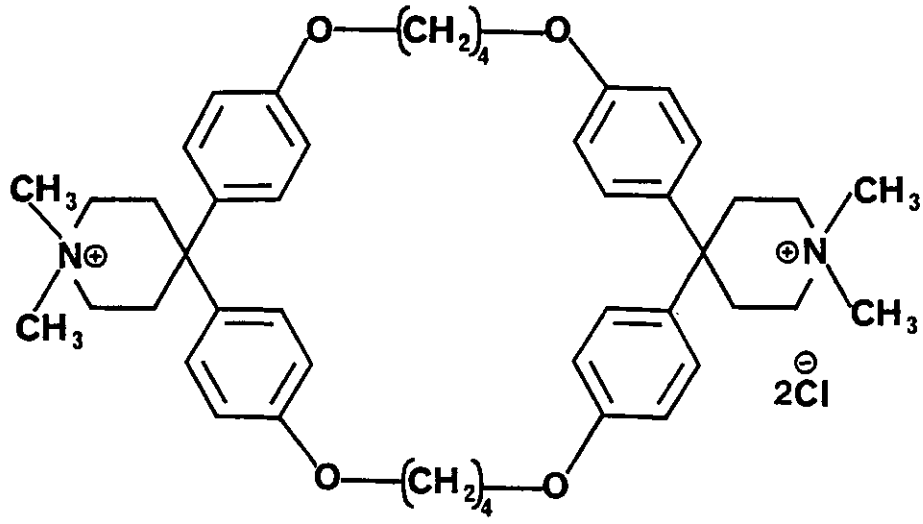
(43) R=SiMe$_3$

Compounds (44) and (45) are not very rigid. At one extreme conformation, (44) contains a cavity of cross-section 6 x 5Å. Compound (45) has a slightly larger void 8 x 5Å in size. Both molecules however, at the other extreme of conformation, contain only very small cavities. Clearly these molecules need to be made more rigid. This could be achieved by additional bridging across the shorter sides of the molecule.



(44) n=2

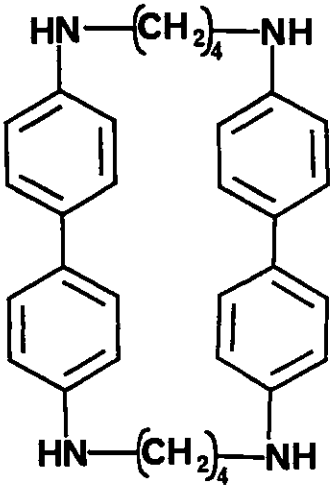
(45) n=3



(46)

Molecule (46) has been shown to contain a hydrophobic binding site[48] by fluorescence and ^{1}H nmr spectroscopy. The charged nitrogen moieties which enable the compound to dissolve in aqueous, neutral media are very remote from the cavity and, it is believed, do not effect the hydrophobic binding site unduly.

Some 30 years ago Stetter described a biphenyl containing tetra-aza[6.0.6.0]paracyclophane (47)[49]. This, he claimed, was able to strongly complex both benzene and 1,4-dioxan within an intramolecular cavity. An X-ray structure published recently[50] shows the benzene complex to be intermolecularly bound. This illustrates the danger of assuming intramolecular complexation without having access to all the evidence.



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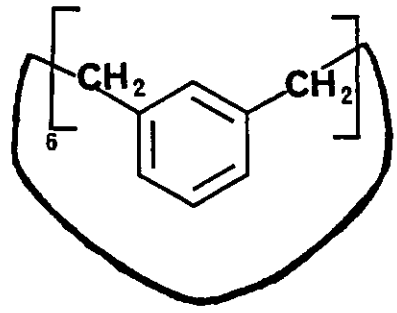
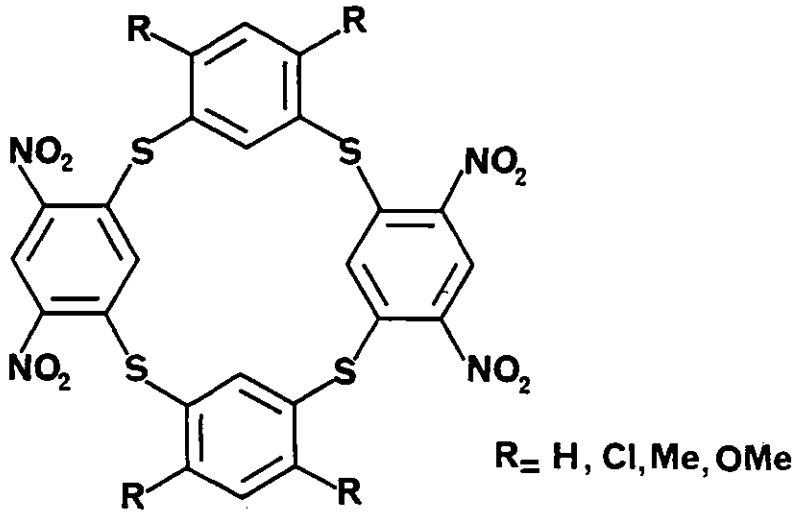


(48)

Finally this review will consider some molecules which are known to form inclusion compounds but whether these are intramolecular complexes or intermolecular clathrates in unclear.

A series of Japanese patents[51,52,53] examines the complexation properties of a metacyclophane (48). This formed inclusion compounds with cinnamaldehyde, cinnamyl alcohol, propylbenzene isopropylbenzene, cyclohexanol, 1,4-dimethylcyclohexane, 1,3-dimethylcyclohexane, and cyclohexanone. Some of these guests could be released by distillation. A thia[1.1.1.1]metacyclophane (242) has also been made[54] and forms stable inclusion complexes with high-boiling polar solvents. However, this is almost certainly an intermolecular interaction.



(242)

In conclusion, host-guest chemistry involving this type of macrocycle is still very much in its early stages but it is pleasing to note the growing impetus in the design and uses of these compounds. Only a few intramolecular inclusion complexes have been definitely characterised but it may be hoped that over the next few years some of the early work described in this review will come to a successful conclusion, and that macrocyclic host-guest chemistry will start to rival the more established fields of cyclodextrins and crown ethers.

CHAPTER 2

SYNTHESIS OF CATECHOLIC SIDEROPHORES

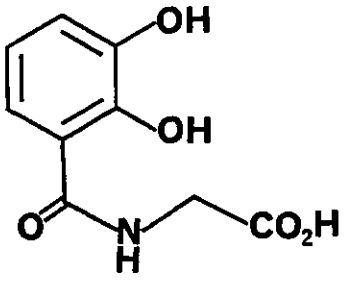
Siderophores are nonporphyrin, nonprotein, iron-containing, or iron-binding compounds derived from bacteria, fungi, and microalgae. Apart from their role as high affinity iron transporters, siderophores may act as growth or germination factors, and some are potent antibiotics. They have found clinical use as iron chelation agents for iron overloaded patients[55], this being a troublesome and often very serious condition in people under treatment with regular blood transfusions.

Siderophores may be divided into two broad classes, the hydroxamic acid type exemplified by the ferrichromes, rhodotorulic acids, mycobactins and the fusarinines, and the catecholate types such as enterobactin (49).

Whilst reviews[56,57,58,59] have appeared on various aspects of siderophores, and on the more general topic of microbial iron compounds[60], little systematic coverage has occurred on the synthesis and properties of naturally derived or wholly synthetic catecholates, and the purpose of this survey is to fill this gap.

In 1958 it was found that cultures of *Bacillus subtilis* when grown under conditions of iron deprivation, excreted a ferric-ion binding agent into the medium[61]. This material was crystallised and eventually identified as 2,3-dihydroxybenzoylglycine (50).

The final structural proof came from a synthesis of the material by a dicyclocarbodiimide (DCC) coupling between 2,3-dihydroxybenzoic acid and the ethyl ester of glycine, followed by ester hydrolysis. Publication of this work marked the start of the subsequent investigations into catecholate chemistry.



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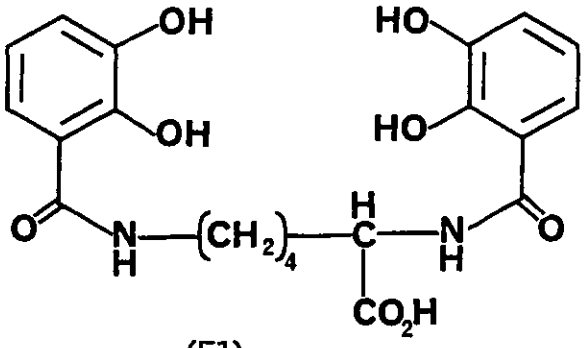


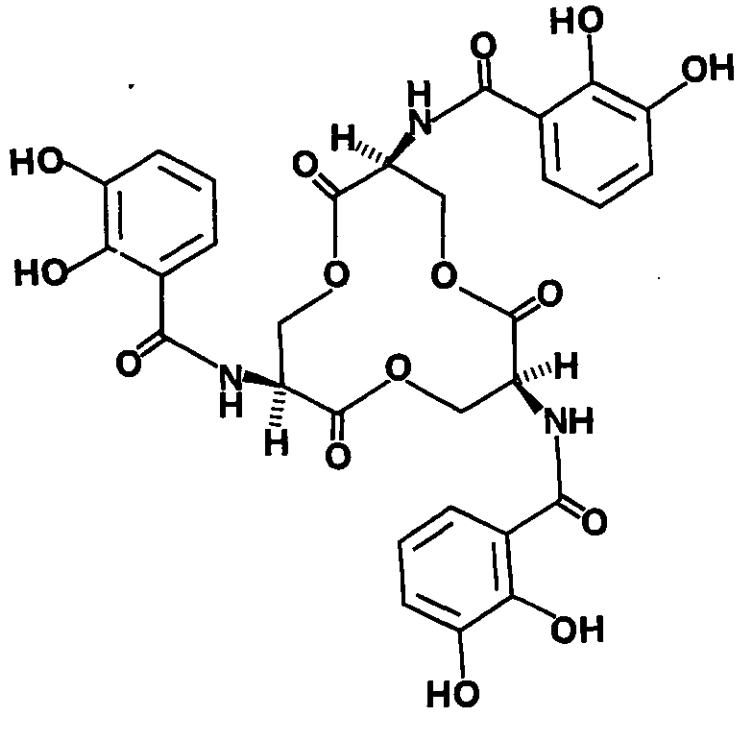
(51)

Corbin and Bulen[62], whilst investigating the nitrogen fixing species *Azobacter vinelandii* in iron-deficient media, isolated two fluorescent phenolic compounds. One was identified as 2,3-dihydroxybenzoic acid, whilst the other was eventually shown to be N,N' di-(2,3-dihydroxybenzoyl)-L-lysine (51). This material was also synthesised by a DCC coupling, this time of 2,3-diacetoxybenzoic acid and L-lysine methyl ester dihydrochloride, followed by ester hydrolysis. This substance has turned out to be of a special significance since it was isolated from a nitrogen fixing species. As nitrogenase is

endowed with a rich complement of iron, it is possible that this particular siderophore is involved in the biosynthesis of this very important enzyme.

In 1970 two independent groups isolated and characterised the best known example of this class of compounds, enterobactin (49), from cultures of *Escherichia coli*[63] and *Samonella typhimirium*[64]. The structure is a macrocyclic trimer of 2,3-dihydroxy-N-benzoyl-L-serine (DBS) (52), and has been shown to be the most powerful chelator of iron(III) yet discovered. A spectrophotometric study reports a formation constant of 10^{52} l mol^{-1} for enterobactin, this being some 7-12 log units greater than the overall formation constants of a whole series of monocatecholates also examined, and some 20-30 log units larger than any of the hydroxamate siderophores [65,66,67]. This massive stability constant makes enterobactin (49) thermodynamically capable of removing iron from transferrin (the mammalian iron transport protein). This is also a kinetically favourable process, but the use of the molecule in chelation therapy is unfortunately precluded by its extreme lability[68].

The compound (49) is utilised by enteric bacteria to transport iron across the cell membrane. As it binds so strongly to the metal ion, the enterobactin has to be hydrolysed inside the cell to release the iron. Thus each enterobactin molecule only makes one journey through the cell wall.



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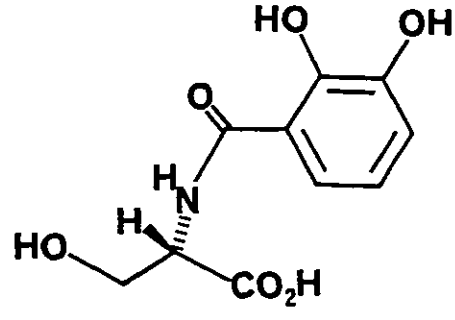
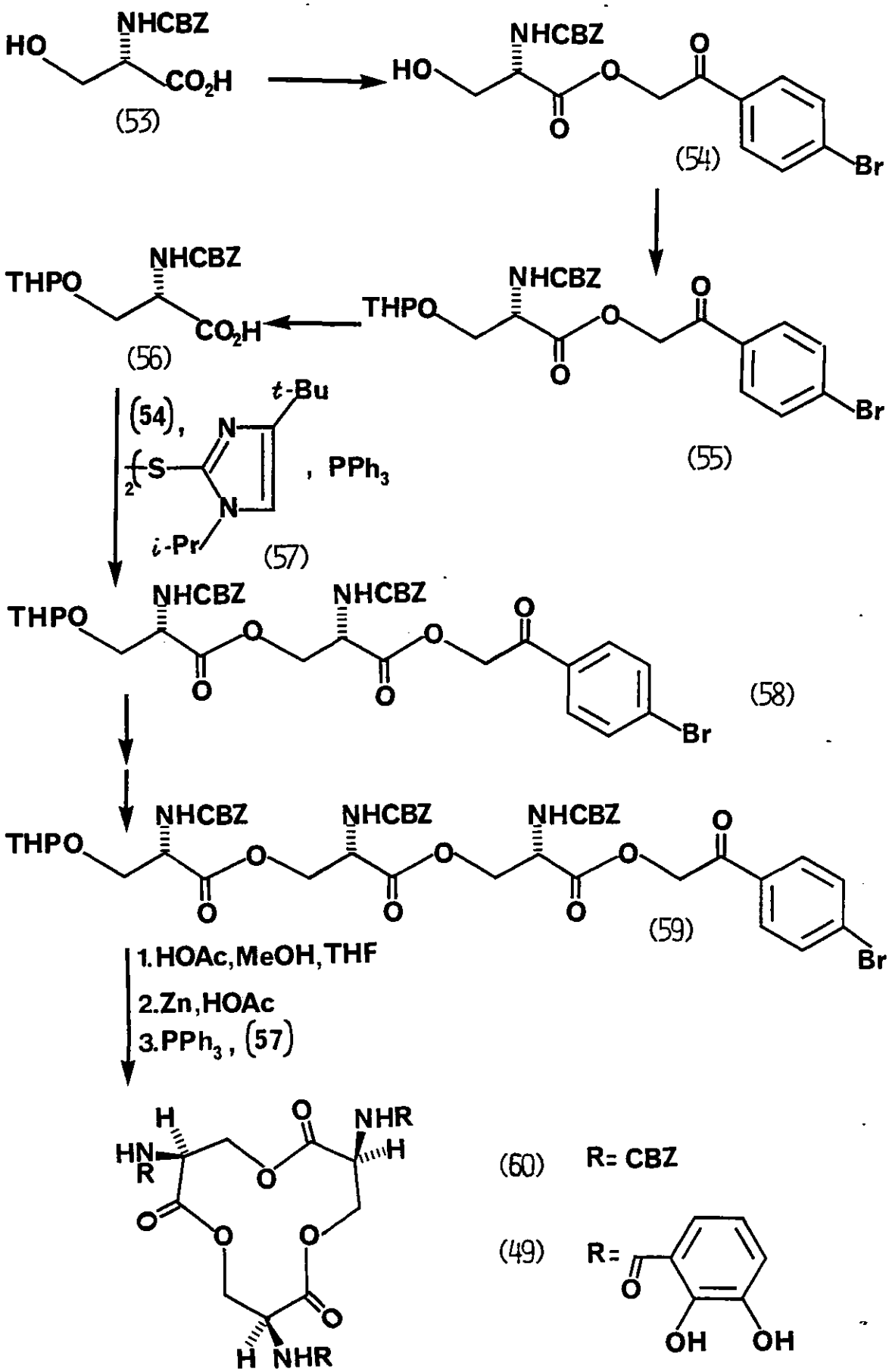


(52)

The first synthesis of enterobactin (49) was achieved by Corey[69] and started from N-benzyloxycarbonyl-L-serine (53) (Scheme 4). Conversion of compound (53) to the 4-bromophenacyl ester (54) was followed by reaction with dihydropyran to give the completely protected serine derivative (55). Reductive cleavage of the phenacyl group by zinc dust in aqueous acetic acid afforded the O,N-protected amino acid (56). This product was coupled with the hydroxy ester (54) in the presence of disulphide (57) and triphenylphosphine to give the diserine derivative (58). The procedure was essentially repeated to give the triserine compound (59). Deprotection of the terminal acid and alcohol functions left the way clear for macrocyclisation[70] mediated by triphenylphosphine and the disulphide (57) to yield the


NHCBZ
HO
CO2H
(53)
HO
NHCBZ
O
O
O
(54)
Br
THPO
NHCBZ
CO2H
(56)
THPO
NHCBZ
O
O
O
Br
(55)
(54),
t-Bu
N
S
2
N
i-Pr
, PPh3
(57)
THPO
NHCBZ
NHCBZ
O
O
O
O
O
Br
(58)
THPO
NHCBZ
NHCBZ
NHCBZ
O
O
O
O
O
O
O
Br
(59)
1. HOAc, MeOH, THF
2. Zn, HOAc
3. PPh3, (57)
H
HN
R
O
NHR
H
O
O
O
O
O
H
NHR
(60) R= CBZ
(49) R=
O
OH
OH

SCHEME 4

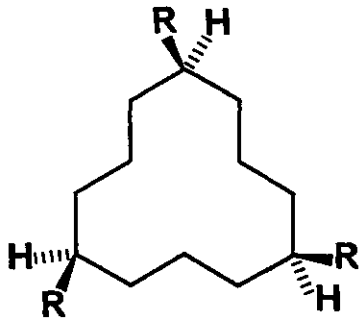
tri-N-protected cyclic triester (60). This compound was deprotected and reacted with the acid chloride of 2,3-dihydroxybenzoic acid, to give enterobactin (49).

The synthesis is a long and tedious one relying as it does on protecting group strategies. The cyclisation step to give the triester (60) is a good illustration of the double activation method of macrolactonization and proceeds in the workable yield of 40%.

The second reported synthesis of enterobactin (49) by Rastetter *et. al.*[71] is not fundamentally different in strategy to the Corey procedure. The only major differences comes in their choices of protecting groups for the acid moiety for which the second synthesis employs a methyl anthraquinone group. This second synthesis has also been used to produce enantioenterobactin, the antipode of enterobactin (49), based on D-serine. It is interesting to note that the enantio-species fails to support the growth of *E. coli* mutants[72]. This indicates an outer membrane receptor specificity for the L-seryl backbone.

Enterobactin (49) has been intensively studied because of the interest in the mechanism of uptake of iron by bacteria. However, as already mentioned, the molecule in itself is not very useful as a therapeutic agent due to its instability at physiological pH's. Thus, a great deal of effort has been directed at preparing analogues of this compound.

Corey's[73] group has synthesised the carbocyclic equivalent of the compound (62). The all *cis*-cyclododecane-1,5,9-triol (63), was converted to the tris tosylate (64) and treated with sodium azide in N,N-dimethylformamide to give a tris azide (65). Catalytic hydrogenation led to the triamine (66) which was acylated with the acetonide of 2,3-dihydroxybenzoyl chloride (67). The triamide (68) was deprotected in refluxing 80% acetic acid to leave the desired analogue (62).

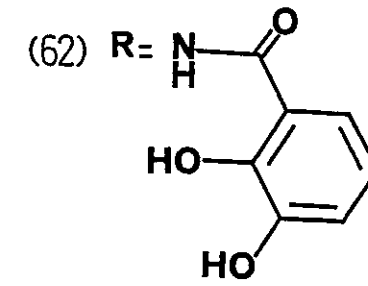


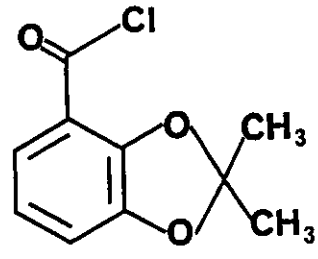
(63) R= OH

(64) R= OTs

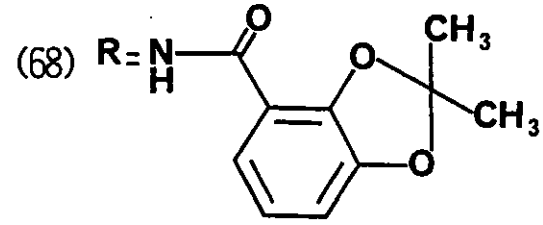
(65) R= N_3

(66) R= NH_2



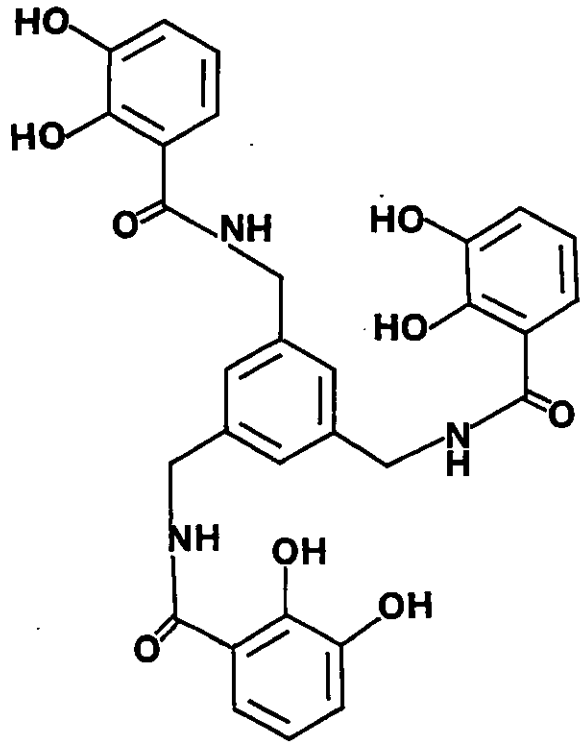


(67)

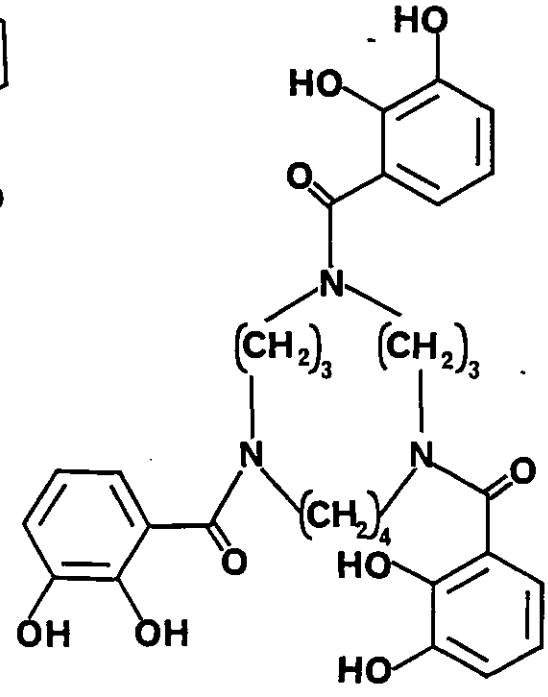


The resultant compound (62) was also shown to be an extremely powerful binder of iron, and proved to be about 75% as effective as enterobactin (49) in bacterial iron transport. However the compound (62) has not yet found widespread use in iron chelation therapy.

Futher investigation how centred around two new analogues (69) and (70).

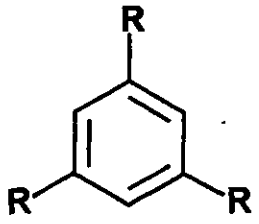


(69)



(70)

The mesitylene derivative (69) was reported almost simultaneously by two different groups. Raymond's[74] synthesis of the compound started from 1,3,5-trichlorocarbonylbenzene (71), which was converted to the triamide (72) with ammonium hydroxide solution. Diborane reduction gave the triamine (73) which was acylated with 2,3-dimethoxy-



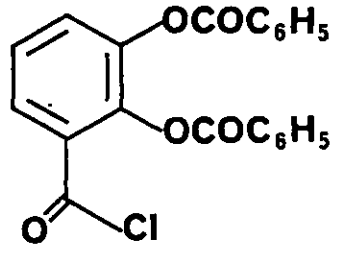
(71) R= COCl

(72) R= $CONH_2$

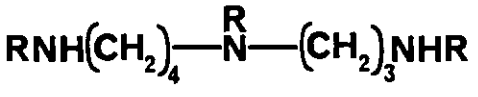
(73) R= CH_2NH_2

(74) R= CH_2NHC(=O)–(2,3-dimethoxyphenyl)

(75) R= CH=NOH

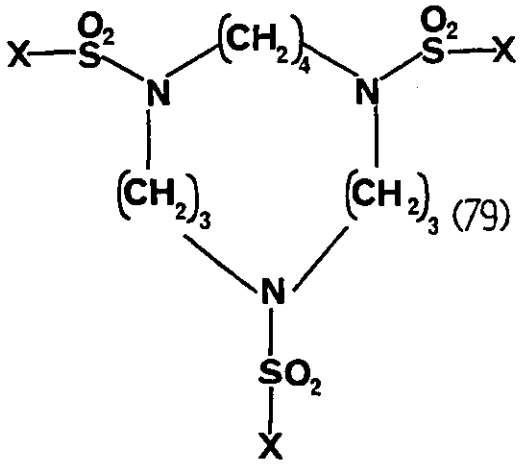


(76)



(77) R= H

(78) R= SO_2–(4-methylphenyl)



(79) X= (4-methylphenyl)

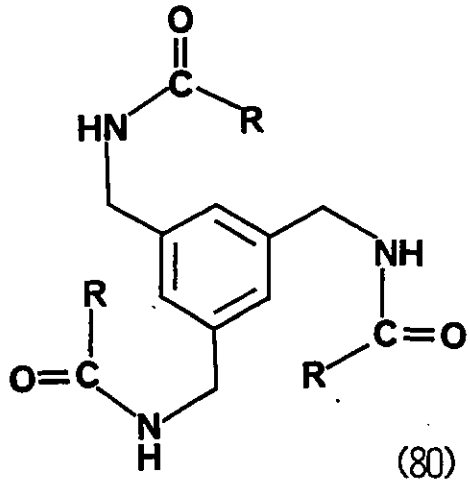
benzoyl chloride to produce the protected triamide (74). Demethylation with boron tribromide in dichloromethane yielded the desired compound (69). Neilands'[75] route started from 1,3,5-benzenetrialdoxime (75) which was catalytically reduced to give Raymond's triamine derivative (73). This in turn was acylated with 2,3-dibenzyloxybenzoyl chloride (76) and the resultant material hydrogenated to produce the desired analogue (69).

The tricatecholate (70) has been prepared[76] starting from spermidine (77). Tritosylation of this triamine was performed, and the resultant compound (78) was treated with two equivalents of sodium hydride and 1,3-di-(4-toluenesulphonoxy)propane in N,N-dimethylformamide to give the cyclised compound (79) in 76% yield. Detosylation, acylation and deprotection led to the desired ligand (70).

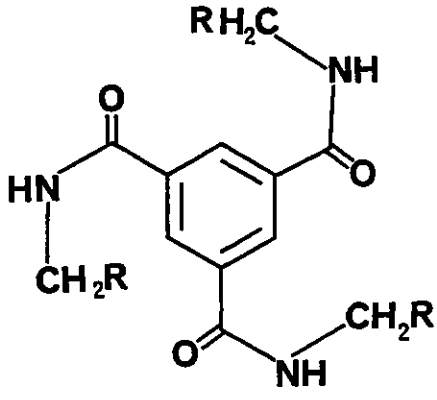
The two compounds (69) and (70), although different with respect to the rigidity of their cyclic backbones, both have a massive affinity for ferric ions. The formation constant[77] for the ferric complex of the mesitylene derivative (69) has been estimated as 10^{46} l mol^{-1}. The compound with the cyclised spermidine backbone (70) has a somewhat smaller fomation constant of 10^{40} l mol^{-1}, this being due to the fact that at high pH, the ligand coordinates through only five of the phenolic oxygens, probably due to steric strain resulting from its endocyclic amide structure. The compounds are both totally resistant to hydrolysis over a wide pH range, and they are also able, like enterobactin (49), to remove significant amounts of iron from transferrin under conditions where the hydroxamates are totally

ineffective[68]. The compounds were considered promising candidates for iron overload therapy and were used for clinical trials.

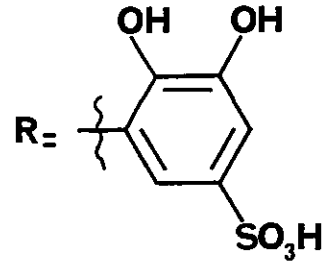
Sulphonation of compound (69) in 30% fuming sulphuric acid gave the sulphonic acid (80) in 50% yield[78]. The trisulphonic acid (81) was made by unremarkable means from the tricarboxylic acid



(80)



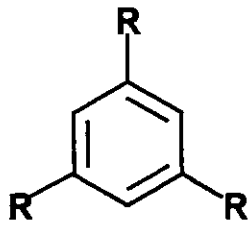
(81)

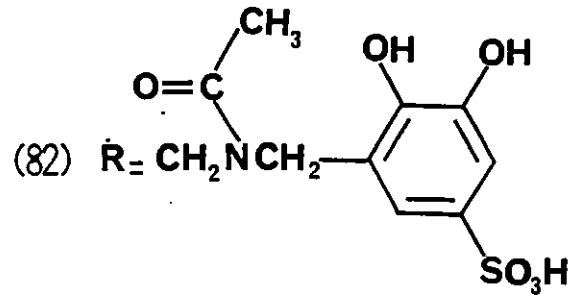


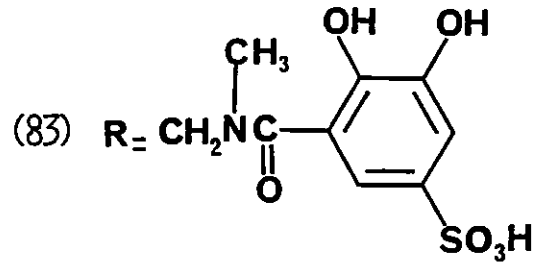
chloride (71). The sulphonation of these tricatecholates favourably

modified the properties of the ligands. They became water-soluble, much more resistant to air oxidation than their unsulphonated analogues, and were found to be hydrolytically stable over a wide pH range. The lower ligand protonation constants of the sulphonated catecholates enhanced their effectiveness at physiological pH[79]. These sulphonated analogues of enterobactin are also the subject of animal tests for their *in vivo* efficacy.

Two further tertiary nitrogen containing, sulphonated analogues

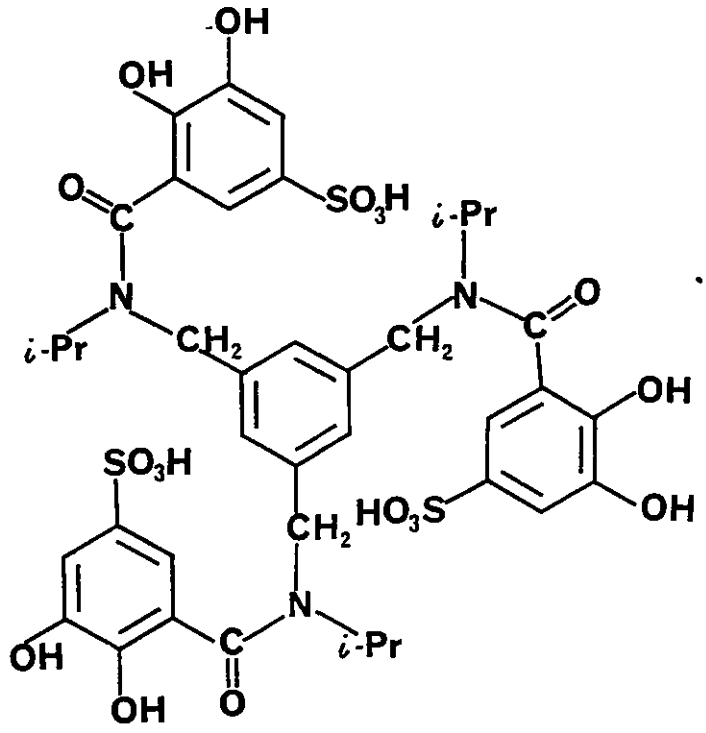






have been prepared[80]. Compounds (82) and (83) contain modifications in order to protect them from nonspecific peptidase activity in the body. Compound (83) is able to mobilise iron from ferritin even in the presence of ascorbate, which is administered with iron sequestrating agents. An unusual property of compound (82) is that one catechol dissociates from the iron(III) at low pH to form a bis-chelating species.

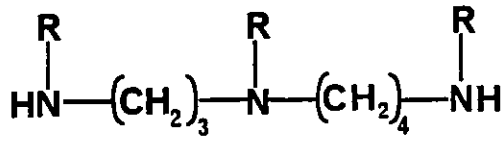
Apart from chelating with ferric ion, enterobactin (49) also forms complexes with chromium(III)[81] and rhodium(III)[82] species. This observation has led to the use of some sulphonated analogues to sequestrate other metals[83]. Ligand (84) has been found to bind both



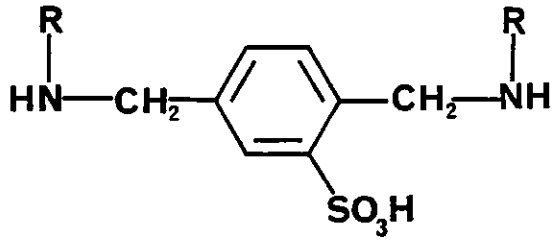
(84)

gallium and indium and the complexes have been used as radioactive tracers *in vivo*. Formation constants for the metal complexes are of the order of 10^{40} l mol^{-1}. It is anticipated that modifications of these ligands will lead to even more useful compounds. At present these complexes show an affinity for the excretory organs, such as the kidneys, but planned alterations to the structure, it is hoped, will increase their affinity for nonexcretory organs. The compound (84) has also been found not to be acutely toxic but no LDS data is available.

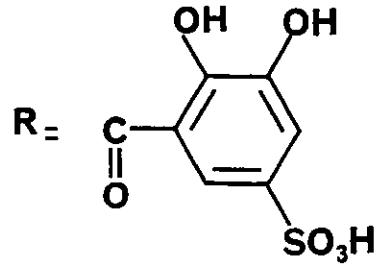
Turning next to synthetic, linear catecholates, it can be seen that much work has been done with the spermidine (77) skeleton. The first compound of this type described was the trisulphonated derivative (85)[78] which was made, much as one would expect, by condensation of a catechol protected acid chloride with spermidine (77) itself. Deprotection and sulphonation gave the linear tricatecholate (85) in good yield. The dicatecholate (86) was prepared[78] by condensation of 1,4-xylylenediamine (164) with 2,3-dimethoxybenzoyl chloride. Again a sequence of deprotection and sulphonation gave compound (86) in respectable yield. The compounds proved to be unremarkable in their



(85)

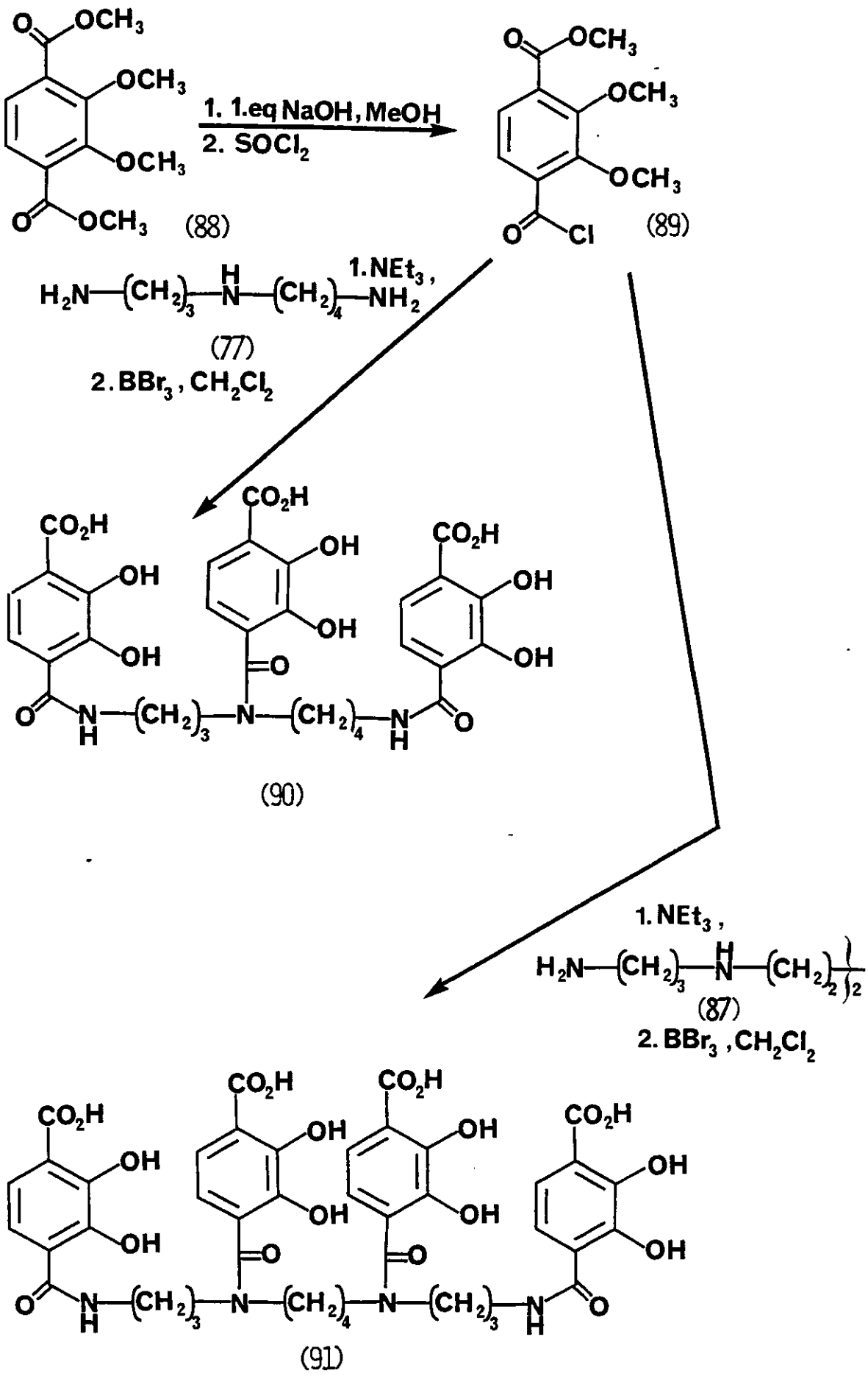


(86)



properties, chelating with ferric ion very readily, but no better than any of the other analogues described thus far. However compound

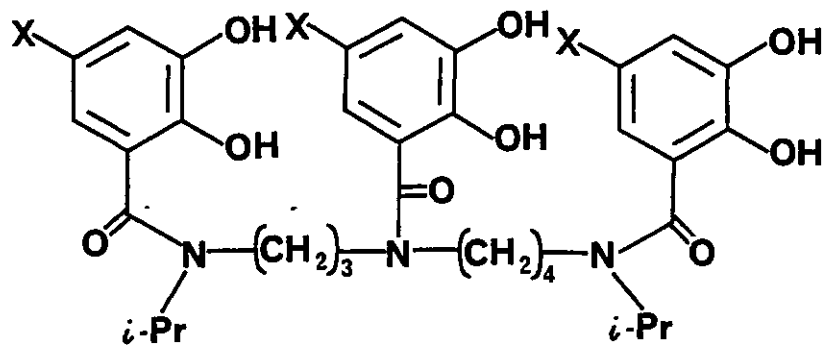
SCHEME 5


1. 1.eq NaOH, MeOH
2. SOCl2
(88)
(89)
1. NEt3,
(77)
2. BBr3, CH2Cl2
(90)
1. NEt3,
(87)
2. BBr3, CH2Cl2
(91)

(85) proved important in that modifications to the structure led to a series of sequestrating agents for ferric ion and plutonium(IV) that were active *in vivo*. Addition of a carboxylic acid group in position 4 of the catechol, instead of the sulphonic acid in position 5, led to these new compounds. Both the triamine, spermidine (77), and the tetraamine, spermine (87), were used in this study[84].

Although unremarkable the synthesis is notable for the selective mono hydrolysis of a diester, a useful but difficult transformation to achieve. Both compounds (90) and (91) proved efficacious in removing injected plutonium from mice. The spermine derivative (91) is in fact the most effective compound of this type to date. The spermidine tricatecholate (90) is also a good sequestrator of plutonium but lacks the ability to fill all the metal's coordination sites. However, compound (90) is also a very good chelator of iron, and is able to remove ferric ion from saturated human transferrin at essentially the same rate as enterobactin (49). These compounds have shown no observable signs of toxicity and are the most promising candidates yet devised for metal chelation therapy.

A series of compounds have been made from spermidine (77) by the selective reductive alkylation of the terminal nitrogen atoms. This was achieved by Schiff base formation with aldehydes and ketones followed by catalytic hydrogenation. The resultant compounds were acylated and deprotected in the usual manner[85]. One of these compounds (92), has proved to be a very useful radioactive tracer in conjunction with gallium and indium in much the same way as compound (84)[83]. Sulphonation of (92) gave the derivative (93) which was also used in tracer studies.

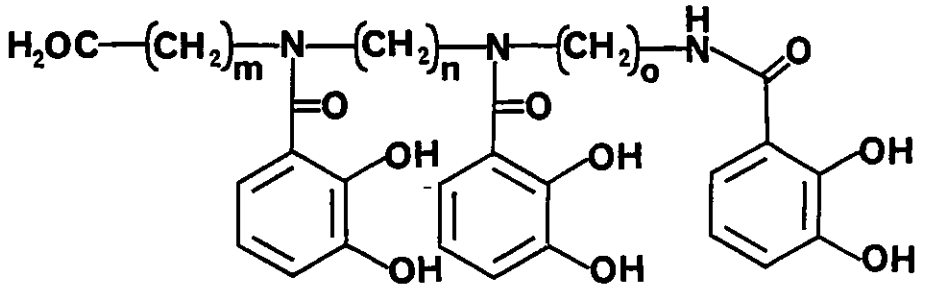


(92) $X = H$

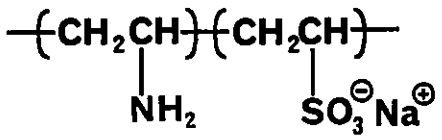
(93) $X = SO_3H$

An interesting variation to the ligands described above comes in the shape of polymerically mounted catechol derivatives[86]. Linear tricatecholates (94) were prepared and mounted on a random copolymer, poly(vinyl amine-vinyl sulphonate sodium salt) (95).

The pM values for all these polymeric adducts, and for a polymeric monocatecholcarboxamide (96) that was also prepared, showed that they could all bind to ferric ion more tightly than the iron protein transporter, transferrin. However none were as effective as desferrioxamine B, the currently used clinical drug, or enterobactin (49). Of the polymers, compound (96) possessed the highest binding affinity. Biological testing of this polymer is now in progress.



(94) m,n,o = 3-5



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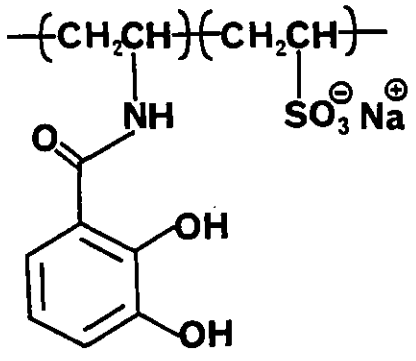
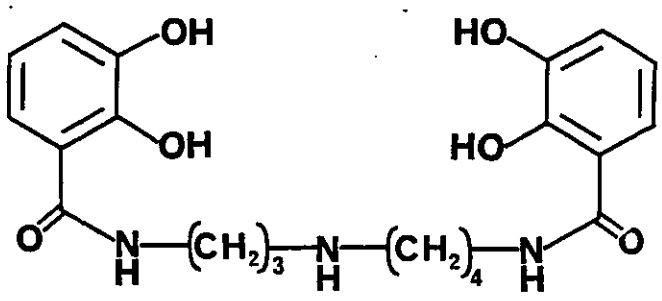
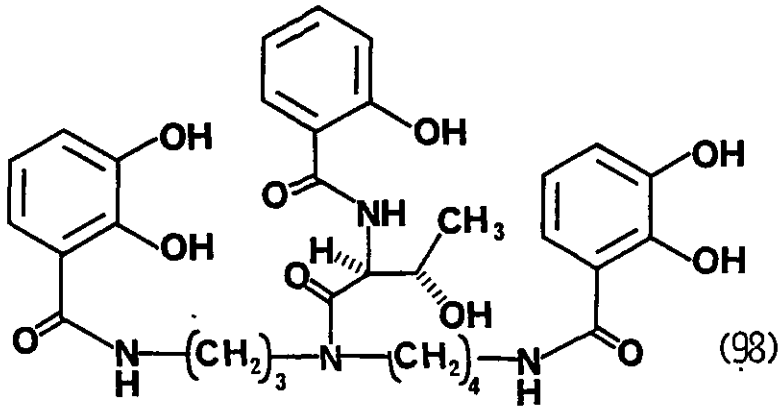


(96)

Naturally occurring linear catecholate siderophores have also been isolated and synthesised in recent years. Tait isolated two new compounds from *Micrococcus denitrificans*[87] to which he tentatively assigned the structures (97) and (98).



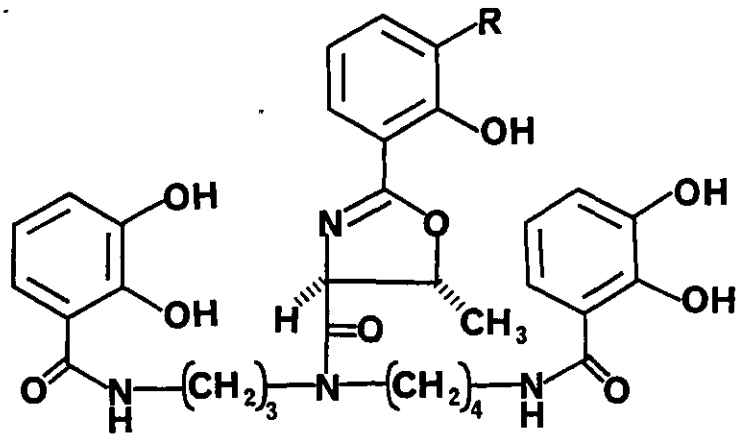
(97)



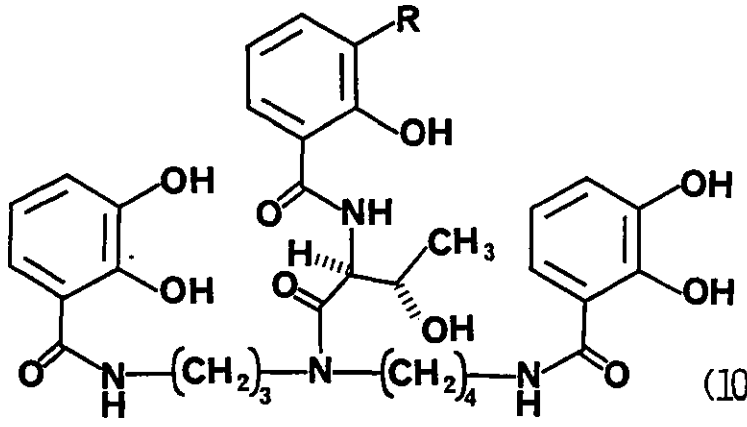
(98)

Agrobactin (99), a siderophore from *Agrobacterium tumefaciens* was discovered by Nielands[88]. He also reinvestigated Tait's compound (98) and has reassigned the structure, calling the molecule parabactin (100)[89]. The two compounds vary only in the number of hydroxy groups they contain.

Synthesis of agrobactin A (101), the hydrolysis product of agrobactin (99), confirmed the structure of the natural product[90]. 2,3-Dibenzyloxybenzoic acid, was converted into its imidazole ester (102). This was then added to a solution of spermidine (77) in triethylamine and chloroform to give the $\underline{N}^1,\underline{N}^8$-acylated spermidine derivative (103). The 50% yield obtained represents a useful

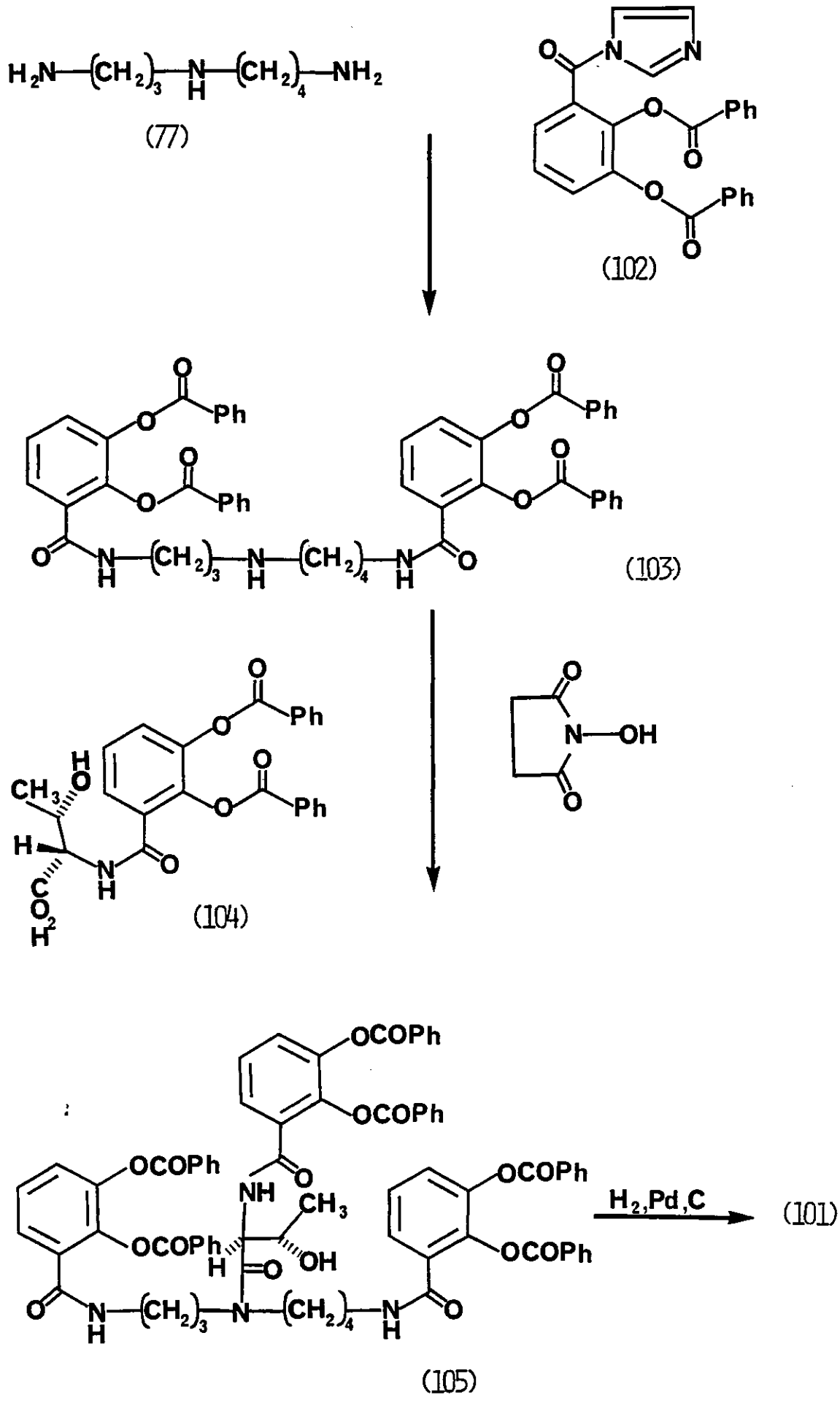


(99) R = OH
(100) R = H



(101) R = OH
(98) R = H

selectivity of acylation, presumably due to steric reasons, at a primary centre over a secondary one. The bisacylated compound (103) was coupled with N-(2,3-dibenzyloxybenzoyl)-L-threonine (104) in the presence of N-hydroxysuccinimide. The hexabenzyl agrobactin A (105) was converted to agrobactin A (101) by catalytic hydrogenation. The material proved identical in every respect to the hydrolysis product of agrobactin (99) itself. The crystal structure of the



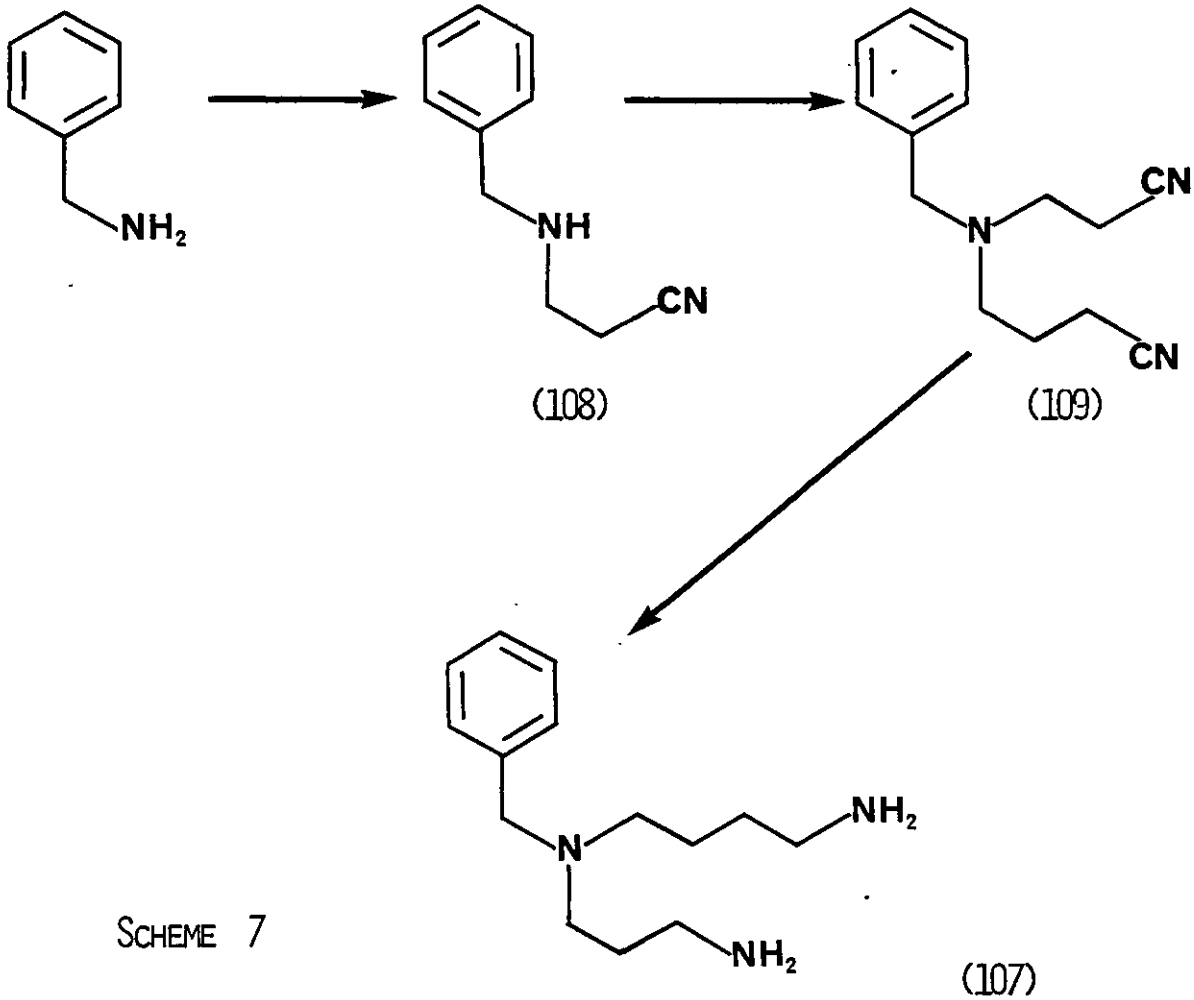
SCHEME 6

compound (99) was determined soon afterwards[91], and confirmed the presence of the oxazoline ring.

A completely different approach to the problem of selective acylation of spermidine (77) to that used by Neilands[90], was proposed by Bergeron[92]. Instead of finding ways of selectively acylating the primary amine functions of spermidine (77) itself, he synthesised an N^4-blocked spermidine derivative (107). The first step, cyanoethylation of benzylamine with acrylonitrile, proceeded smoothly at room temperature. The resulting N-(2-cyanoethyl)benzylamine (108) was easily alkylated with 4-chlorobutyronitrile using potassium carbonate as base. This bis(nitrile) (109) was reduced with a mixture of lithium aluminium hydride and aluminium chloride to give N^4-benzylspermidine (107). Acylation, followed by N^4-deblocking and catechol deprotection, gave one of Tait's[87] original siderophores (97). This latter material has been shown to be less toxic than aspirin, and to be absorbed across intestinal walls, i.e. it is an orally efficacious compound[93]. It has also been shown to be more effective than the currently used desferrioxamine at clearing iron from overloaded rats.

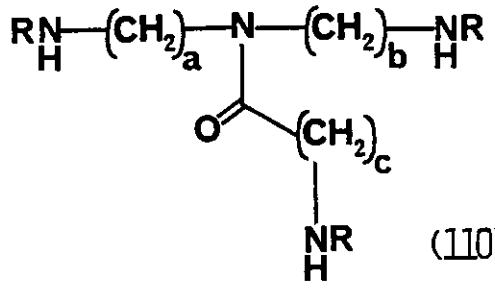
Bergeron[94] has shown the flexibility of his synthetic method by making various polyamine catecholamides of differing chain lengths (110) and (111).

A potential problem encountered in several syntheses using this type of methodology is to remove catechol protecting groups on N^1

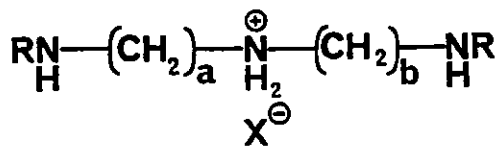


(108) (109) (107)

SCHEME 7

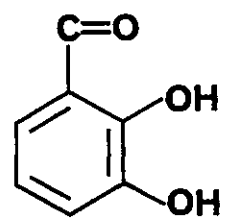


(110)

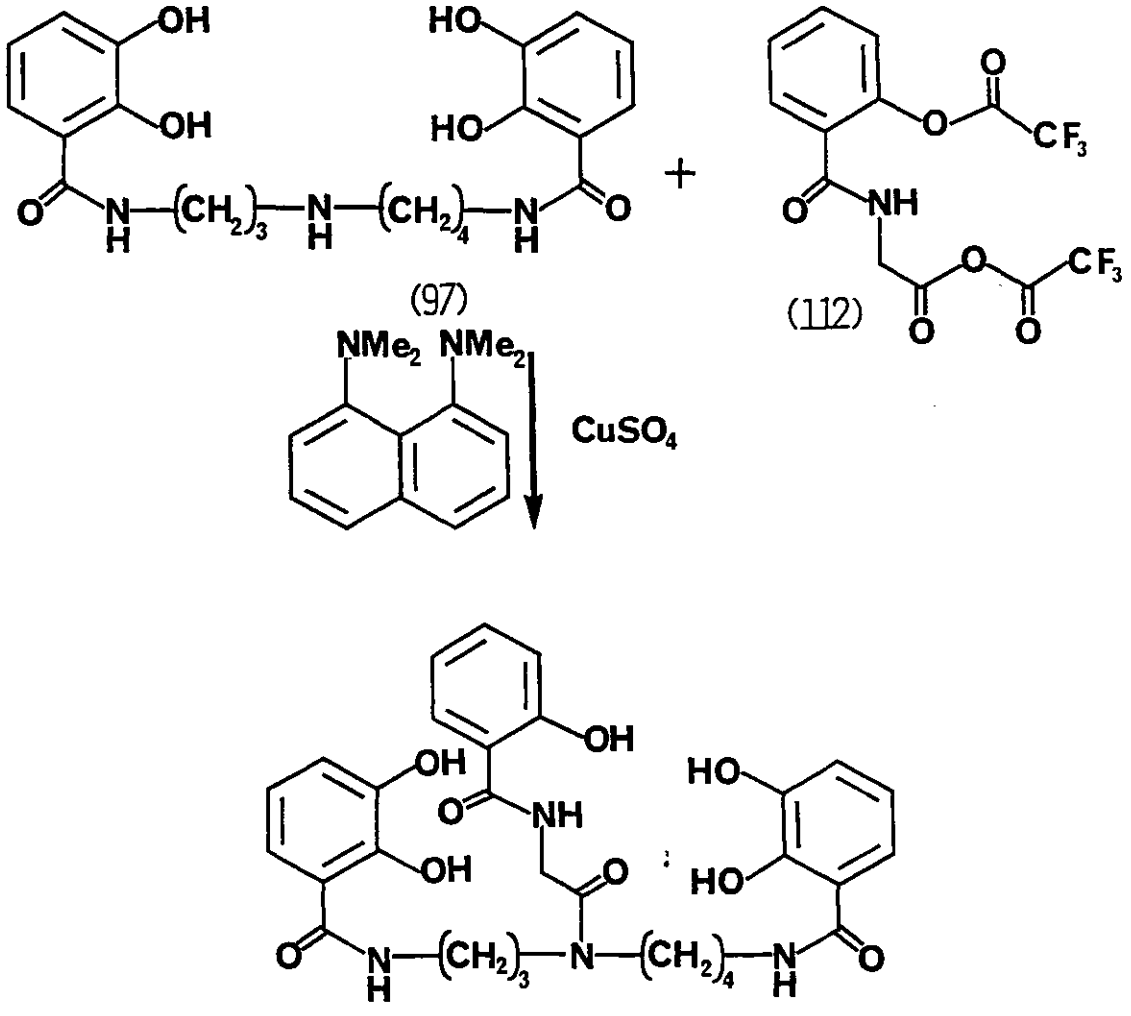


(111)

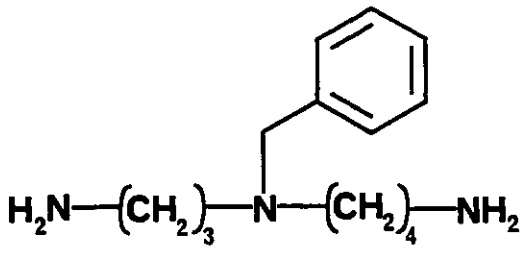
R=



and N^8 without damage to sensitive groups attached to N^4 of spermidine (77). This problem has been overcome by deprotection of the N^1 and N^8-catecholamides before the introduction of an acyl group at the N^4 position. As the free hydroxyl groups could potentially complicate the reaction, copper(II) ions are introduced which provide an *in situ* protection. In this way compound (97) was reacted with N-[2-(trifluoroacetoxy)benzoyl] glycyltrifluoroacetic anhydride (112) in the presence of copper sulphate and 1,8-bis-(dimethylamino)-naphthalene to give the triacylated compound (113) directly in 70% yield[95] (Scheme 8).



SCHEME 8



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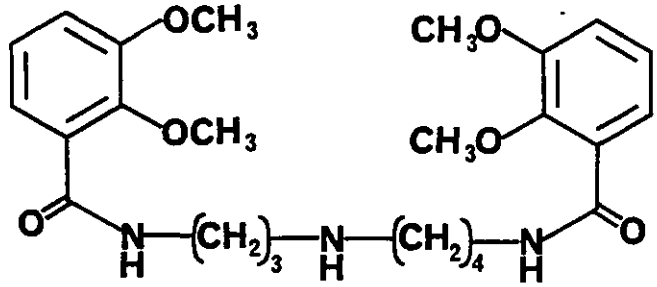
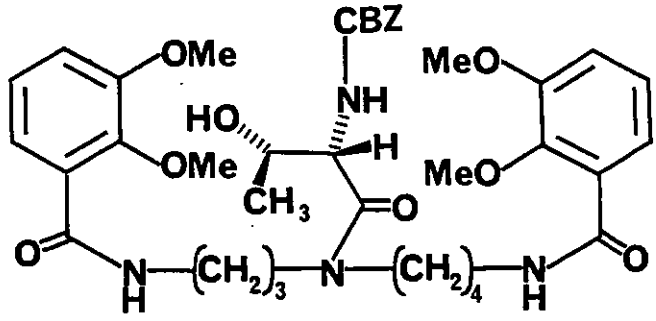


(114)



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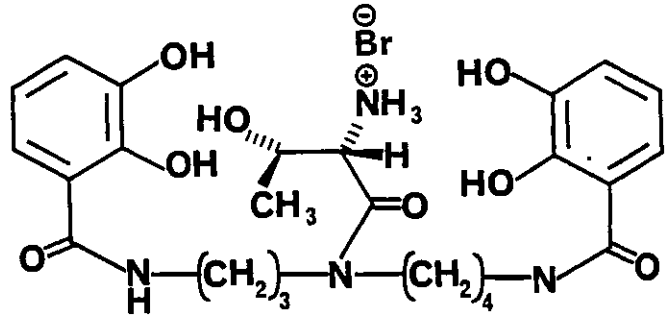

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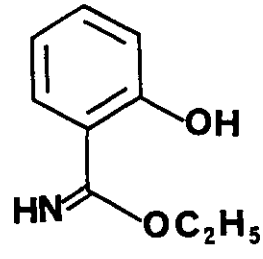


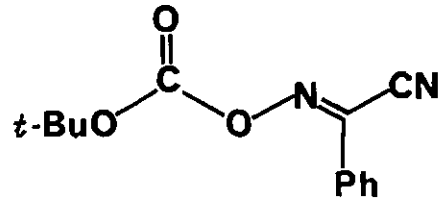
(117)

(100)

SCHEME 9

This synthetic strategy has been applied to a synthesis of parabactin (100)[96]. Starting from N^4-benzylspermidine (107), acylation with 2,3-dimethoxybenzoyl chloride, followed by catalytic hydrogenation leads to N^1,N^8-bis-(2,3-dimethoxybenzoyl)spermidine (114). This compound was coupled with N-carbobenzoxy-L-threonine via the N-hydroxysuccinimide ester to give the trisacylated product (115) in 90% crude yield. Removal of the carbobenzoxy group by catalytic hydrogenation, followed by demethylation gave compound (116). Condensation of compound (116) with 2-hydroxybenzimino ethyl ether(117) in methanol led directly to the natural product (100) (Scheme 9).

Selective acylation of the N^4 position of spermidine can be performed by reacting N^4-benzylspermidine (107) with the carbonate (118)[97]. This leads to the biscarbamate (119) which can be hydrogenated to unmask the N^4 site for acylation. The carbamate groups can be removed by use of trifluoroacetic acid.



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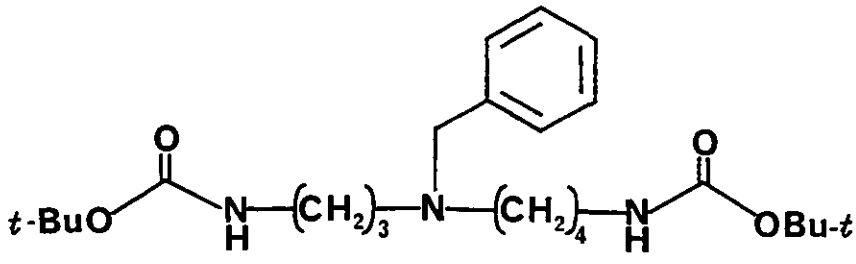
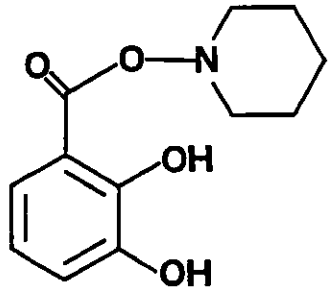


(119)

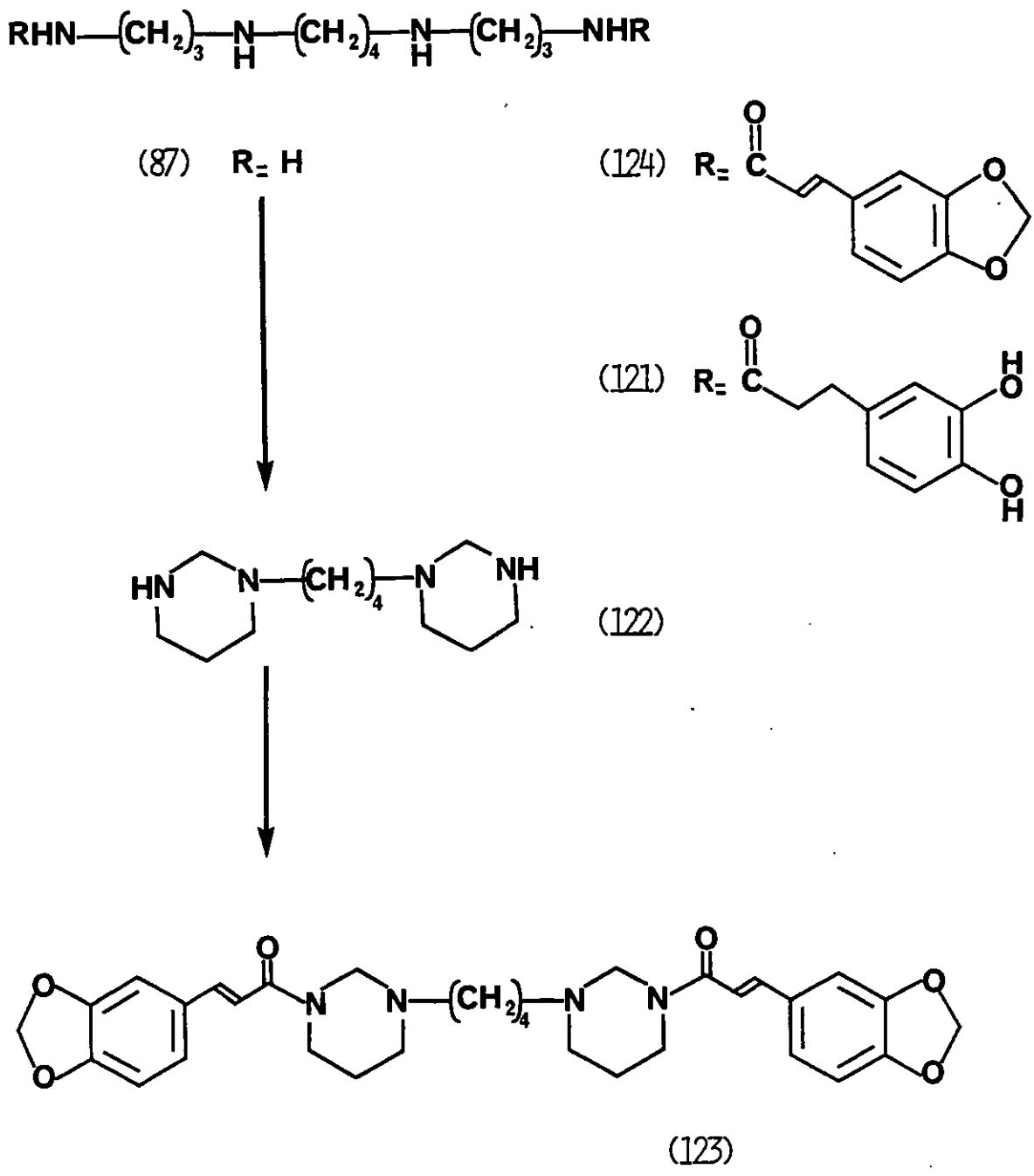
A very recent publication[98] has shown a further way of selectively acylating the $\underline{N}^1$ and $\underline{N}^8$ positions of spermidine (77). The active ester (120), prepared in two steps from 2,3-dihydroxybenzoic acid in 75% yield,followed by treatment with spermidine (77) gives directly the required bisacylated compound (97) in 55% yield. This represents a significant improvement over the Neiland's method[90], which had to resort to the use of protecting groups, and their concomitant disadvantages.



(120)

Natural products derived from spermine (87) have also come under scrutiny. Kukoamine A (121), an antihypertensive constituent of *Lycium chinense*, has been synthesised[99]. Direct acylation of spermine (87) occurs randomly and affords a mixture of products. A method had to be found to acylate only the primary positions of this polyamine (Scheme 10). Tandem protection of the two 1,3-diaminopropyl groups occurred on treatment of compound (87) with aqueous formalin solution leading to the crystalline bis-hexahydropyrimidine (122). Acylation with 3,4-methylenedioxycinnamoyl chloride led to compound (123). Deprotection was achieved by a Knoevenagel reaction and the resultant caffeoylspermine derivative (124) reduced, and deprotected

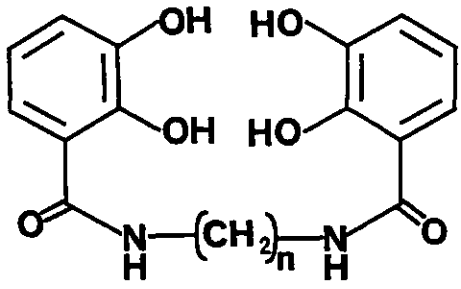
to give (±) kukoamine A (121) in an overall yield of 62%.



SCHEME 10

Linear diamines have also been functionalised with catechols[100]. A series of compounds (125) were made by heating the relevant diamine

with potassium carbonate and the acid chloride (126). These compounds were not found to be of any use in the treatment of iron overload.



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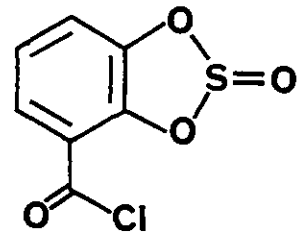


(126)

Synthetic and natural catecholates have attracted a good deal of attention because of their potential use as pharmaceuticals. A vast range of compounds now exist that are potently capable of complexing ferric ion and other metals, and some of these should find their way into widespread clinical use over the next few years, for treatment of all types of metal overload, including both chronic and acute iron poisoning.

The synthesis of linear catecholates, in addition to providing more potential drugs, has developed the selective acylation chemistry of some very important linear polyamines. It is to be hoped that some of the chemistry described here will lead to many more interesting polyamine containing compounds.

CHAPTER 3

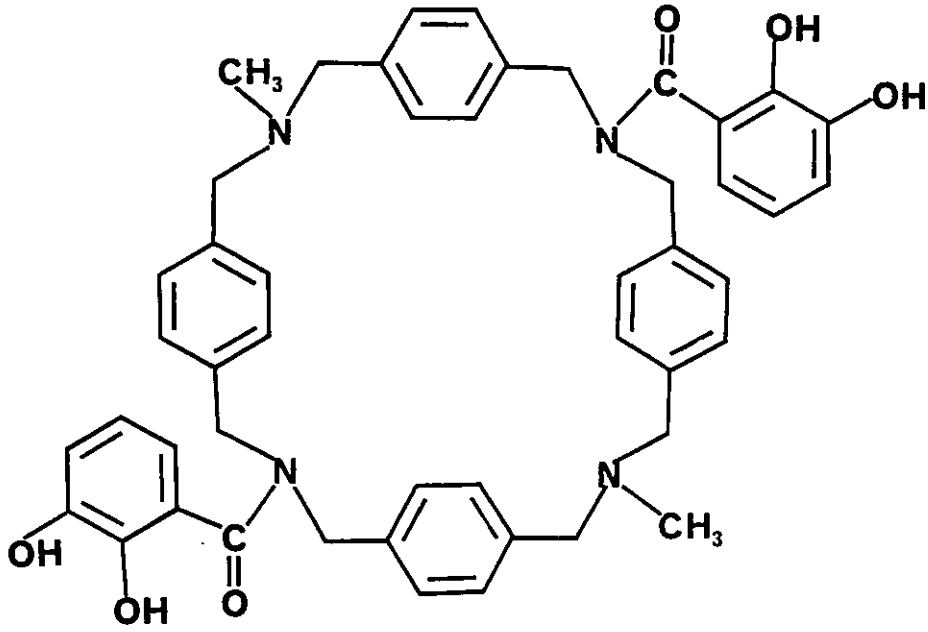
SYNTHESIS AND USES OF SOME AZAPARACYLOPHANE DERIVATIVES

3.1 Introduction

The hydroxylation of unactivated aromatic molecules is at present difficult to achieve. Classical procedures are available, such as the fusion of arenesulphonic acids, or the hydrolysis of haloarenes with alkali hydroxide. The hydrolysis of arenediazonium salts is also a good route to some phenols[101], but all these methods have many shortcomings. The industrial preparation of phenol, the cumene process, is a multi-step procedure, and is commercially viable partly because acetone is also formed during the reaction.

A number of catalytic systems have been developed to achieve direct hydroxylation of aromatic substrates. In 1954 Udenfriend and co-workers[102] used ferrous ion, ascorbic acid, ethylenediaminetetracetic acid (EDTA) and either oxygen or hydrogen peroxide, to hydroxylate a number of aromatic compounds. A recent modification of this system[103], involving the introduction of metallic iron to the reaction medium, has improved the procedure. Hamilton[104,105] found that a mixture of ferric ion, catechol, and hydrogen peroxide would hydroxylate benzene, nitrobenzene, chlorobenzene and anisole, in an aqueous medium. Fenton's reagent, a mixture of ferrous ion and hydrogen peroxide, has been used for similar transformations[106], as have a ferrous ion-thiosalicylic acid-oxygen system[107], and a ferrous ion-2-aminothiophenol-oxygen reagent[108].

This study was aimed at converting benzene to phenol under mild conditions. It was decided to modify the Hamilton system[104,105] by mounting the catecholic part of the catalyst onto an azaparacyclophane, a type of molecule known to contain a hydrophobic cavity into which aromatic substrates can bind, in the hope of solving some of the problems inherent in this catalytic procedure. The introduction of the azaparacyclophane was expected to help in three ways. Firstly its presence was supposed to increase the rate of the hydroxylation by providing both a binding site and a catalytic site in close proximity. Secondly, Hamilton's system is known to produce polyhydroxylated species. As benzene could be expected to have a greater affinity for the hydrophobic cavity of the catalyst than phenol, and as it was hoped that hydroxylation would occur mainly with species encapsulated within the cavity, a lessening of this problem was to be anticipated. If the system was ever to constitute an efficiently functioning catalytic process, the benzene and the oxidant would be introuduced in a continuously flowing system. Thus any phenol formed during the procedure would, on leaving the cavity, be rapidly removed, leaving a very low concentration of this compound near the catalyst and hence leading to a further suppression of polyhydroxylation. Finally, the catechol itself, under the normal conditions of the reaction[104], was shown to become hydroxylated very quickly, leading to a rapid loss of catalytic ability. It was hoped that the steric bulk of the azaparacyclophane would protect the catechol to some extent from this particular mode of decomposition, prolonging its life and thus allowing more phenol to be formed. In the longer term it was planned to mount the catalytic system onto a polymer support thus



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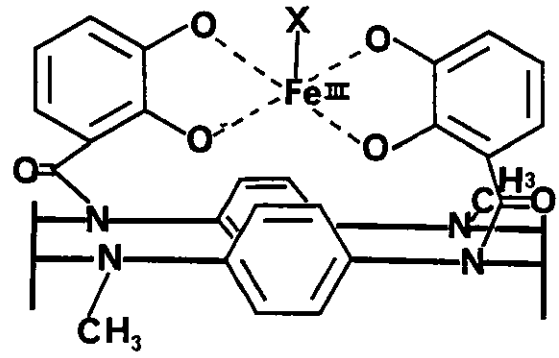


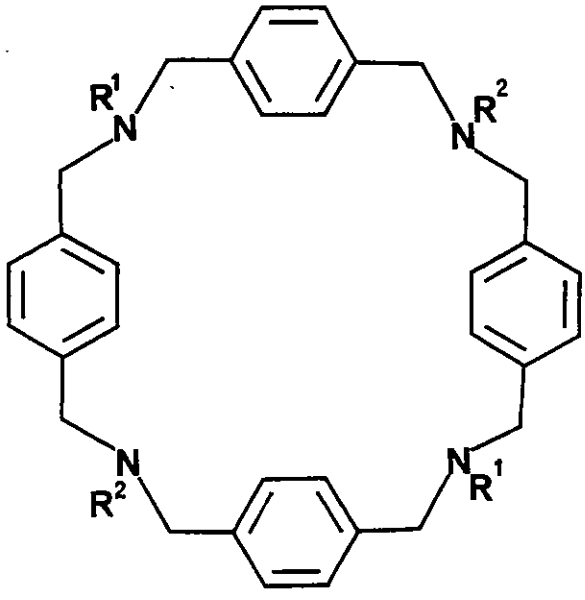
Proposed Conformation of Catalyst - Iron(III) Complex

isolating each catalytic site and lessening still further this degradative problem.

The initial aim of the project was to make the paracyclophane catechol species (127), which, on complexation with ferric ion, would adopt the conformation shown.

3.2 Approaches to Tetra-aza [3.3.3.3] paracyclophanes

As a first target, molecules of the type (128) were considered. Tetra-azaparacyclophanes are normally made by high-dilution reactions between diamines and diacid chlorides[10,18]. The system under consideration did have the additional complication of containing a particular substitution pattern. In principle the need was for an



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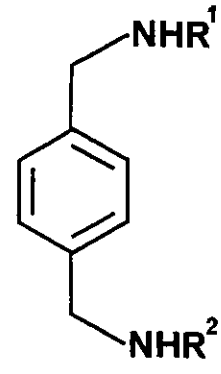

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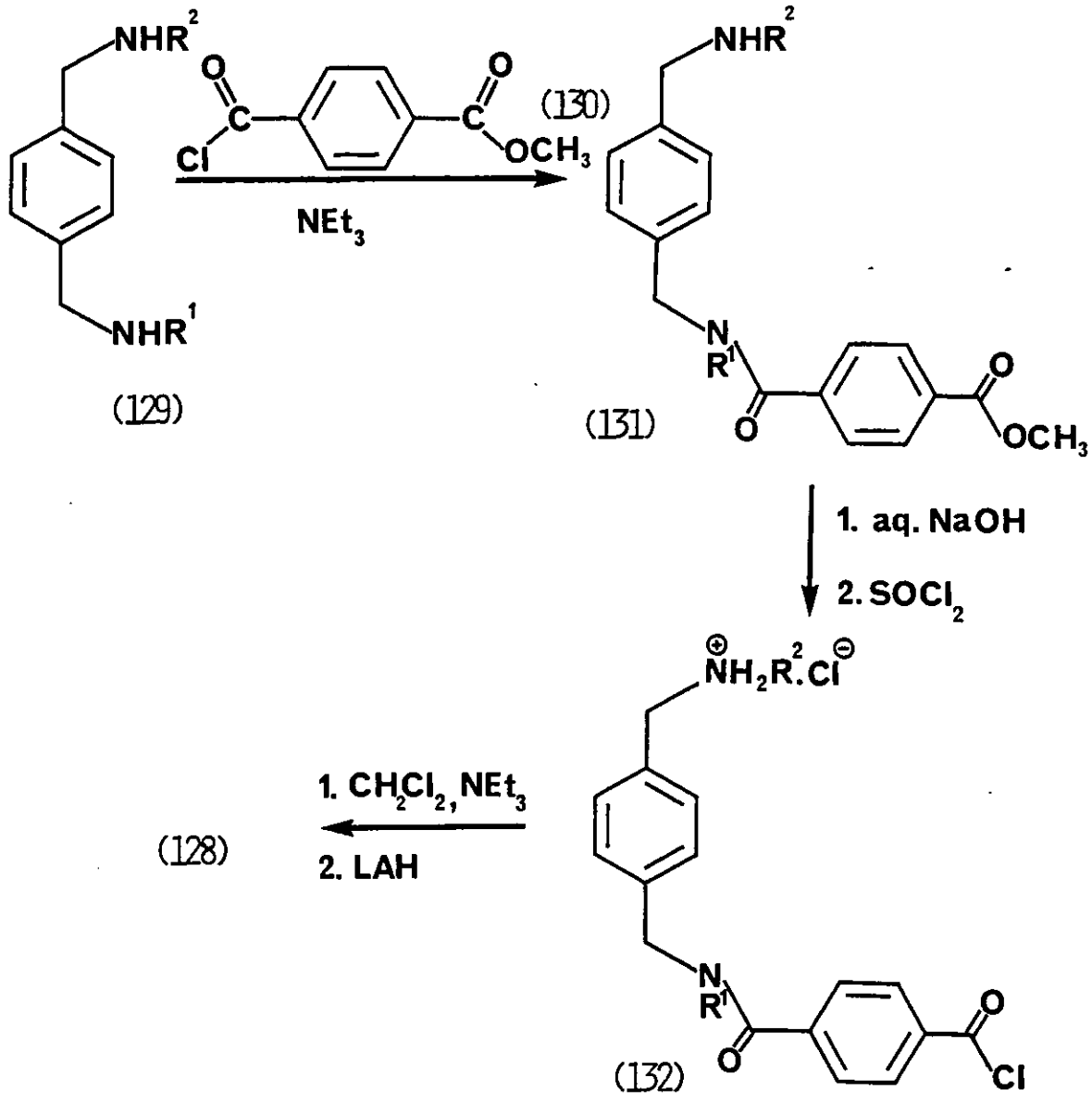
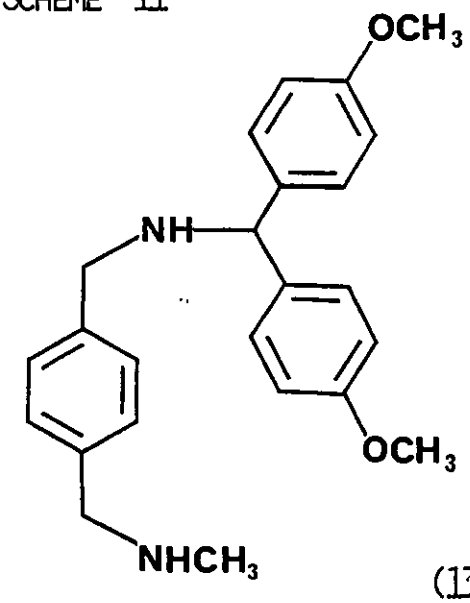


SCHEME 11

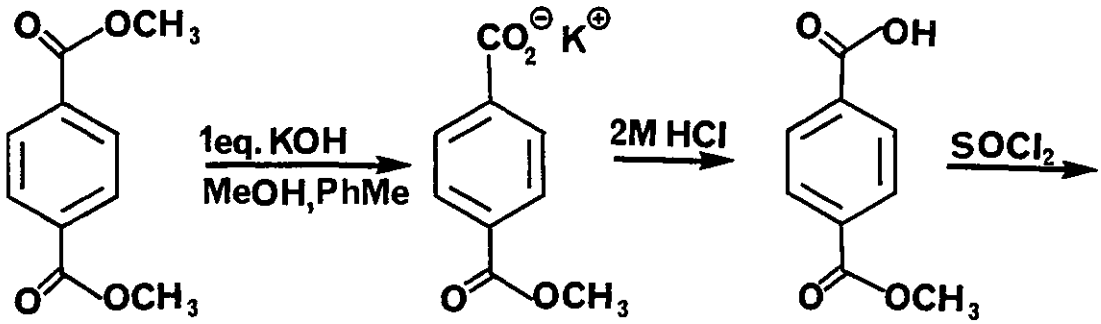


(133)

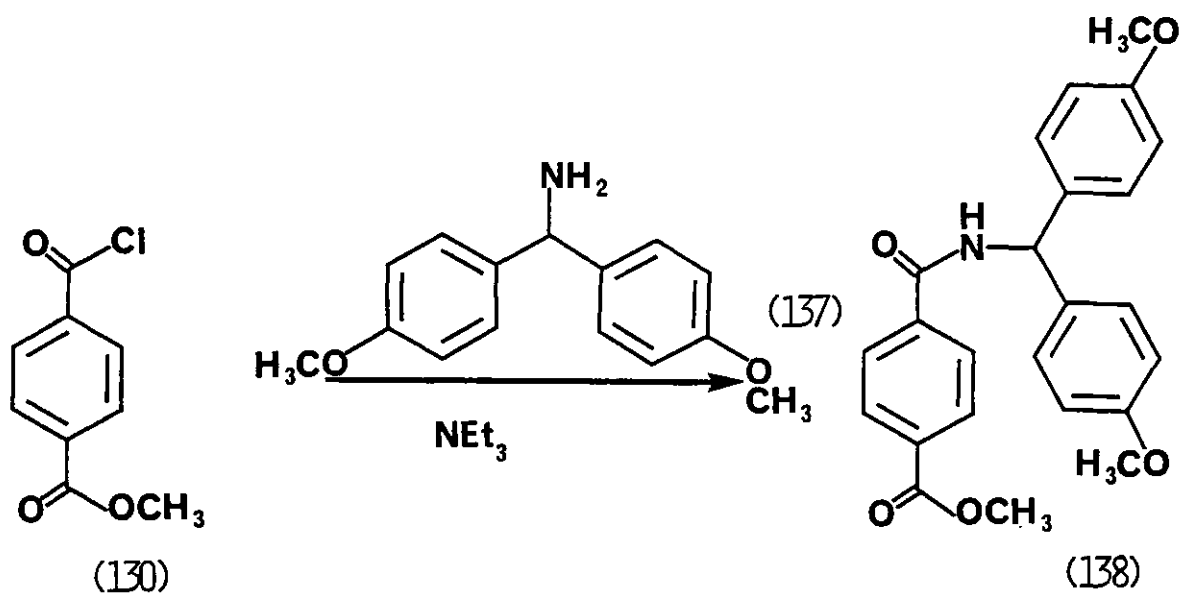
unsymmetrical diamine (129) that would react at only one terminus with an acid chloride. If such a unit could be found then a "2+2" cyclisation directly into the paracyclophane system could be considered.

The first asymmetric diamine examined was compound (133). With this molecule it was hoped to distinguish between the two amine moieties on the grounds of steric congestion. The 4,4′-dimethoxybenzhydryl protecting group has been used by Trost[109] in his synthesis of (±) gebaculene, and may be removed by the action of lithium aluminium hydride. Whether it was bulky enough to force the acid chloride (130) into reacting at the other, secondary amine, centre remained to be seen. Scheme 12 outlines the approach to diamine (133).

The monohydrolysis of dimethyl terephthalate (134) proceeded smoothly due to the insolubility of the resultant potassium salt (135) in methanolic toluene. Treatment of the salt with hydrochloric acid generated the acid (136) which reacted with thionyl chloride to give the acid chloride (130)[5]. This sequence proceeded in excellent yield, (90%). Addition of the acid chloride to a dichloromethane solution of 4,4′-dimethoxybenzhydrylamine (137) and triethylamine afforded the monoamide (138). This was converted to the bisamide (139) by reaction with an ethanolic solution of methylamine as described by Barrett and Simpson[110]. Conversion of the bisamide (139) to the diamine (133) proved rather problematical. Diborane reduction[111] of the bisamide (139) gave a green oil which clearly, from spectral evidence, contained the fully reduced compound (133). Unfortunately a

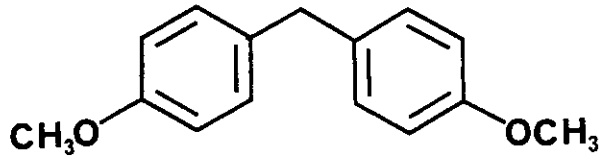


(134) (135) (136)



SCHEME 12

large amount of boron containing residues were also evident, characterised by broad high-field humps in the ^{1}H nmr. Column chromatography on both alumina and silica failed to significantly purify the material and bulb to bulb distillation led to a decomposition of the product, yielding only bis-(4-methoxyphenyl)methane (140). Whether this material was formed during the reaction, or during the distillation by residual boron hydrides was unclear. However, an experiment performed whereby cyclohexene was added to the reaction mixture after reduction was complete, to react with any active hydride species, again gave a green oil that proved completely involatile. This suggested that the high temperature of the distillation coupled with the presence of boron hydrides had led to the earlier decomposition. Attempts to

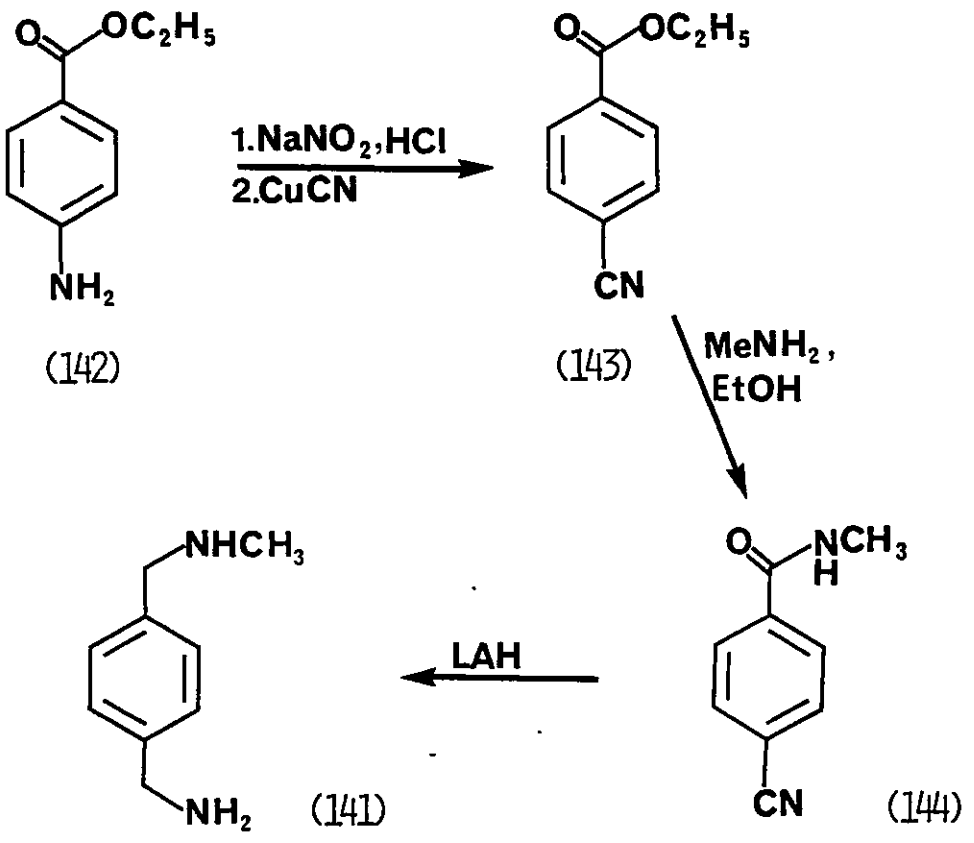


(140)

make the di-4-toluenesulphonic acid, or dihydrochloride salt of the diamine (133) failed as did the attempted benzoylation of the compound.

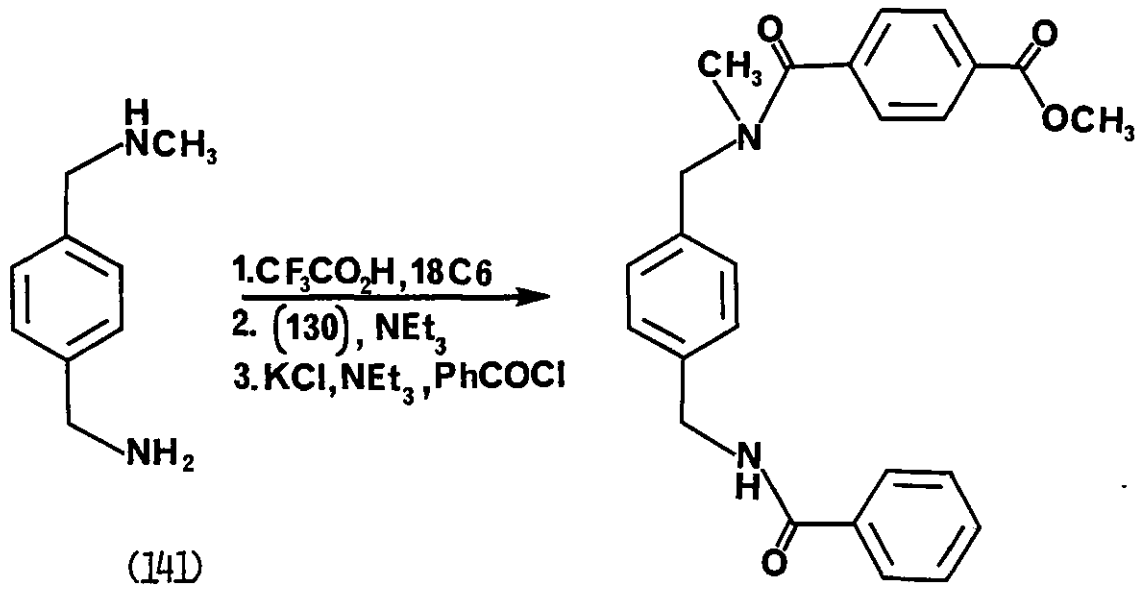
Having failed to make a pure sample of the diamine (139) we turned our attention to the synthesis of a different unsymmetrical diamine (141). This was available in three steps from ethyl 4-amino-benzoate (142). A standard Sandmeyer reaction[112], in which a diazonium salt was displaced by the cyanide anion, led to the 4-cyano compound (143) in 47% yield. The next step, treatment of the ethyl ester (143)

with ethanolic methylamine proceeded in excellent yield to the cyanoamide (144). A lithium aluminium hydride reduction of this material proceeded slowly, but in good yield, to the diamine (141).



SCHEME 13

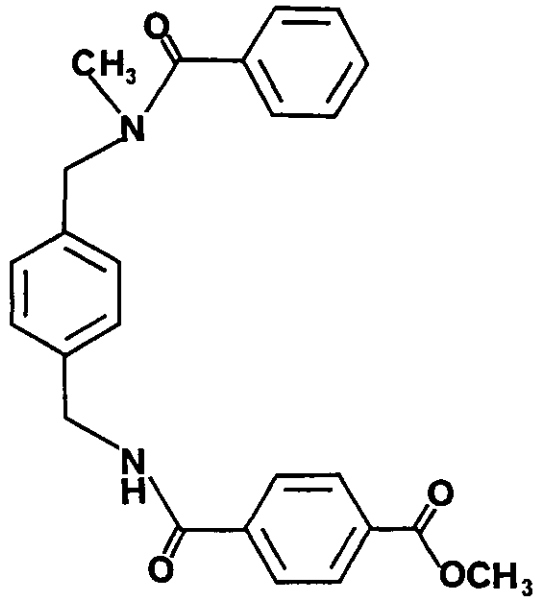
It was unreasonable to expect any difference between the two amine reactivities on steric grounds in the case of compound (141). However, a method of dynamic protection does exist, whereby secondary amines can be acylated in the presence of primary ones, using an 18-crown-6 complex[113,114]. 18-Crown-6 forms complexes with alkyl-, and arylammonium salts *via* three hydrogen bonds and pole-dipole interactions in the 2.7Å cavity[115]. Secondary ammonium salts form less stable complexes due to a reduction in hydrogen bonding. Thus in the presence of one equivalent of acid, and one equivalent of 18-crown-6, a primary amine will complex, and hence be protected, in



(141)

(145)

SCHEME 14



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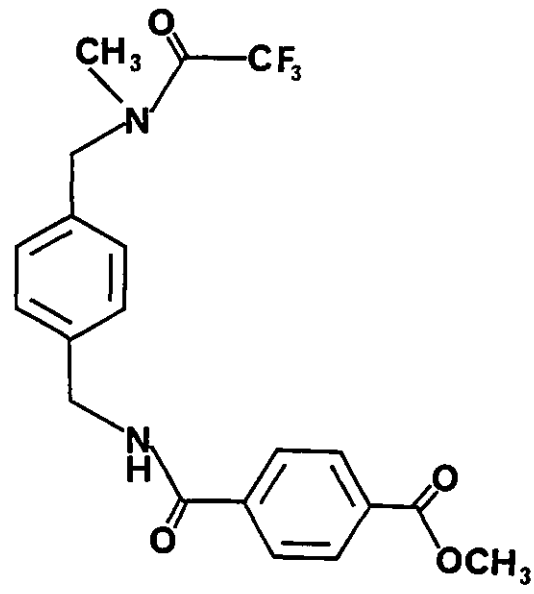


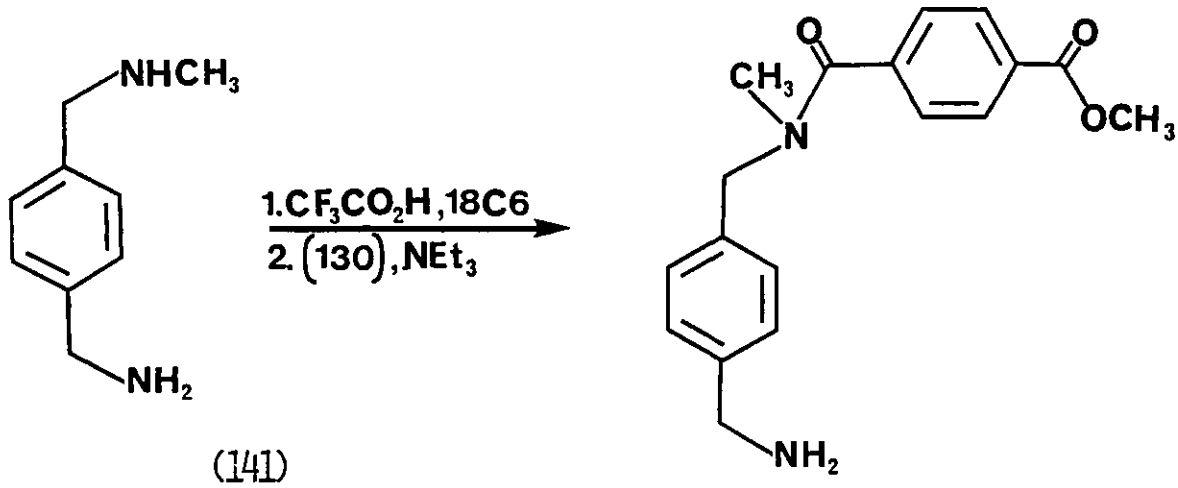
(147)

preference to a secondary amine, leaving this centre free for reaction.

In order to establish this procedure as a viable one in this case, the diamine (141) was dissolved in dichloromethane, and one equivalent each of trifluoroacetic acid and 18-crown-6 were added. After equilibration had occurred, one equivalent of the acid chloride (130) was added followed by some base. This first reaction having occurred, potassium chloride was introduced which immediately complexed with the 18-crown-6 in preference to the ammonium salt. Having unmasked the primary amine, this was free to react with any further acid chlorides that might be introduced. Benzoyl chloride was added and the expected bisamide (145) was isolated, after column chromatography, in 42% yield. This was clearly a single compound by ^{13}C nmr and was shown to be the correct isomer (145) from the mass spectrum. A blank reaction where no 18-crown-6 was used, gave a mixture of isomers (145) and (146) by ^{13}C nmr and by the mass spectrum. Several minor products could be seen in both reactions and one of these, the trifluoroacetamide (147) was isolated in a yield of 11%.

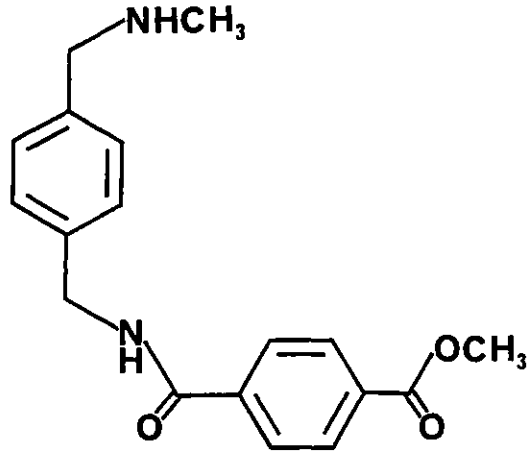
To further establish the selective nature of the reaction with 18-crown-6, the product after the first acylation (148) was isolated. Three monoacylations were performed in all, the first condensing the diamine (141) and the acid chloride (130) with neither acid, nor crown ether added, the second with just acid present, and the third with both acid and crown ether present. The first two reactions produced a 1:1 mixture of the two possible monoamides as judged by ^{1}H nmr. When both acid and crown ether were introduced to the reaction

mixture only one isomer (148) was observed. The differences in the ^1H nmr in the two cases were distinct. In the benzylic region for the



(141) (148)

SCHEME 15



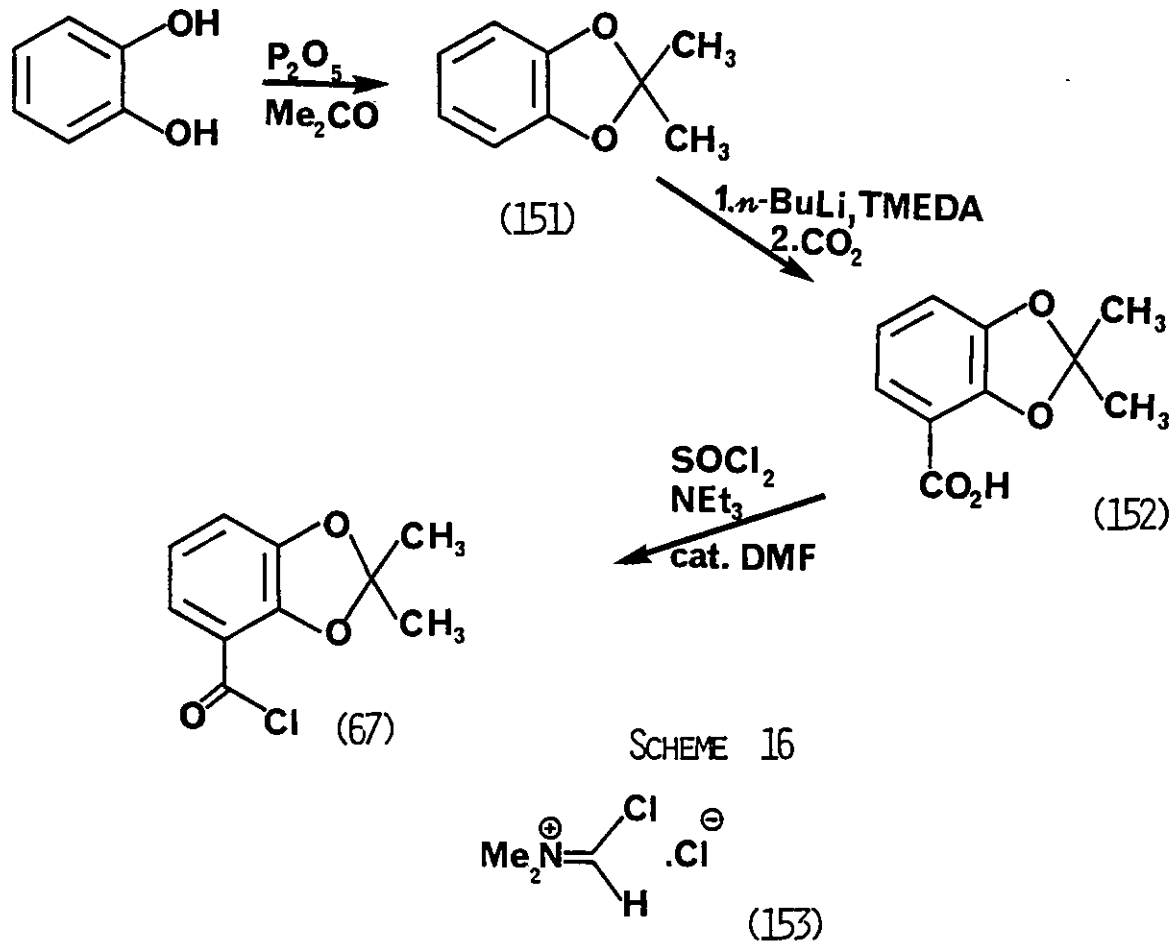
(149)

mixture of isomers (148) and (149), two peaks could be seen at δ3.75 and 3.65 ppm. When a single isomer (148) was isolated from the crown reaction, the higher field peak had disappeared. Thus it could be assigned as the Ar-CH_2-NHMe proton peak in compound (149). Similarly a peak at δ2.40 ppm present in the mixture of isomers was

absent in the pure sample (148) and could be assigned as the N-methyl protons in the unwanted isomer (149). Infrared analysis gave further proof that the acylation was selective. In the presence of crown ether, only one amide carbonyl stretching frequency at 1637 cm^{-1} could be observed, whereas when no 18-crown-6 was present, both secondary (1672 cm^{-1}) and tertiary (1640 cm^{-1}) amide carbonyl peaks could be clearly seen.

Having established to our satisfaction that acylation was selective, the next step was to make a bisamide from which a suitable paracyclophane could evolve. Instead of quenching the monoacylated compound (148) with benzoyl chloride, it was decided instead to use the acid chloride of 2,3-dihydroxybenzoic acid acetonide (67) prepared from catechol in three steps. Conversion of catechol to its acetonide (151) was achieved, by adapting the method of Sloof[116], in 45% yield. Metallation of this material with n-butyllithium in TMEDA and hexane for six hours at 0^{o}, followed by a carbon dioxide quench afforded the acid acetonide (152)[73]. The transformation to the acid chloride (67) requires 1.1 equivalents of thionyl chloride and a catalytic amount of DMF which presumably formed the Vilsmeier intermediate salt (153).

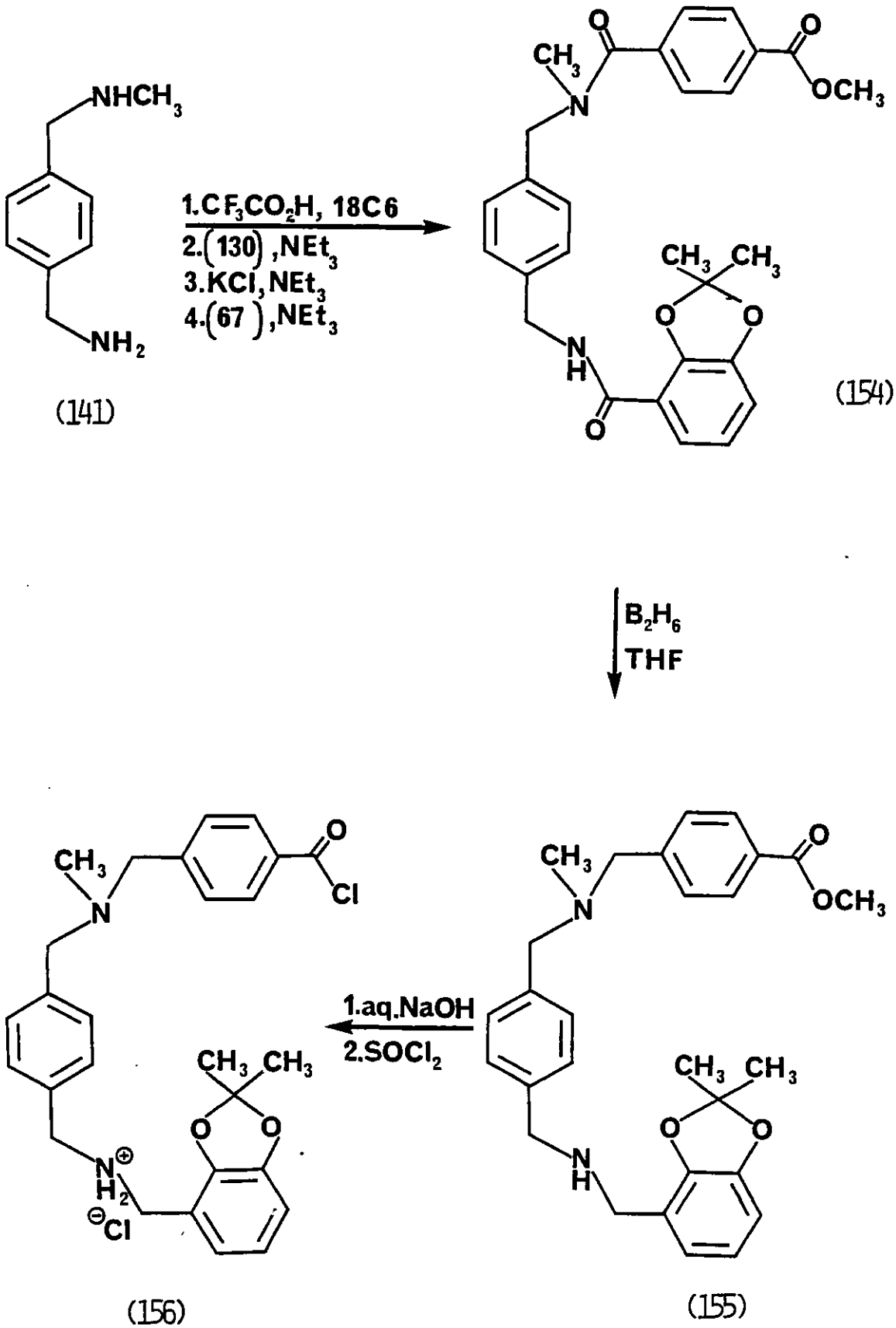
A bisacylation was performed, using firstly the acid chloride (130), and secondly a freshly prepared sample of compound (67), to give the desired product (154) in 43% yield.



SCHEME 16

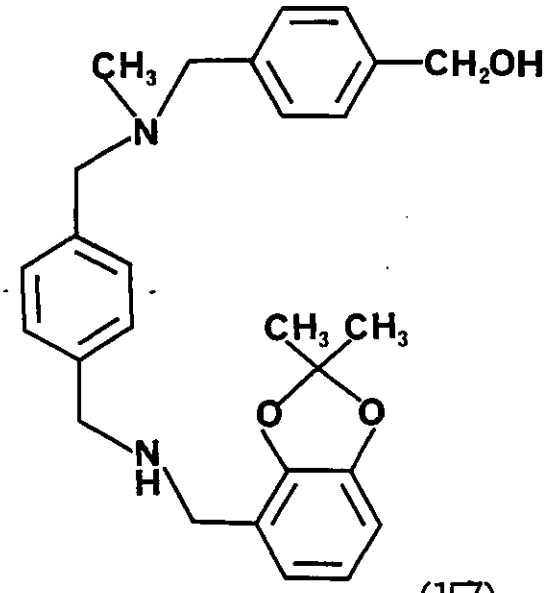
(153)

Reduction of the bisamide (154) proved very difficult to perform. Treatment of a THF solution of the compound (154) with a slight excess of diborane reduced the tertiary amide smoothly enough but did not appear to touch the secondary amide. Use of a larger excess of the reducing agent and prolonged reaction times started to reduce the secondary amide but also started to effect the methyl ester. At no time did the reaction go to a satisfactory completion. Similar attempts at reduction with lithium aluminium hydride to give the fully reduced compound (157) led to a material where partial deprotection of the acetonide group had also occurred. This problem of incomplete reduction could not be satisfactorily solved and an



(141) (154) (155) (156)

SCHEME 17

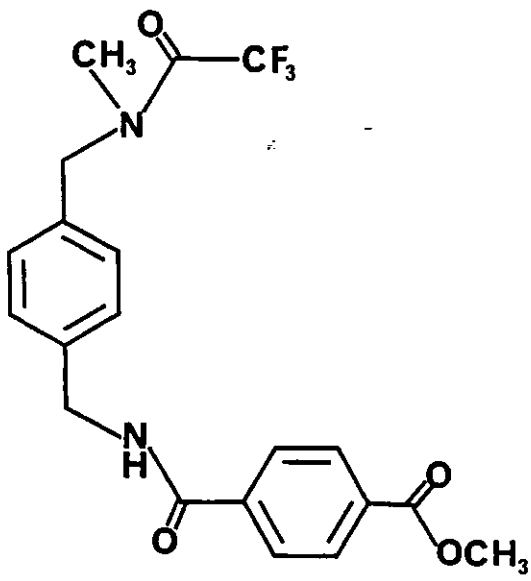


(157)

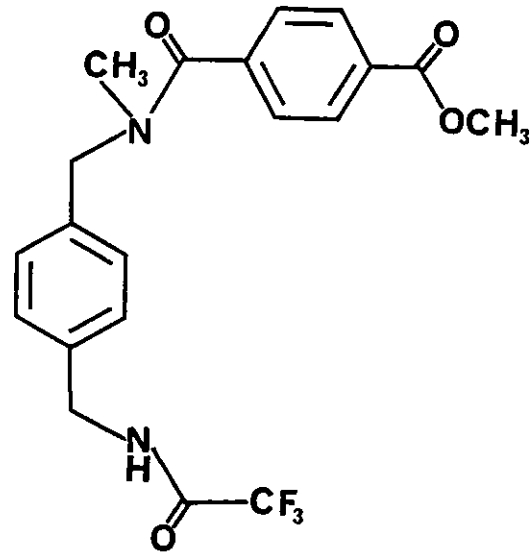
alternative method was required. The question of poor yield in the acylation reactions was also one that needed investigation.

Although the acylations had been shown to be selective, several by products could be isolated from the reactions. Three of these in particular could be identified as the trifluoroacetamides (147) and (158) and the bisamide (159). T.l.c. spots corresponding to these seemed to reoccur in every acylation reaction attempted. Although no individual compound was observed in large yield, the cumulative effect of several of these led to serious diminutions of the overall yield. Having identified the compounds it was possible to postulate how they were arising and how to suppress their formation.

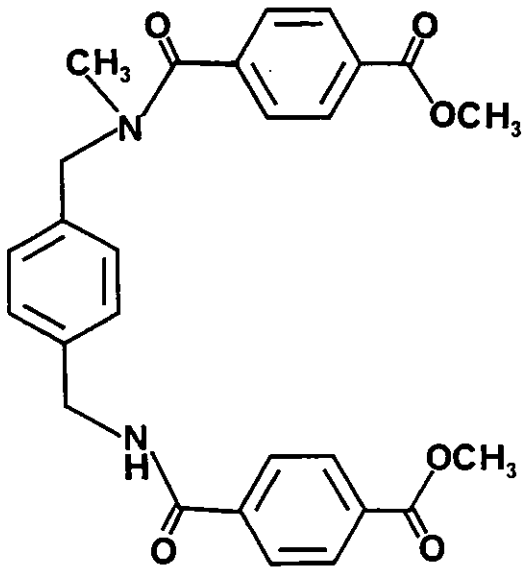
It was decided that the presence of the trifluoroacetamides (147) and (158) was due to the formation of a mixed anhydride (160). This



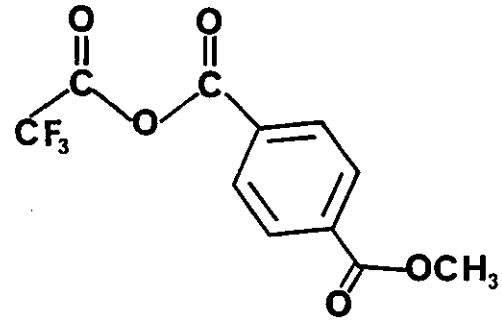
(147)



(158)

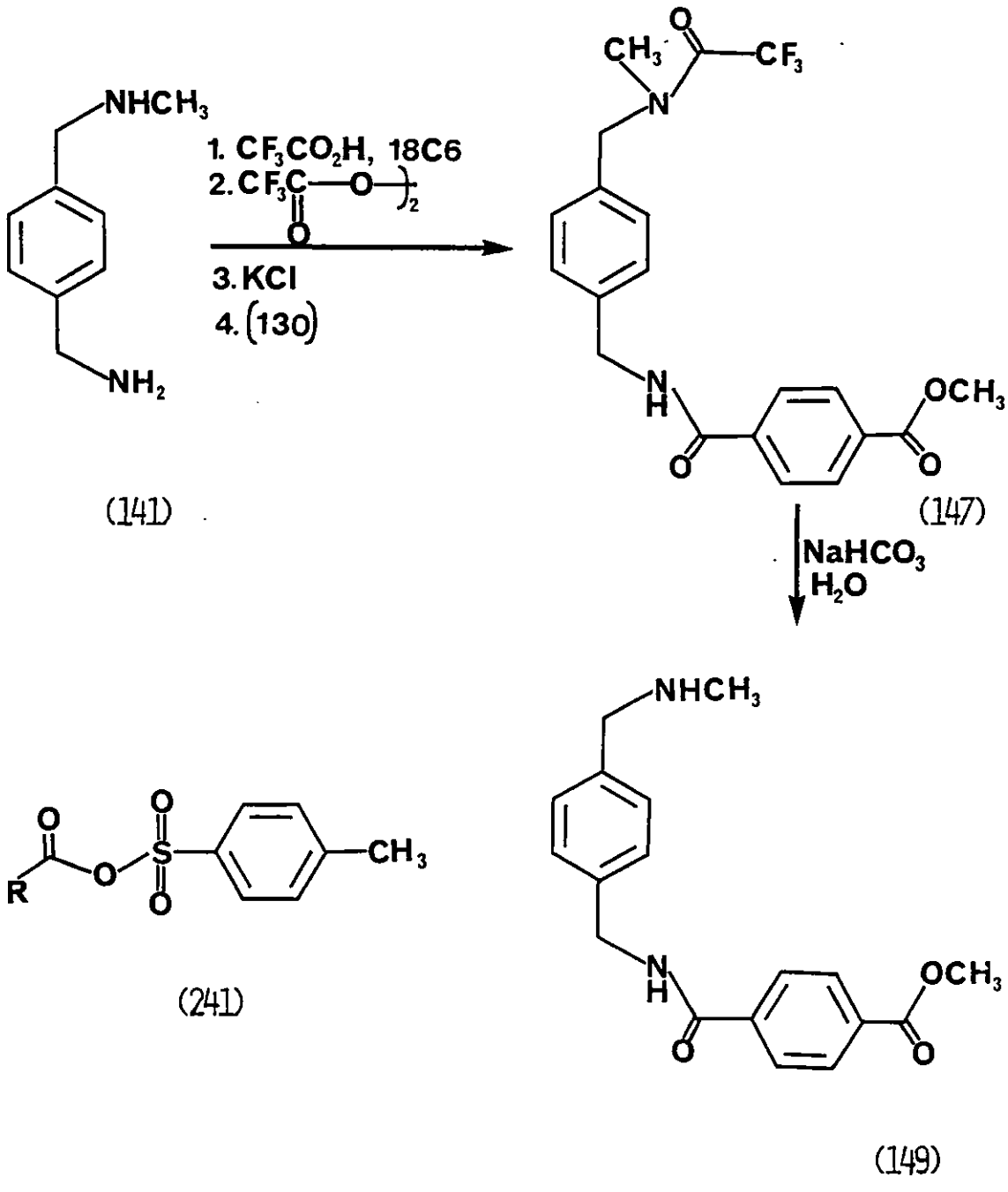


(159)



(160)

arose because of the enhanced nucleophilicity of the trifluoroacetate anion in the presence of 18-crown-6. This led to some of the primary ammonium species present in solution deprotonating and thus becoming deprotected. The diamine (141) was able to indiscriminately attack the mixed anhydride leading to a series of monoamides. As plenty of the acid chloride (130) was also present, the remaining amine functionality on these unprotected compounds was rapidly acylated leading to all the observed by products.



SCHEME 18

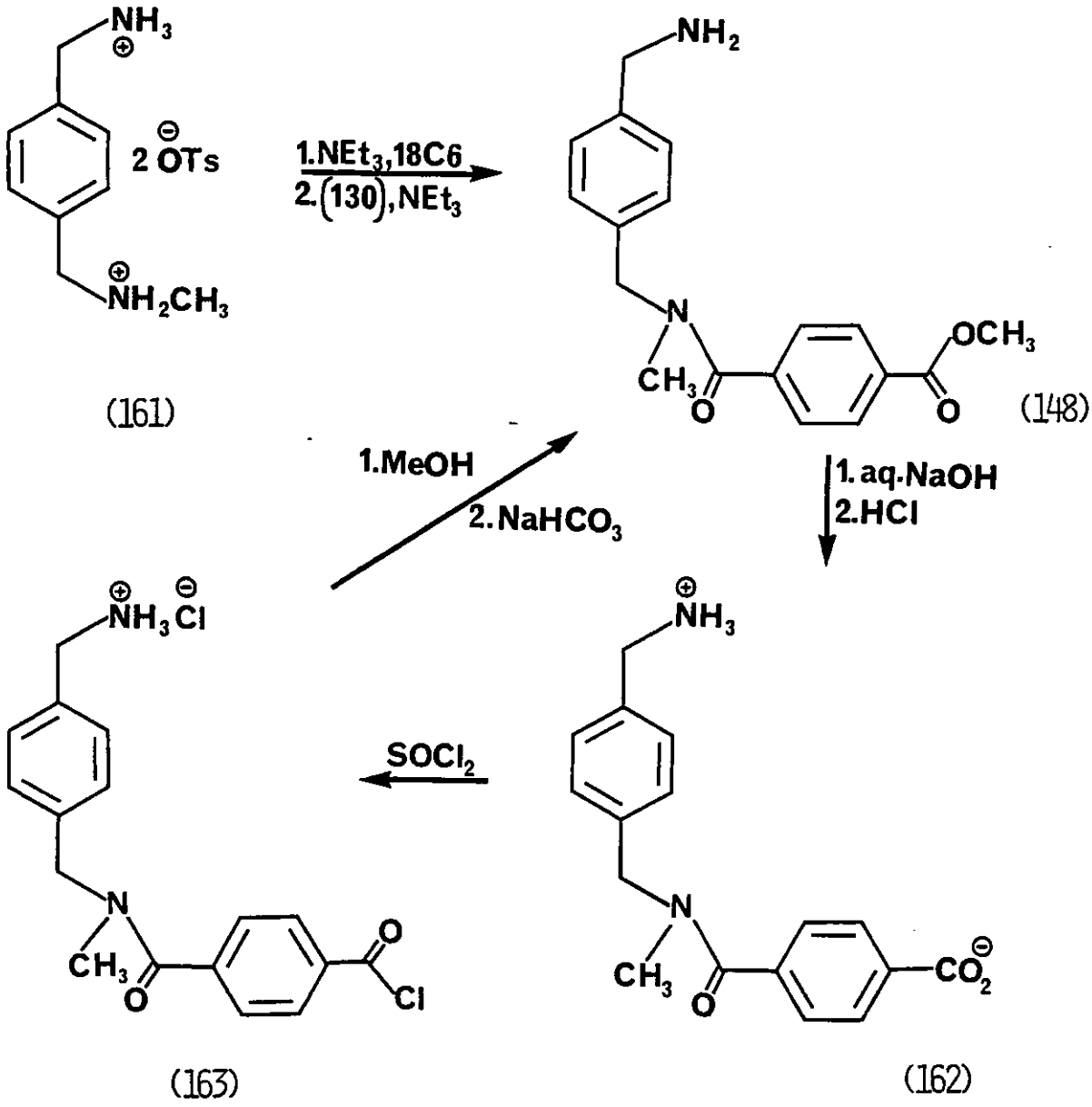
An attempt was made to synthesise compound (147) selectively in the hope that this could be used to make a cyclisation precursor instead of the bisamide (154), the reduction of which had been difficult. The reaction however, using trifluoroacetic anhydride as the acylating agent, was unsuccessful, with almost equal amounts of compounds (147), (158), and (159) being formed in very poor yield. This reaction, although preparatively useless, did help to confirm the identity of the by products from the previous reactions.

To improve the yield in the selective acylation, a fundamental change had to be made to the system. It was decided at this stage to use 4-toluenesulphonic acid as the proton source in the procedure instead of trifluoroacetic acid. The di-4-toluenesulphonic acid salt of N-methyl-1,4-xylylenediamine (161) was made and the model bisamide (145) was synthesised in the much improved yield of 63%. No other non-polar products could be seen on tlc. This improvement suggested that the 4-toluenesulphonate anion was not a sufficiently naked nucleophile to cause the same problem as the trifluoroacetate anion. It should be remembered however that even if an acyl-sulphonic anhydride species (241) was being formed, this is an acylating agent and so a much smaller variety of compounds would result from the procedure, but the yield and purity of the product indicated that little, if any, deprotection of the primary amine moiety was occurring.

We now return to the problem of making a suitable cyclisation precursor for a high-dilution reaction. The failure to reduce the

bisamide (154) has been discussed earlier and mention has also been made of an attempt to make compound (149) *via* the trifluoroacetamide (147). A third possibility had to be considered, that of making monoamide (148), a molecule that had been synthesised in the course of investigating the selectivity of the acylation procedure. Its isolation in 75% yield had been considered excellent proof for the method. The yield was increased to 88% when the ammended reaction was performed using the di-toluene-4-sulphonic acid salt (161) as described above. Although primary amines have been shown by Barrett and Godfrey[5] not to cyclise very easily, this approach was none the less pursued at this stage, in the hope that the 2+2 approach to cyclisation[18] would prove more successful than the previously attempted 1+1+1+1 cyclisations[5].

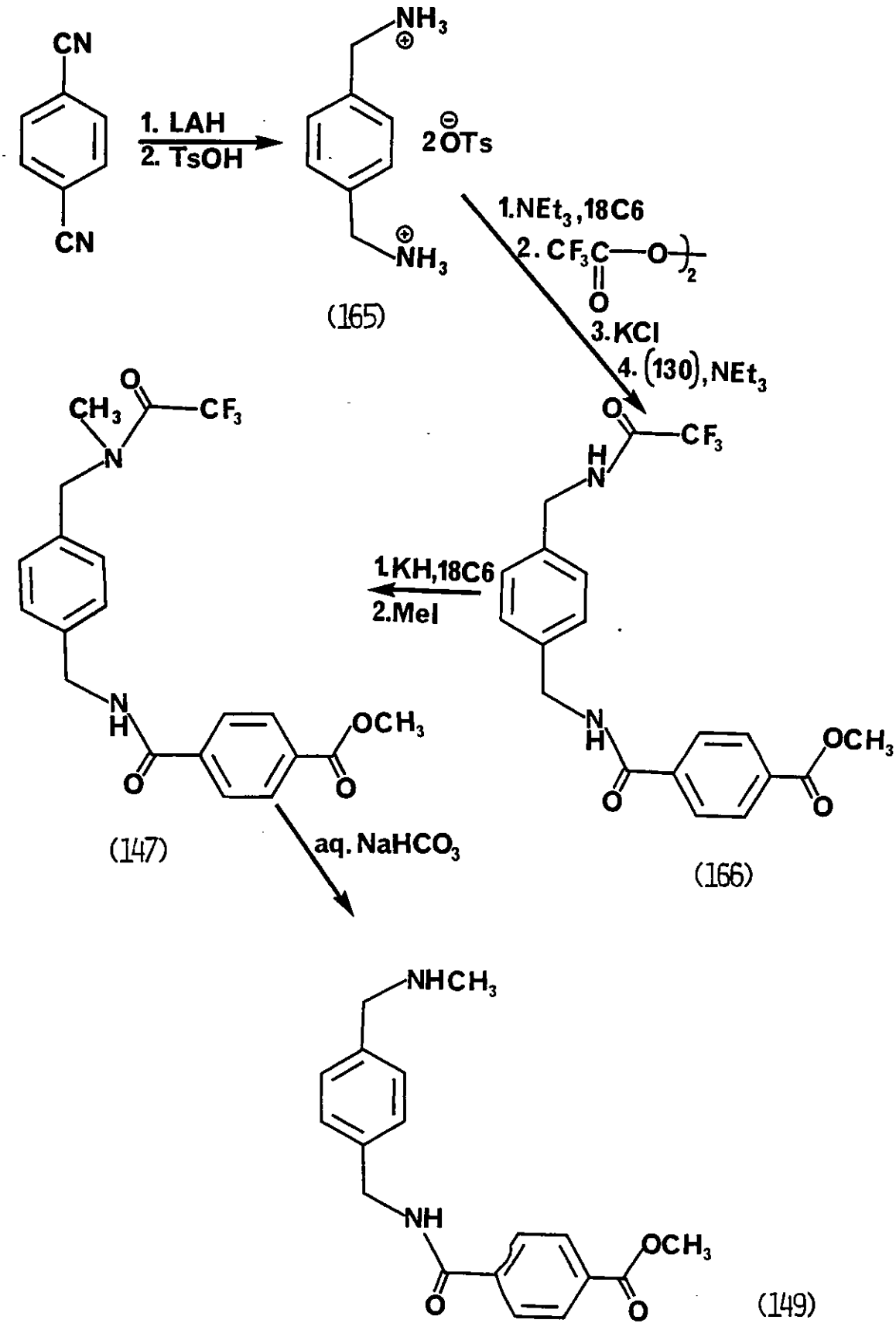
The monoamide (148) was treated with one equivalent of an aqueous sodium hydroxide solution in methanol to give the amino acid (162). This extremely insoluble material could not be fully purified and was never fully characterised. Treatment of the impure acid with thionyl chloride gave a material that contained the amino acid chloride (163) as judged by infrared spectroscopy. Confirmation of this structure came from treating this impure material with methanol to regenerate, on basification, the monoamide (148). Although in principle the acid chloride (163) could have been used in a cyclisation attempt, the reaction was not performed for three reasons. Firstly, the compound could not be obtained in a satisfactory state of purity. Secondly, high-dilution reactions of this type give very poor



SCHEME 19

yields, and so have to be performed on large scales to give significant amounts of product. It proved very difficult to make and isolate large amounts of the amino acid (162). Thirdly, with the experience of previous primary amine cyclisations behind us, it was decided to spend no further time on this route.

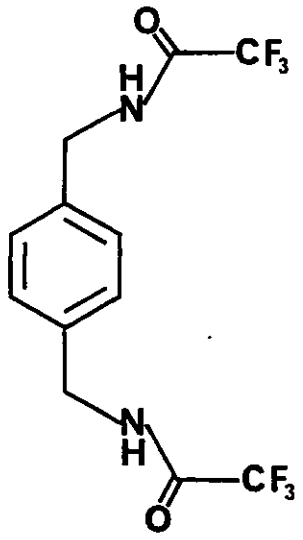
Meanwhile, another approach to the monoamide (149) was being


CN
CN
1. LAH
2. TsOH
NH3
2 OTs
NH3
(165)
1.NEt3,18C6
2. CF3C—O)2
O
3.KCl
4. (130),NEt3
O
CF3
H
N
1.KH,18C6
2.MeI
CH3
O
CF3
N
N
H
OCH3
O
O
(147)
aq. NaHCO3
N
H
OCH3
O
O
(166)
NHCH3
NH
OCH3
O
O
(149)

SCHEME 20

investigated as shown in Scheme 20. 1,4-xylylenediamine (164) was made in excellent yield from 1,4-dicyanobenzene and converted to its di-4-toluenesulphonic acid salt (165). In the hope of mono-acylating this primary diamine, the 18-crown-6 dynamic protection protocol was used. The results proved disappointing and the desired trifluoro-acetamide (166) was isolated in a yield of only 16%. The major problem proved to be the insolubility of all the reagents concerned. The crown ether complex of diamine (164), for example, appeared totally insoluble in dichloromethane, whereas in the equivalent situation, the N-methyl diamine (141) had been completely soluble. The products too proved very insoluble and hence extremely difficult to chromatograph. It had been hoped with compound (166) to deprotonate the secondary trifluoroacetamide moiety with potassium hydride and 18-crown-6, following the precedent of Nordlander[117], and to then quench the anion with methyl iodide. This would yield the tertiary trifluoroacetamide (147), the target of an earlier route, which could be hydrolysed as before (Scheme 18) providing the precursor (149) to the more desirable secondary amine cyclisation.

Even a reaction to make the bis-trifluoroacetamide (167), to examine whether the potassium hydride deprotonation would work, ran into serious difficulties. The insoluble nature of the product precluded any isolation of large amounts of pure compound (167).

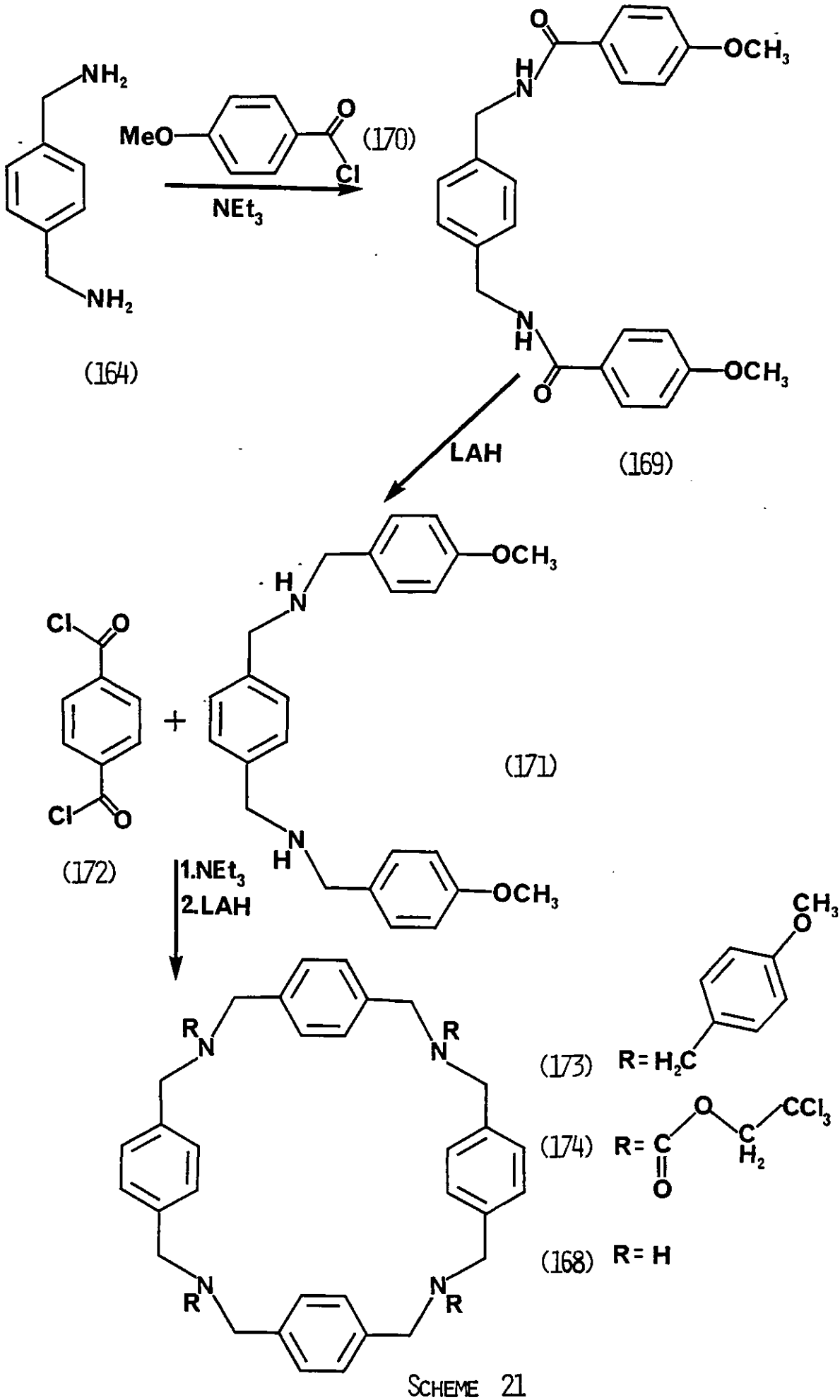


(167)

The routes employing selective acylation had unfortunately to be abandoned. Despite the painstaking work in establishing the selective nature of the operation and in improving the yields, and the initial successes in obtaining useful compounds, none of the materials made could be developed into satisfactory precursors for a 2+2, high-dilution cyclisation.

Attention next turned to a tetra-azaparacyclophane (168) that has already been synthesised[5] in the hope of selectively functionalising it across opposite nitrogen atoms.

The route started by the synthesis of the bisamide (169) from 1,4-xylylenediamine (164) and 4-methoxybenzoyl chloride (170). The very insoluble material precipitated out of solution and was isolated by filtration in 77% yield. Very large amounts of this compound could be made in one reaction and so this proved a highly satisfactory precursor to a high-dilution reaction. Lithium aluminium hydride reduction of the bisamide in refluxing THF gave the known bisamine (171)[5] in almost quantitative yield. An unusual


NH2
NH2
MeO
O
Cl
(170)
NEt3
(164)
O
H
N
OCH3
N
H
O
OCH3
(169)
LAH
Cl
O
Cl
O
+
H
N
OCH3
(171)
N
H
OCH3
(172)
1.NEt3
2.LAH
R
N
R
N
N
R
N
R
(173) R= H2C
CH3
O
(174) R=
O
C
O
C
H2
CCl3
(168) R= H

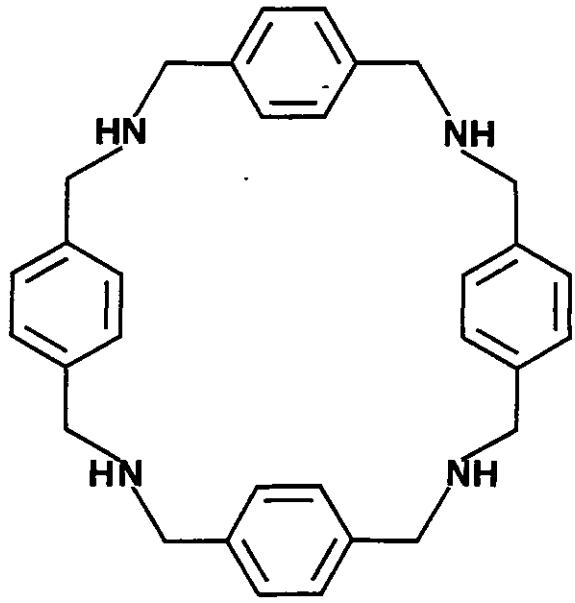
SCHEME 21

feature of this reaction are the colours obtained during the heating. The reaction suspension, whilst hot, is a purple red colour which on cooling goes bright green! The presence of the 4-methoxybenzyl moiety must be responsible for a charge transfer complex forming but the exact nature of this is unclear as is the apparent temperature dependance of the colours that are produced. The use of a 4-methoxybenzyl group should be explained. Because of empirical observations[5] made, that secondary amines were required in 1+1+1+1 cyclisations reactions, a suitable protecting group had to be found which was stable to a variety of conditions, most importantly lithium aluminium hydride reductions. The 4-methoxybenzyl group met the description and also proved relatively simple to remove, even in the presence of the benzyl groupings of the paracyclophane (168) itself[5]. A recent synthesis[118] of an N-benzyl protected azapara-cyclophane gave a very poor yield during a reduction step, suggesting that this particular group may not be compatible with the paracyclophane system.

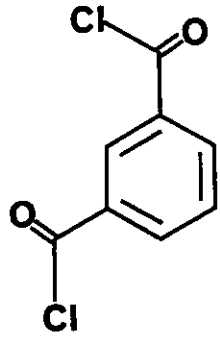
The diamine (171) and terephthaloyl chloride (172) were subjected to a high-dilution reaction, in a specially designed apparatus similar to one described by Vögtle[119] (see Appendix I for diagram). The reaction was performed in refluxing dichloromethane, and the crude mixture of polyamides formed was treated with lithium aluminium hydride to give, after repeated column chromatography, a 12-15% yield of the desired tetra-N-4-methoxybenzyltetra-aza[3.3.3.3]-paracyclophane (173). Deprotection of this material was achieved in good yield by firstly conversion to a tetra-carbamate (174) with 2,2,2-trichloroethyl chloroformate, followed by base hydrolysis[5].

All was now ready to attempt a bridging reaction across the paracyclophane cavity between nitrogen atoms, to give the bisamide (176). If successful an entry existed into the series of 1,3-disubstituted tetra-azaparacyclophanes (128). The bridging reagent chosen was isophthaloyl dichloride (175) which space-filling models indicated, would be just the correct size to straddle the cavity.

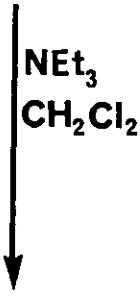
The reaction between the tetraamine (168) and the diacid chloride (175) was performed under high-dilution conditions in dichloromethane. Triethylamine, used as base to neutralise any hydrogen chloride formed, was introduced with the tetraamine (168). Two products were isolated from the reaction, both in low yield. One of these may have been the desired bisamide (176) from mass spectral evidence, but the compound could not be fully characterised. Thus once again a route into 1,3-disubstituted tetra-aza[3.3.3.3]-paracyclophanes (128) had floundered. Hence the tetra-aza system was discarded, attention instead being turned to a di-azaparacyclophane.

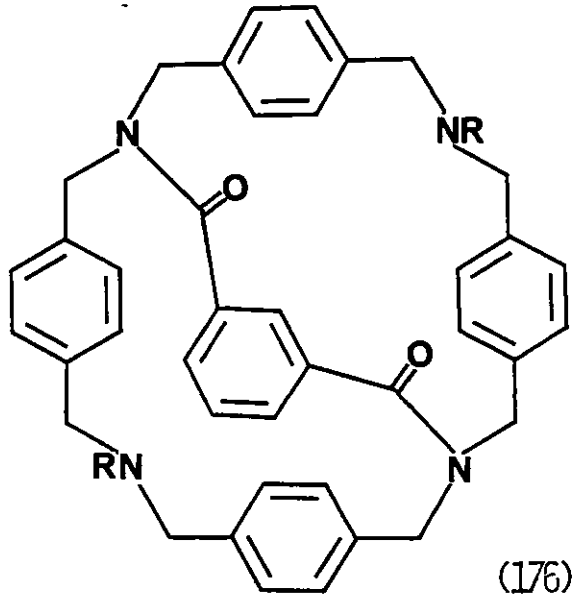


(168)



(175)





(176) $R = H$

(177) $R = CH_3$

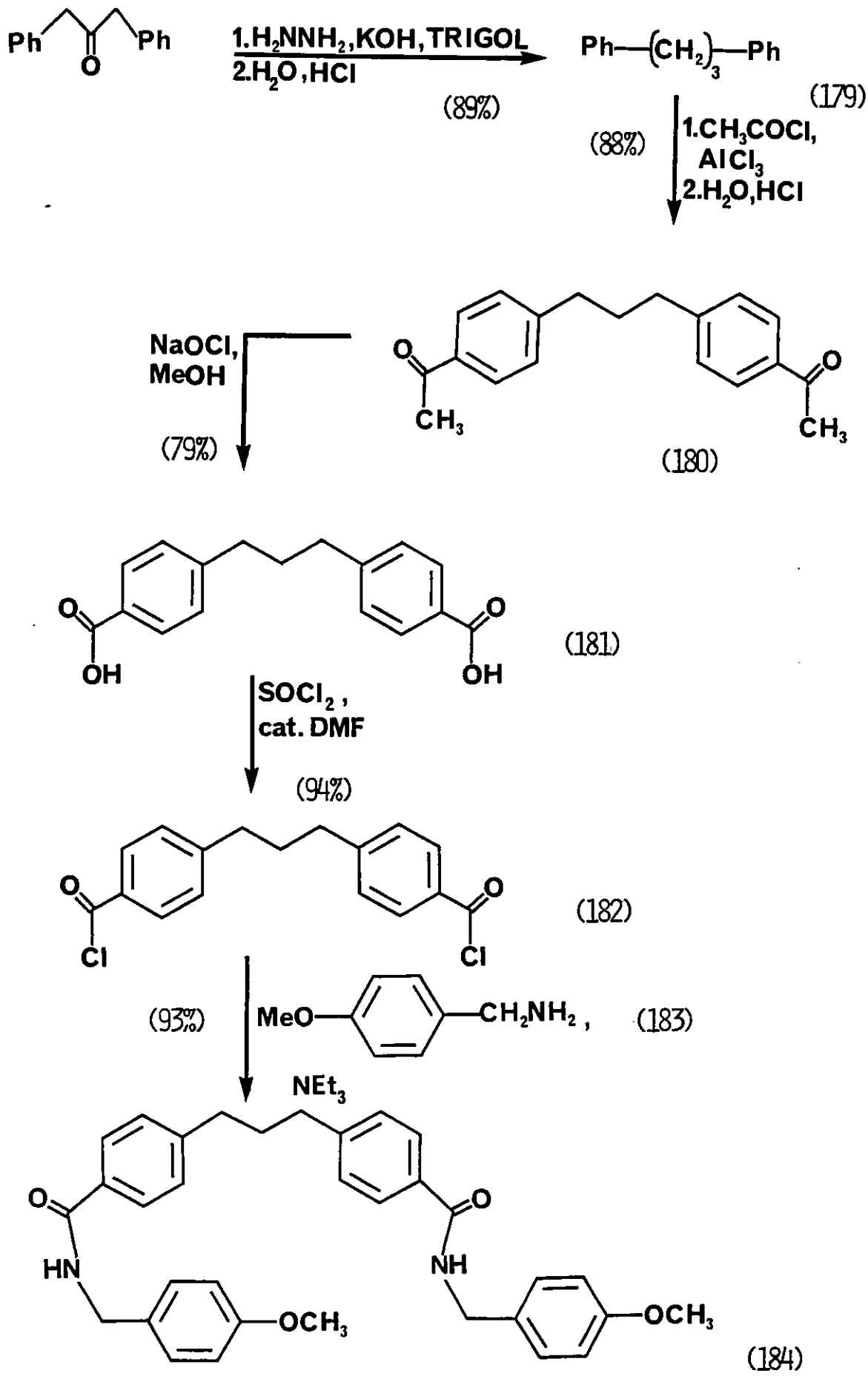
SCHEME 22

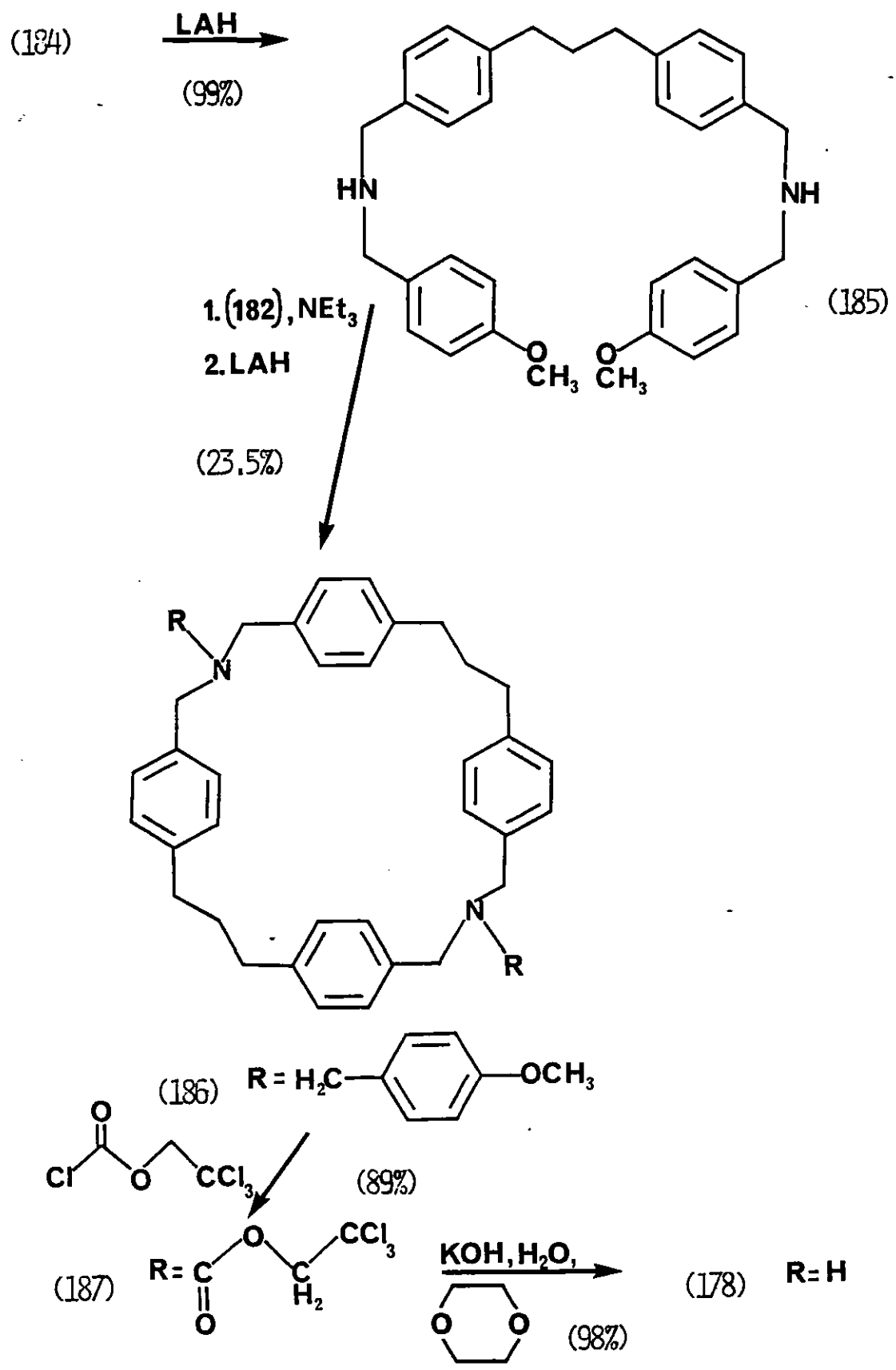
3.3 Preparation of 2,20-Di-aza[3.3.3.3]paracyclophane (178)

CPK space-filling models of the di-azaparacyclophane (178) indicated that this molecule was also capable of existing in a conformation such that it possessed a cavity. This molecule had the added advantage of being considerably simpler to make as it was not necessary to discriminate between the two nitrogen atoms in any way. The route used to make compound (178) is indicated in Scheme 23. Isolated yields of each product are given in parentheses by each arrow.

1,3-diphenylpropane (179) was prepared on multigram scale using a Wolff-Kishner reduction employing a Huang-Minlon modification, as described by Cram and Steinberg[120]. The yield after distillation of 89% compares well with the literature. The diacetyl compound (180) has also been described in the literature[121] but the Friedel-Crafts procedure used to make it involved the use of a huge excess of aluminium chloride and acetyl chloride making the preparation of the compound very difficult to perform on large scale. The system was considerably modified[122] and it was found that in dichloromethane as solvent, far smaller quantities of the agents were required. Thus the reaction could be performed on large scale, essential at this stage of a route, and the literature yield was in fact improved upon.

Oxidation of the diacetyl compound (180) to the dicarboxylic acid (181) could not be performed using the literature[121] procedure which employs potassium hypochlorite solution. It was instead found that both an iodoform type reaction using potassium iodide in sodium


Ph
O
Ph
1.H2NNH2,KOH,TRIGOL
2.H2O,HCl
(89%)
Ph—(CH2)3—Ph
(179)
(88%)
1.CH3COCl,
AlCl3
2.H2O,HCl
NaOCl,
MeOH
(79%)
O
CH3
O
CH3
(180)
O
OH
O
OH
(181)
SOCl2,
cat. DMF
(94%)
O
Cl
O
Cl
(182)
(93%)
MeO
CH2NH2,
(183)
NEt3
O
HN
OCH3
O
NH
OCH3
(184)


(184)
LAH
(99%)
HN
NH
O
CH3
O
CH3
(185)
1. (182), NEt3
2. LAH
(23.5%)
R
N
N
R
(186)
R = H2C
OCH3
O
Cl
O
CCl3
(89%)
(187)
R=
O
O
CCl3
C
H2
KOH, H2O,
O
O
(98%)
(178)
R=H

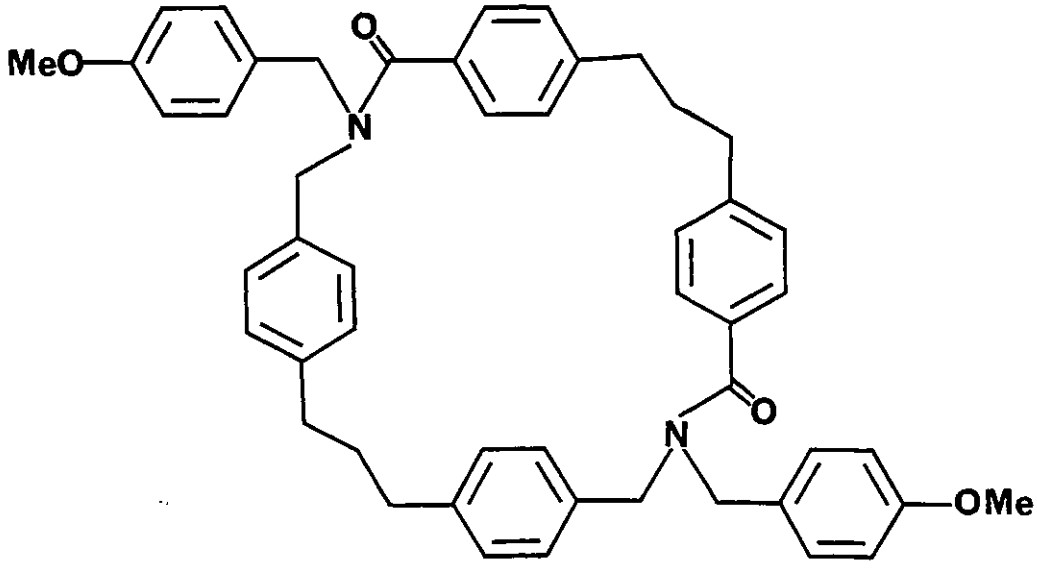
SCHEME 23

hypochlorite, or better still, sodium hypochlorite solution alone, gave high yields of the required dicarboxylic acid (181). This material proved quite difficult to fully purify as it contained a good deal of sodium chloride. Thorough washing with hot water generally gave material that was pure enough for subsequent transformations. The corresponding diacid chloride (182) was made in thionyl chloride at reflux, the rate of reaction increasing dramatically if a few drops of N,N-dimethylformamide were added. Removal of the thionyl chloride followed by dissolution of the product in dichloromethane gave, after a rapid filtration (to remove any inorganic impurities), a pure solution of the diacid chloride, itself one of the precursors to cyclisation.

This acid chloride (182) was very readily converted to the bisamide (184) by addition of a dichloromethane solution of 4-methoxybenzylamine (183) and triethylamine, and the bisamide (184) was rapidly reduced to the bisamine (185) in excellent yield. Two interesting features of this reduction should be noted. Once again colours were produced during the reaction ranging from a purple, when hot, to an olive green when cold. The colour instantaneously dissipated when the reaction was quenched. This phenomenon of coloured lithium aluminium hydride reductions seems to be a peculiarity associated with the 4-methoxybenzyl grouping. The second feature of note is that the reduction occurred much more quickly in this system than in the corresponding bisamide (169). This may be accounted for by the fact that the bisamide (185) is soluble in THF, whereas compound (169) is almost completely insoluble.

Having now made both the cyclisation precursors in a very good overall yield, and with considerable amounts of the compounds being available, a 2+2 cyclisation reaction was attempted using the special high-dilution apparatus (see appendix 1). Dichloromethane was used as solvent and triethylamine as the base. The reagents for this reaction were considerably easier to handle than in the previous approach to the tetra-aza compounds, as both were quite stable and also exceedingly soluble in dichloromethane.

After the cyclisation was complete, it was noted on tlc that very little baseline material could be observed in the isolated material. Encouraged by this, it was decided to attempt a purification at the paracyclophane amide stage (188). Each of the three visible u.v. active spots were isolated by column chromatography but ^{1}H nmr of each fraction clearly indicated that more than one compound was



(188)

present. It would seem that the polymeric material isolated from this reaction was also non-polar enough to move away from the baseline on tlc. The mass spectrum of this crude material suggested that compound (188) was present.

Having failed to isolate the desired bisamide (188), all the crude material was reduced with lithium aluminium hydride and after a 40 hour reflux in THF, a white crystalline material was isolated, which consisted of baseline material and two non-polar spots. The major product, the least polar compound, was isolated by column chromatography in 23.5% yield, and proved to be the desired di-azaparacyclophane (186). The cyclisation, reduction procedure has been repeated on several occasions and yields have consistently fallen in the range of 12 to 24%, with the upper figure especially representing an excellent value for a cyclisation process of this type.

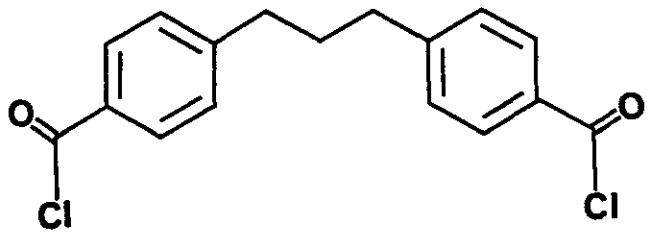
With the ring system in hand, the synthesis was completed by following the methodology used in deprotecting the tetra-4-methoxybenzyl-tetra-azaparacyclophane (172). Thus treatment of compound (186) with trichloroethyl chloroformate[123] gave the dicarbamate (187) in 89% yield after chromatography and removal of any residual 4-methoxy-benzyl chloride at 25°C and 1 x 10^{-4} mm Hg. Hydrolysis of the dicarbamate (187) to the target di-azaparacyclophane (178) was achieved in 98% yield with potassium hydroxide in a two-phase solvent mixture of 1,4-dioxan and water. It was significant that the final compound held onto 1,4-dioxan very tenaciously and this could only be removed by prolonged evaporation at very low pressure. This, it was felt, augered very well for the concept of inclusion complexation as

1,4-dioxan is of just the right size to fit into the paracyclophane cavity.

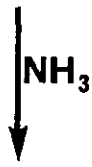
In order to prove that inclusion complexation was occurring with this di-azaparacyclophane, a series of attempts were made to grow crystals from solutions containing potential guests. Both pyrazine and tetramethylpyrazine gave amorphous material only under neutral conditions. When one equivalent of pyrazine and two equivalents of 4-toluenesulphonic acid introduced in one arm of a U-tube containing methanol, were allowed to diffuse into the di-azaparacyclophane introduced into the other arm, the resultant thin, long needles were unsuitable for X-ray crystallography. The diamine (178) was mixed with one equivalent of sulphuric acid in methanol, but a white, amorphous precipitate formed which completely defied attempts at recrystallisation. Benzene itself produced no useful material, but when the di-azaparacyclophane (178) was allowed to crystallise slowly from 1,4-dioxan, two different types of crystal formed. The first type, small needles, were of very poor quality, but the second type, large and hexagonally shaped were considered suitable for X-ray structure determination. Unfortunately these crystals were rather air-sensitive and although the paracyclophane framework was shown on the crystal structure, no 1,4-dioxan molecules could be pinpointed. Physical parameters suggested that the hexagonally shaped crystals contained 3 or 4 molecules of 1,4-dioxan for every molecule of the host. Some of these clearly had to be in intermolecular cavities within the crystal lattice and were not strongly held. The evaporation of these interstitial 1,4-dioxan units when exposed to the air was responsible for the poor X-ray results. It was encouraging to note

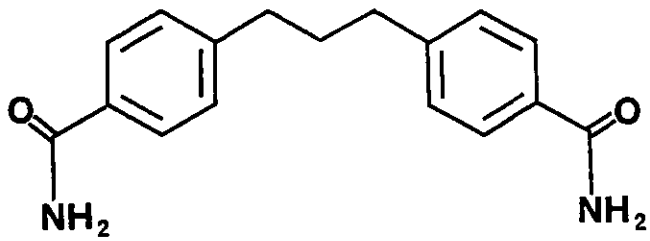
however that in the picture that was obtained (see Appendix II) the di-azaparacyclophane had adopted the desired 'face' conformation with all four benzene rings almost exactly at an angle of 90^{o} to the bottom of cavity. It was also notable that the N-H groups were pointing right into the cavity suggesting that in addition to hydrophobic interactions between the host and any possible guest, some hydrogen bonding was also occurring.

A final series of reactions led to a primary bisamine (189) which it was thought might have been used directly in a cyclisation to give the final paracyclophane (178) in one step. In the event this reaction was not attempted, as when compound (178) was made by the more conventional route described above, it was such a polar material that separating it from polymeric molecules formed in the cyclisation may well have been an insurmountable problem. The bisamine (189) did find other use later, as will be described. It was made by reaction between a dichloromethane solution of the acid chloride (182) with 0.88 ammonia solution. The insoluble primary amide (190) formed immediately as a white precipitate. Treatment of the crude bisamide (190) with lithium aluminium hydride in refluxing THF for 24 hours led to the required diamine (189) in a reasonable yield.

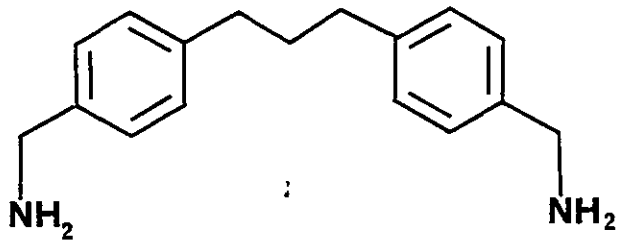


(182)





(190)



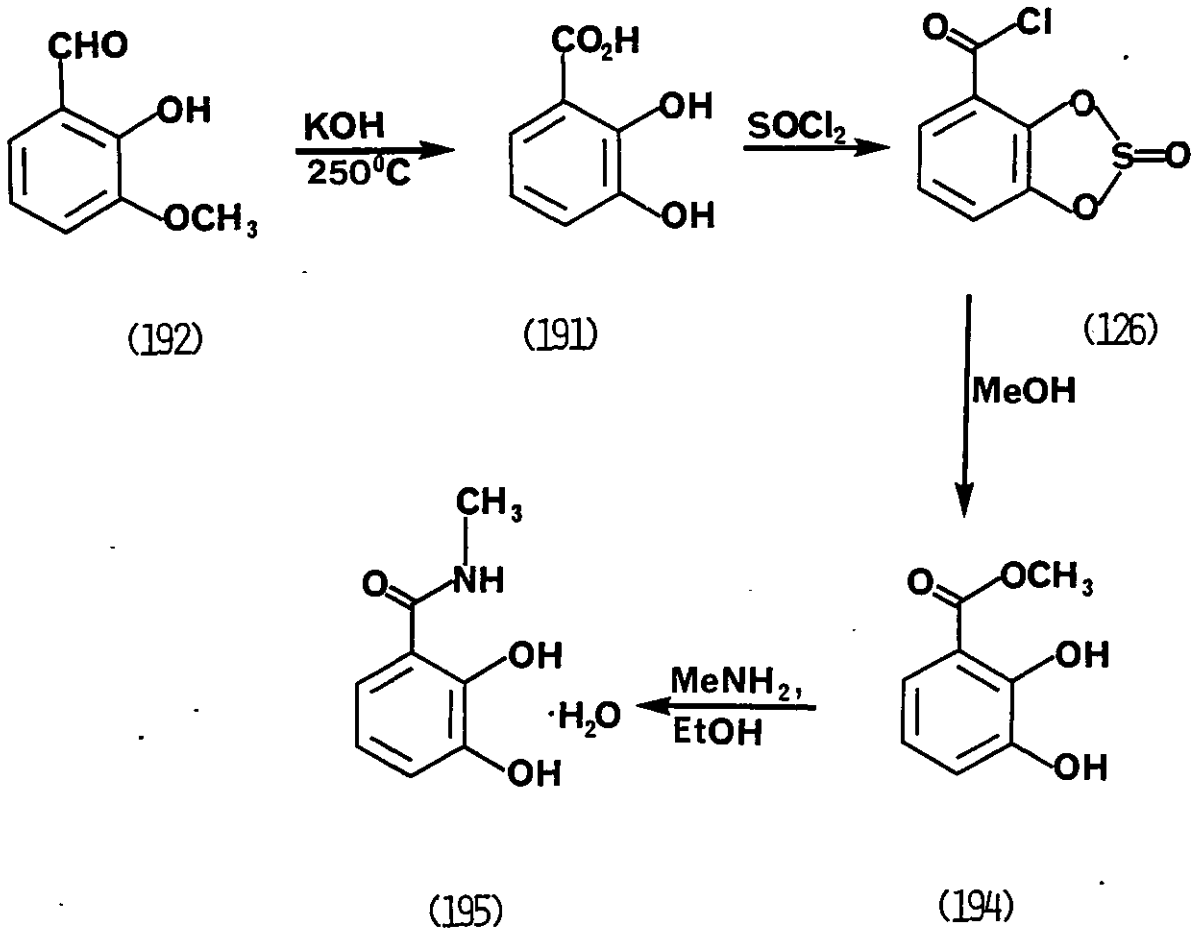
(189)

SCHEME 24

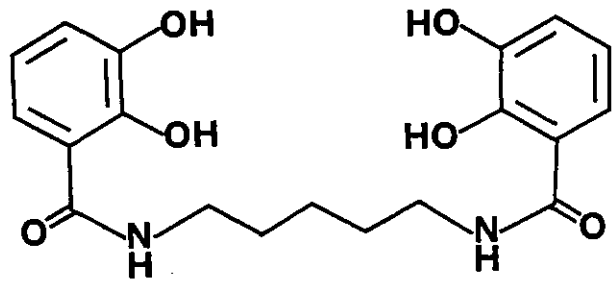
3.4 Synthesis Of Some Catechol Derivatives

With the completion of the synthesis of the di-azaparacyclophane (178) attention was turned to the new challenge of making a catechol derivative of the paracyclophane and several catechol containing model compounds. 2,3-Dihydroxybenzoic acid (191) was prepared by heating a mixture of 3-methoxysalicaldehyde (192) and potassium hydroxide to 250°[124]. This violent procedure gives good yields of the acid *via* an air oxidation and a de-O-methylation. Reaction of the acid with refluxing thionyl chloride for five hours gave the known acid chloride (126). This was once described by Corey as "2,3-dihydroxybenzoyl chloride"[69] but Raymond[76] has shown the structure to contain the cyclic sulphite unit a finding confirmed by this present work. Because of the cyclic sulphite group, this acid chloride is rather unreactive and is not an attractive synthon unless large excesses of a nucleophile are present. Conversion to the methyl ester (192) is rapid, however, when methanol is used as the solvent. The methyl ester, although initially insoluble when treated with methylamine in ethanol, slowly dissolved during the course of the reaction. The compound formed, the first of the required catecholamides (195), was isolated in 73% yield and fully characterised as its monohydrate.

Unfortunately, methyl 2,3-dihydroxybenzoate (194) did not prove useful in the synthesis of the dicatechol (196). Thus when the ester (194) and cadaverine were dissolved in dry methanol and heated to 120° in a sealed glass tube, no product could be observed. Instead only polymeric material could be seen. A less direct route had to be found.

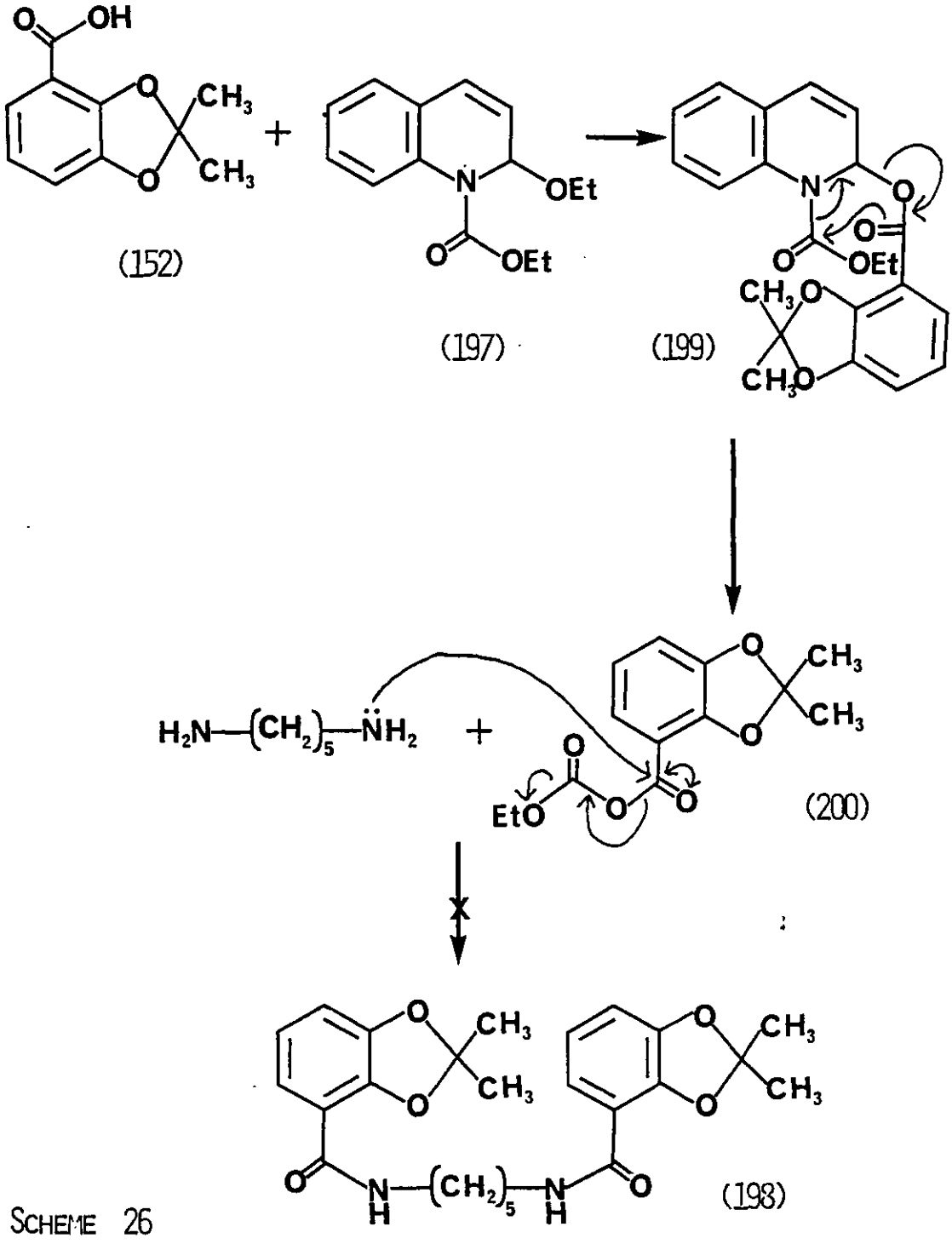


SCHEME 25



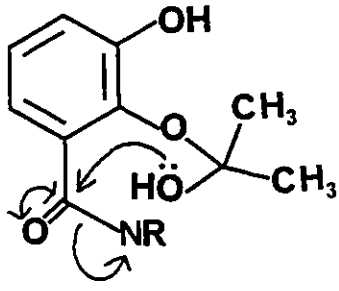
(196)

A coupling reaction was attempted between cadaverine and 2,3-dihydroxybenzoic acid acetonide (152) in the presence of EEDQ (197)[125], a dihydroquinoline containing reagent. Although some of the desired protected dicatechol (198) was obtained, a large amount of a quinoline containing impurity, probably compound (199), was also isolated.

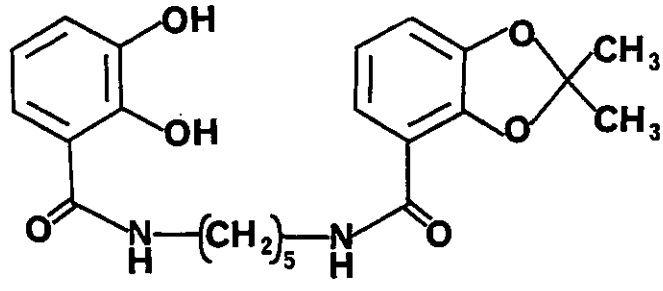


SCHEME 26

Although prolonged reaction times were used to force compound (199) to decompose to the ethoxy anhydride (200) no real success was evident. The protected derivative (198) was finally made in good yield by condensation of cadaverine with the acetonide of 2,3-dihydroxybenzoyl chloride (67). Deprotecting the molecule (198) proved impossible. The literature method[73] using an 80% aqueous solution of glacial acetic acid furnished a mixture of the monoacetonide (201) and 2,3-dihydroxybenzoic acid (191). Thus the hydrolysis conditions were vigorous enough to cleave the amide bonds at approximately the same rate as deprotection of the catechol. The amide hydrolysis may be especially facile in this case due to the intermediacy of a partially deprotected moiety (243) that was acting as an internal nucleophile. More dilute acetic acid solutions were



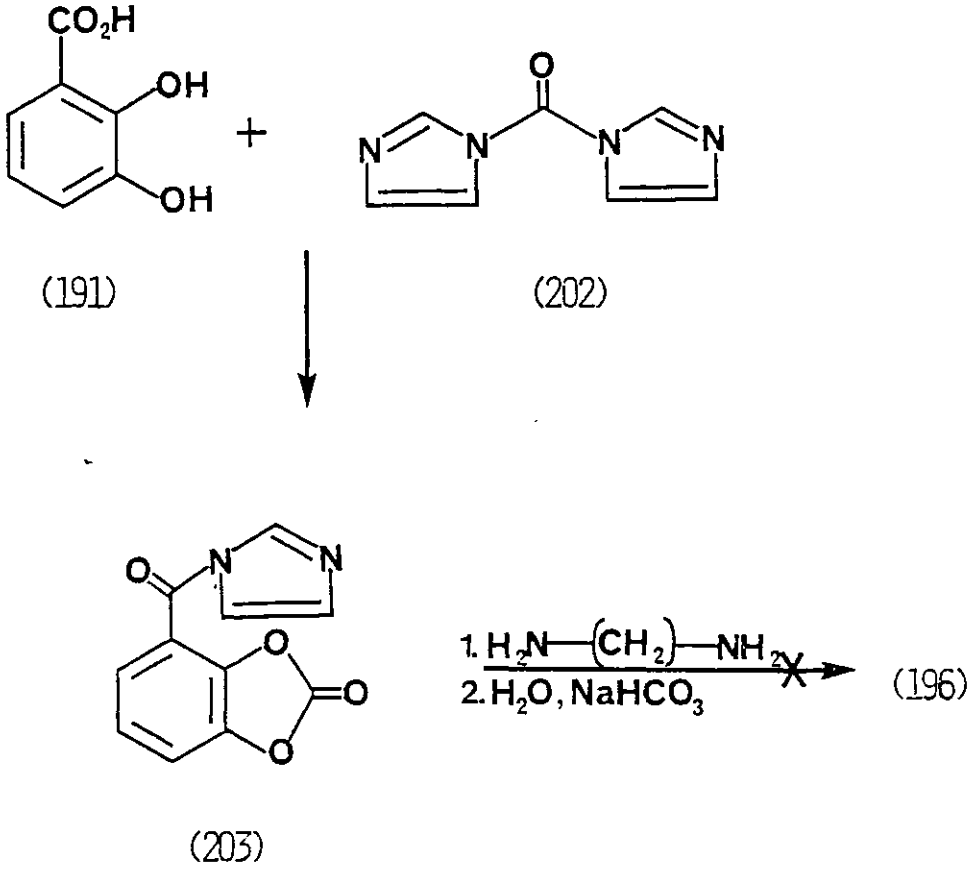
(243)



(201)

used in the hope of being rather more selective but no suitable conditions could be found. A solution of hydrochloric acid led, after reflux for half an hour, to only baseline materials by tlc.

The acetonide group was causing so many problems that its use was abandoned. Attempts at using a diphenylsilyl protecting group[126] led only to complex mixtures of products. Cyclic carbonate methodology was also tried. 2,3-Dihydroxybenzoic acid (191) was reacted with 1,1′-carbonyldiimidazole (202) which gave the crude protected imidazole ester (203). Treatment of this with cadaverine followed by an aqueous work up procedure, led to an intractable mixture of several compounds, one of which was the desired tetraphenol (196) as evidenced by the mass spectrum. The route was completely unsatisfactory as none of the intermediate compounds could be properly purified or characterised.

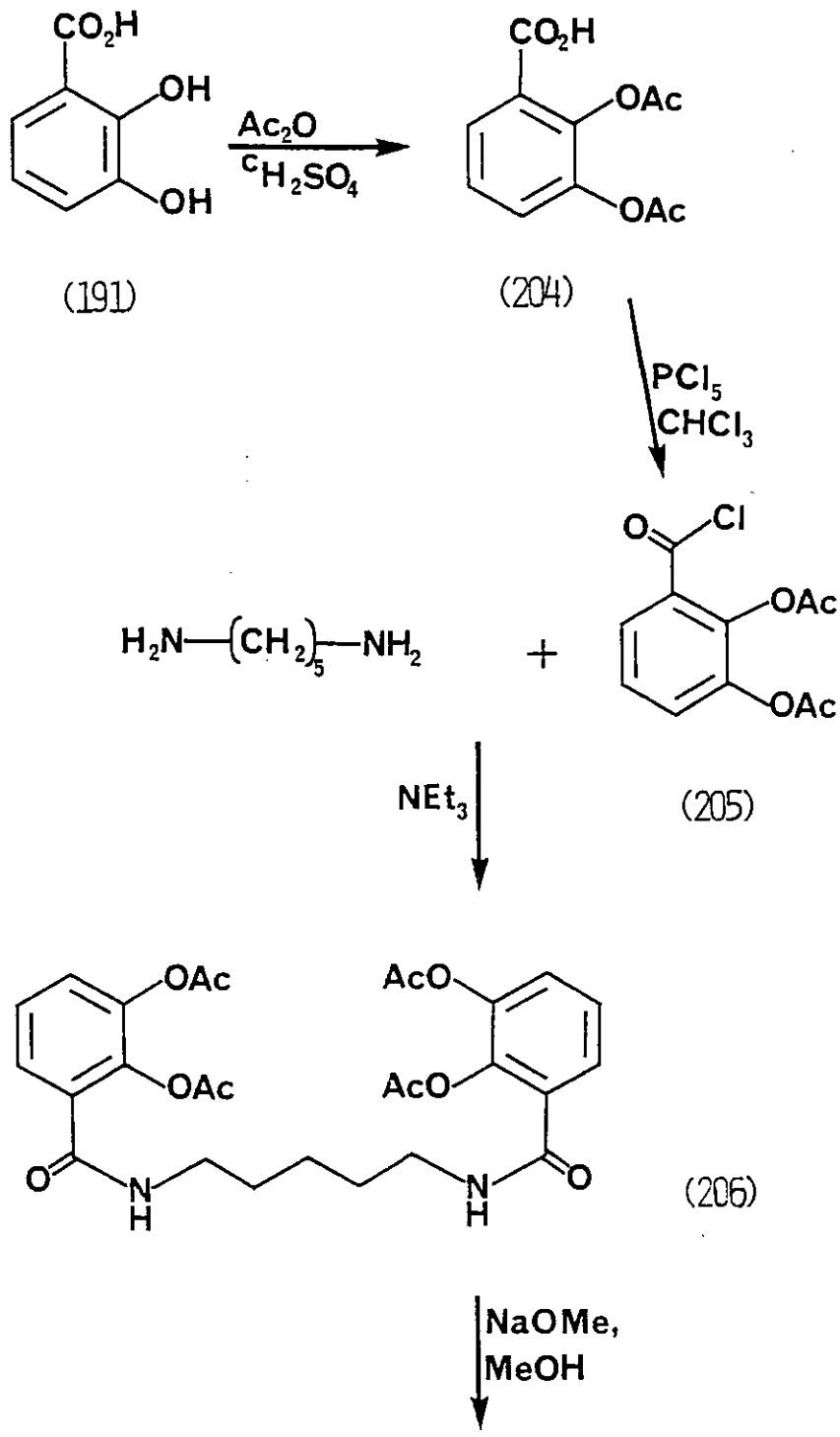


SCHEME 27

Whilst work leading to the biscatechol (196) was in progress the molecule was in fact synthesised in the literature[100] from the acid chloride (126) and cadaverine by direct condensation. However as this synthon in our hands had not previously been of any use and because the yield of the final product was poor (40%), work continued to look for a better procedure.

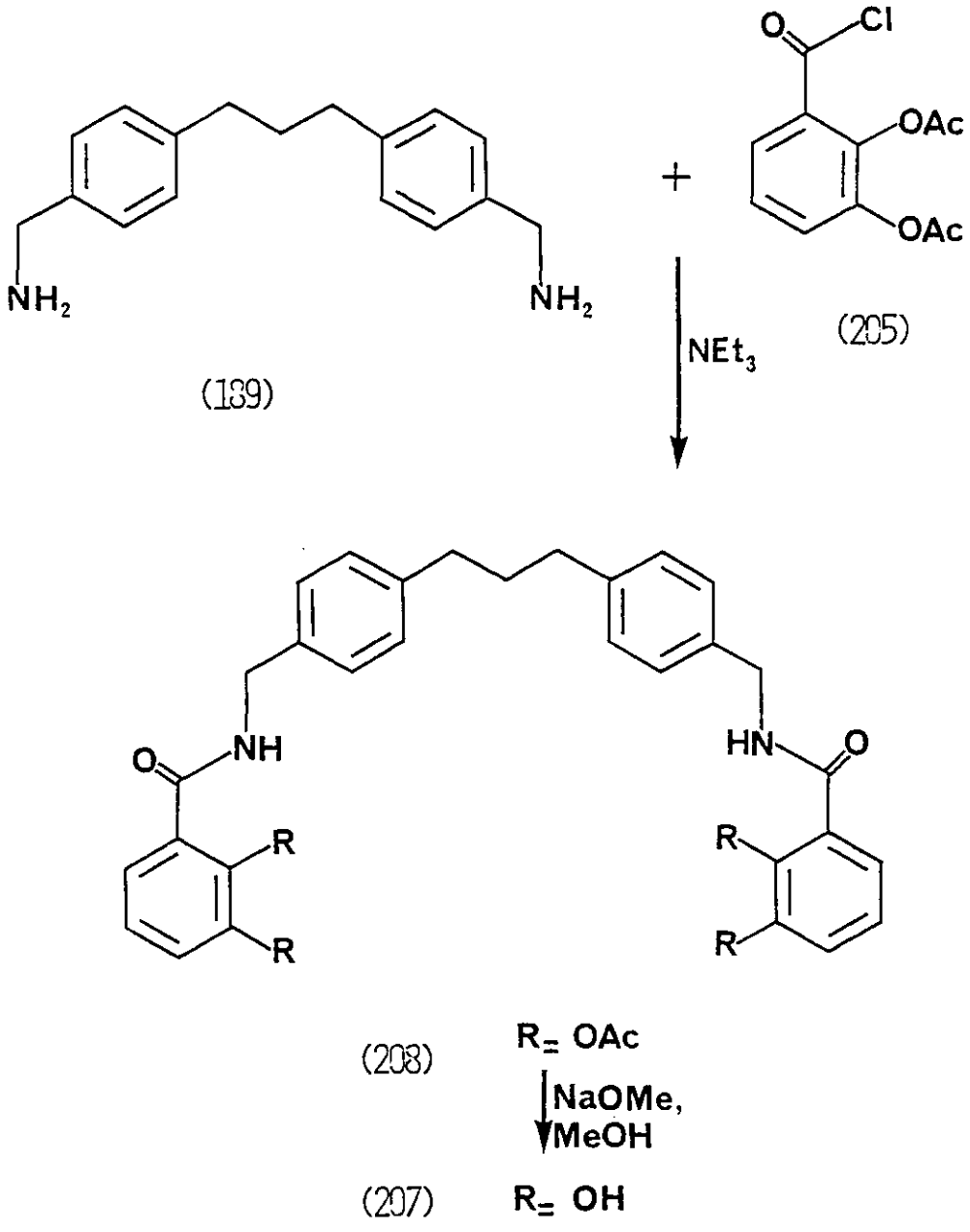
We turned next to a more conventional protecting group, the acetate moiety. Following a method of Bergeron[92], 2,3-diacetoxybenzoic acid (204) was made in 91% yield from 2,3-dihydroxybenzoic acid (191). Conversion to the acid chloride (205) was also achieved by a known route[92]. The tetraacetoxy catechol (206) was obtained by treatment of the acid chloride (205) with cadaverine in 95% yield and this material was deprotected with a very slight excess of sodium methoxide in methanol in 85% yield. It was essential to carry out the deprotection under an inert atmosphere as the intermediate catecholate anions are very air-sensitive.

With the establishment of this synthetic method, another primary bisamine (189) was treated in exactly the same way and the final tetraphenol (207) isolated in small, but workable yield. The yield of the final deprotection in this scheme was rather poor due to a problem of quinone formation that could not be fully supressed.

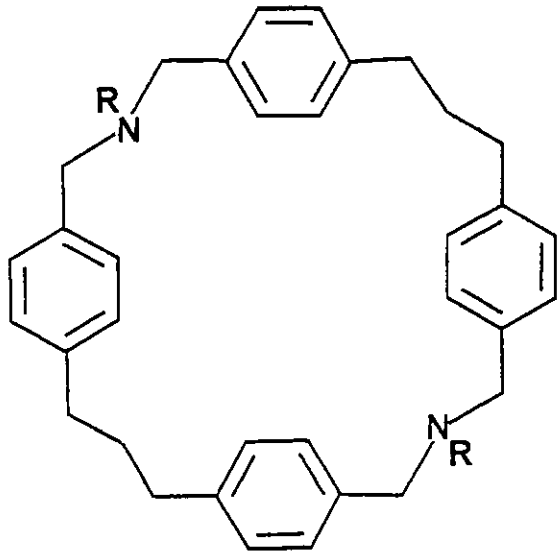

CO2H
OH
OH
Ac2O
cH2SO4
CO2H
OAc
OAc
(191)
(204)
PCl5
CHCl3
O
Cl
OAc
OAc
H2N—(CH2)5—NH2
+
NEt3
(205)
OAc
OAc
AcO
AcO
O
N
H
N
H
O
(206)
NaOMe,
MeOH
(196)

SCHEME 28

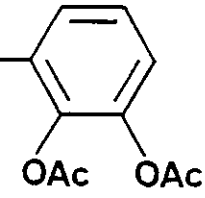
SCHEME 29

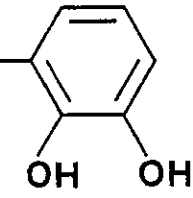


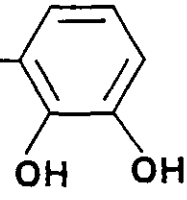
Having successfully made three model compounds, the azapara-cyclophane (178) was derivatised. Conversion to the tetraacetate (209) was achieved in quantitative yield. Deprotection led to the tetraphenol (210) but this compound unfortunately could not be fully characterised. Spectral data indicated however that the crude material was mainly the desired compound (210) and so this was used as isolated in the subsequent hydroxylation reactions.



(178) R= H

(209) R= C(=O)– 

(210) R= C(=O)– 

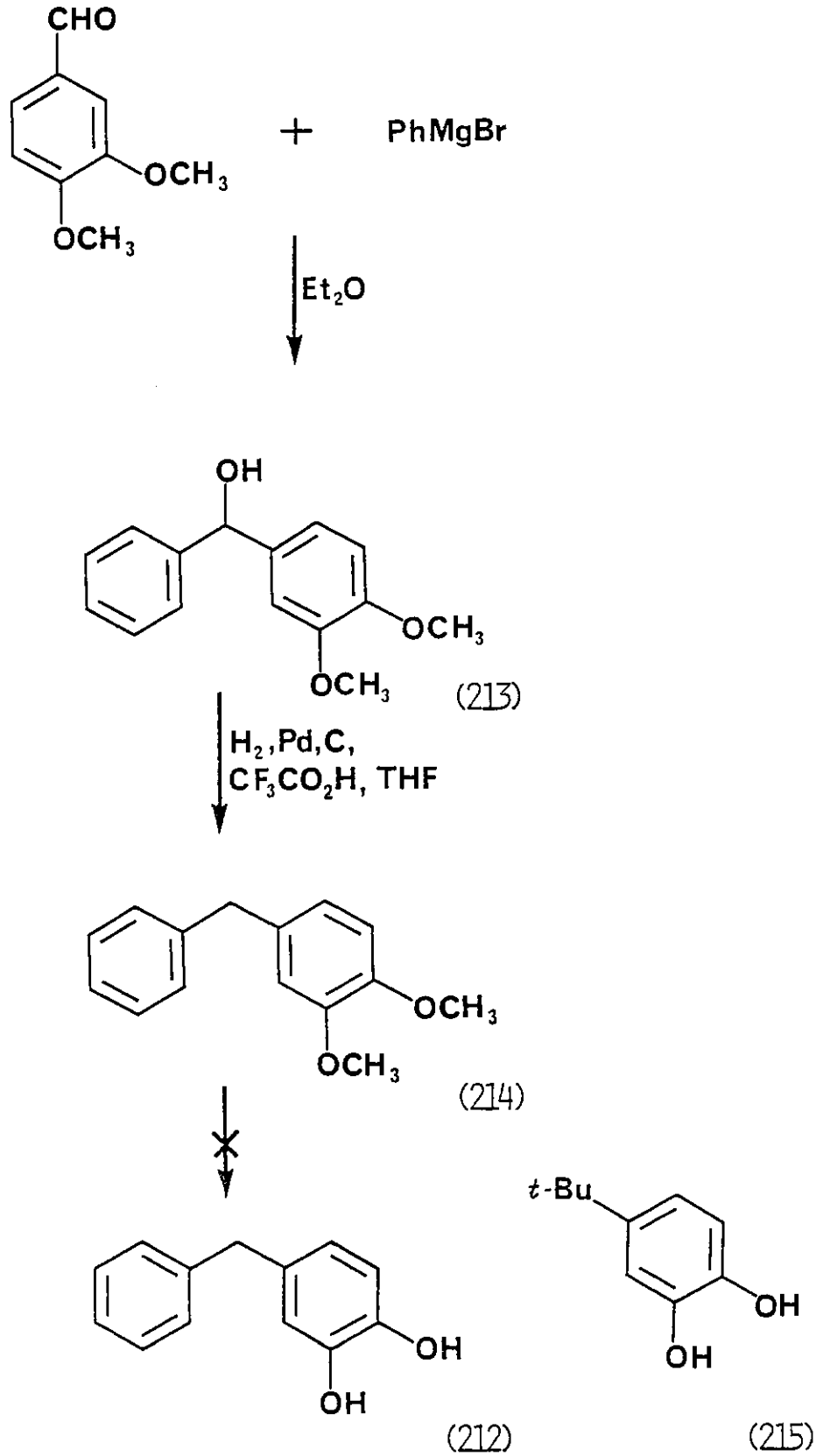
(211) R= H_2C– 

As it was desirable to examine the hydroxylation process with a catalyst containing an amine rather than an amide nitrogen, to see what effect, if any, this would have on the shape of the cavity, a series of reductions were attempted.

The model tetraacetates (206) and (208) were subjected to reduction with both lithium aluminium hydride and diborane, but the desired secondary amine catechols could not be isolated, presumably due to the formation of very tightly bound complexes with the metal ions from the reducing agents.

When the paracyclophane tetraacetate (209) was reacted with diborane however, the tertiary amide group smoothly reduced and the protecting acetates removed, after a twenty four hour reflux in THF, quenching and reflux with methanol, and column chromatography. Thus this key compound (211) was isolated in 57% yield and both amine and amide paracyclophane catechols were available for further study.

Whilst this work was in progress some Japanese workers[127] reported on a study of the hydroxylation of benzene with various substituted catechols, ferric ion and hydrogen peroxide. One of the best catechols they used was 4-benzylcatechol (212) and for the purpose of comparison, it was deemed desirable to have available a sample of this material. 3,4-Dimethoxybenzhydrylalcohol (213) was prepared by a Grignard reaction between phenyl magnesium bromide and 3,4-dimethoxybenzaldehyde. Hydrogenation of the alcohol using palladium on charcoal and trifluoroacetic acid gave (3,4-dimethoxyphenyl)phenylmethane (214) in a 53% yield. Unfortunately the deprotection of this material proved very difficult. The literature method[130] which utilises hydrogen bromide in acetic acid gave incomplete deprotection. Trimethylsilyl iodide[128,129] was used but this failed to give any reasonable product. The use of hydrogen iodide led to a black tar. Other agents such as boron tribromide were not used as 4-t-butylcatechol (215), a commercially available compound, similar to many of the catechols used by the Japanese[127], was considered a suitable agent for the required task of comparison.


CHO
OCH3
OCH3
+
PhMgBr
Et2O
OH
OCH3
OCH3
(213)
H2,Pd,C,
CF3CO2H, THF
OCH3
OCH3
(214)
OH
OH
(212)
t-Bu
OH
OH
(215)

SCHEME 30

3.5 Hydroxylation Studies

Four synthetic dicatechols, (196), (207), (210), and (211), one synthetic monocatechol (195) and two commercially available compounds, catechol (216) and 4-t-butylcatechol (215) were all used in conjunction with ferric ion and hydrogen peroxide in an hydroxylation study of benzene.

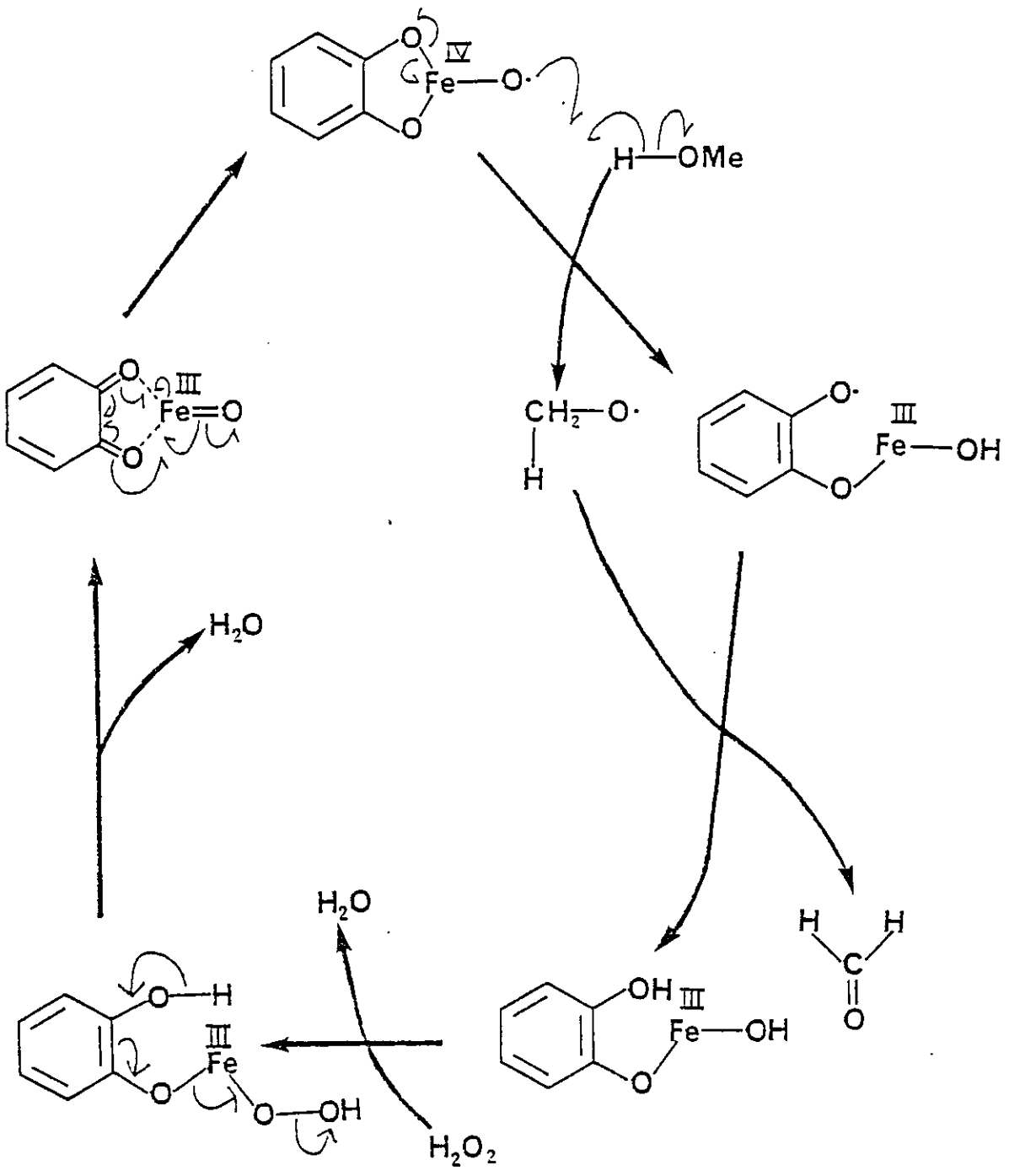
The first approach consisted of trying the hydroxylation in a single-phase system, using enough methanol to achieve homogeneity in a solution that contained both benzene and an aqueous buffer. The original investigation of this system by Hamilton[104,105] had taken place in a single, aqueous, phase saturated with the aromatic substrate under study. More recent Japanese work[127.131] uses two-phased systems.

The single-phased reaction, when attempted with 4-t-butylcatechol (215) as catalyst and 10 equivalents of hydrogen peroxide, showed that phenol was appearing as the peroxide was used up. However, actual amounts of phenol produced were very small despite consumption of all the oxidant. Hamilton[104] has demonstrated that in his system the rate of the reaction has a first-order dependence on the hydrogen peroxide concentration. Our system however could produce no meaningful kinetic data, as the presence of large amounts of methanol and benzene made the potassium permanganate titration, used to assay for hydrogen peroxide, too inaccurate to indicate anything other than rather general trends. To deduce whether the reaction was stopping because of destruction of the ferric-catechol "catalyst" or for some other reason, a further experiment was performed. With

conditions as before, several aliquots of hydrogen peroxide were added, a new one being introduced to the reaction mixture as soon as phenol production had stopped. As before, a first aliquot led to the production of a small amount of phenol. When a second, ten equivalents of peroxide was added however, phenol production immediately picked up and stopped only when just about twice the original amount of phenol was present in solution. A third aliquot indicated that phenol production was still taking place at its original rate. Thus one could conclude that the catalyst was remaining active even after the consumption of all the peroxide. However, this did not explain the rapid reaction of peroxide, 99% of which was not being used in hydroxylation.

An answer might be available in the literature[104] where it is suggested that the presence of an organic solvent has an inhibiting effect on the reaction, because it may preferentially react with the activated catechol complex rather than the desired aromatic substrate. The formal mechanism of the hydroxylation process will be discussed later but a brief outline of the reaction of the postulated iron(IV) active species with methanol is shown below.

As can be seen, no destruction of the catalyst occurs in this putative scheme but a smooth production of formaldehyde from methanol could be occurring. In the event a cursory investigation revealed no formaldehyde, but no really sensitive methods were employed to systematically look for this compound, which would probably only be present in very small amounts.


IV
Fe—O·
H—OMe
III
Fe=O
CH2—O·
H
III
Fe—OH
H2O
H2O
H2O2
III
Fe
O—OH
OH III
Fe—OH
H H
C
O

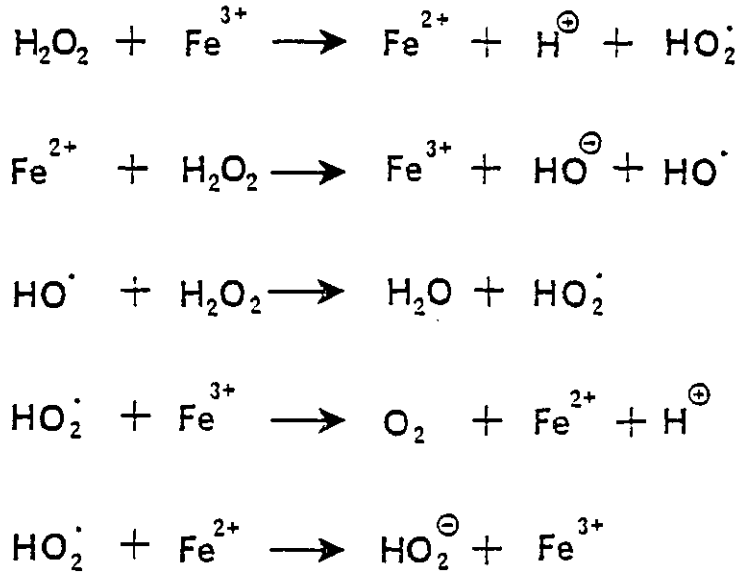
SCHEME 31

Rather discouraged at this stage, the two-phase system was considered. Using a modification of Hotta's conditions[127], the iron(III)–catechol complex was formed in a benzene and water mixture. In some cases, the dark blue complex coloured the aqueous layer, in others the benzene phase, whilst with some of the dicatechols it was totally insoluble.

A few reactions were first performed to establish the best conditions for the reaction and initial results were promising. Again using 4-t-butylcatechol (215) and 10 equivalents of hydrogen peroxide, 9.5 μmoles of benzene were converted to phenol. Thus having started with 10 μmoles of the catechol (215) the system could almost be considered catalytic. On this occasion about 90% of the peroxide was unaccounted for. Again repetitive additions indicated that the catalyst was still active, and after five or six aliquots, that is fifty to sixty equivalents of peroxide, significantly large amounts of phenol had been formed. When N-methyl-2,3-dihydroxybenzamide (195) was used as the catalyst, 30.5 μmoles of phenol were formed from 10 μmoles of catalyst and 600 μmoles of hydrogen peroxide. Addition of a seventh aliquot of hydrogen peroxide led to no further phenol production, with the catalyst apparently destroyed. Details of exact amounts of phenol formed during this iterative procedure may be found in tabular form under the relevant experimental method. A comparison of our yields and the reported Japanese yields[127] was instructive at this stage. It can be seen that the amount of phenol formed by equivalent amounts of catalyst in the two studies was about the same, with our yields comparing favourably with the best

Japanese ones. However when hydrogen peroxide usage is considered, the Japanese procedure is about ten times more efficient.

No reasons could be given to resolve this conflict, but it would seem that in our system some non-destructive process was occurring to consume the peroxide. A qualitative experiment was performed in the presence of an oxygen electrode, whereby hydrogen peroxide was added to an aqueous, buffered solution of the ferric ion–N-methyl-2,3-dihydroxybenzamide (195) complex. Oxygen evolution occurred very rapidly. Some blank experiments where either the catechol (195) or iron(III) were left out, led to a very much slower disproportionation of the hydrogen peroxide. Hitherto nobody has mentioned such a process in connection with the iron (III)–catechol system but there is evidence in the literature[132] that ferric ion, with certain ligands, can act as a catalyst for oxygen evolution from hydrogen peroxide. One can envisage a process as shown below, occurring. The mechanism, if correct, shows that although the oxidation level of the iron changes several times as two moles of peroxide are decomposed, eventually the desired ferric species is regenerated. However in addition to the oxygen produced, several very reactive species appear in the solution at various times which can only help to destroy the catalytic activity of the system. The disproportionation reaction is pH dependant, with the rate increasing as the solution becomes more basic.



SCHEME 32

Having now established a catalytic system, which despite consuming large amounts of peroxide gave reasonable yields of phenol, a systematic investigation was performed for all seven catechols to see which was the best catalyst. The results are shown in Table 1. The reactions were performed in 5M acetate buffer (pH 4.2) using 100 equivalents of hydrogen peroxide. 10 μmole of each catalyst was used.

TABLE 1

CATECHOL X NO.	POSITION OF COMPLEX	PHENOL FORMED/μmole	DURATION OF REACTION/MIN.
(216)	SOLUBLE AQUEOUS	27	80
(215)	SOLUBLE BENZENE	35	110
(195)	SOLUBLE AQUEOUS	32	80
(196)	SOLUBLE AQUEOUS	59	170
(207)	INSOLUBLE	54	160
(210)	INSOLUBLE	47[a]	-[b]
(211)	INSOLUBLE	48	110

a. 200 equivalents peroxide required

b. As two aliquots were required of peroxide no time was recorded

Considering first the yields of these reactions - the monocatechols (215), (216), (195) all gave similar amounts of phenol, with the best appearing to be 4-t-butylcatechol (215) with 35 μmoles of product.

The dicatechols (196) and (207) gave just under twice the amount of phenol compared with the monocatechols, and most disappointingly the two paracyclophane dicatechols (210) and (211) gave more phenol than all the monocatechols but less than the other dicatechol species. This implied that the azaparacyclophanes were not shielding the attached catechols sufficiently to prevent autodegradation.

Apart from phenol, small amounts of by products were noted in each reaction, these presumably being polyhydroxylated species. The presence of the paracyclophane seemed to lead to no significant lessening in the amounts of these compounds.

Although no accurate rate measurements could be obtained due to the two-phase nature of the reaction medium, the time taken for maximum phenol production was measured. This showed that the rate of reaction associated with the paracyclophane catechol (211) was slightly greater than the rates shown by the other catalysts. Here at last was some evidence that the paracyclophane was performing a useful function in the system, but as this species produced less phenol than other similar dicatechols, this finding was of little significance.

Looking at the yields for the monocatechols some surprising contradictions with Hotta's work[127] were noted. He had found that benzene-soluble complexes, were far more efficient catalysts for phenol production than water-soluble ones. He reasoned that this was due to protection of the catechol complex in the benzene phase from the

attack of hydrogen peroxide in the aqueous phase. It has to be reported that we found no such discrimination between the two types of complex with both performing their catalytic function with almost equal efficiency. Again no satisfactory answer to this conflict can be given.

The yields obtained by the dicatechols, especially the paracyclophane ones, were very disappointing. When the project was first conceived it was envisaged that the azaparacyclophane dicatechol would be held together in a fixed, well-defined manner by a bischelated ferric ion. A lot of work has been done[66,133,134,135] on the thermodynamic stability constants of simple iron(III) catechol complexes, and from these it may be deduced that for some catechols, at least, only a monochelated complex exists below pH 6. More recent work[136] suggests that the situation in a solution containing iron(III) and catechol is rather more complicated. Redox reactions are shown to occur below pH 7 to give iron(II) species which are thought to be bis- and tris-catecholate moieties. Thus in solution at various pH, different complexes and combinations of complexes, are believed to occur. However, the thermochemical data for two isolated catechol moieties cannot be directly applied to two linked catechols as the entropy increase observed on bischelation should stabilise such an effect under a wider range of conditions, and so in the case of the paracyclophane an even more complex situation is likely to be prevalent. If at pH 4.2 the predominant paracyclophane catechol species was existing as a monochelate with iron, then the whole conformation of the molecule was likely to be in an unfavourable

mode to allow apecific complexation of the benzene. Unfortunately the results obtained seemed to indicate two possibilities. Firstly, one could postulate that at pH 4.2 a bischelate was being produced but the catalyst was not behaving as had been envisaged. The second possibility was that mainly the undesirable monochelate was being produced at the reaction pH, with the projected increase in entropy being insufficient to stabilise the required bischelate. This would render the molecule unfit to perform in the required fashion. If this second eventuality was correct, then one could look at the dicatechol system attached to the paracyclphane as being little more than two individual catechol groups. Hence, during the reaction, the ferric ion would bind to one catechol moiety only, until this was destroyed (the mode of destruction will be discussed later), and then move over to bind with the spare catechol and continue with the hydroxylation until this too was destroyed.

This would still not explain why the paracyclophane dicatechols were less efficient than even the simple dicatechols (196) and (207), both of which had given approximately twice as much phenol as the monocatechols, as was to be expected from the picture presented above. A plausible explanation may be found in Hamilton's study[104,105] where he found that already hydroxylated species were more reactive towards further oxidation. In the system used by us polyhydroxylation did not appear to be a real problem possibly due to the very dilute nature of the reaction medium. However in the case of the paracyclophane dicatechols, the 'spare' catechol moiety attached to the paracyclophane was held in very close proximity to an active catalytic species (centred

on the other catechol moiety on the molecule) and so it could be expected that this was a candidate for rapid hydroxylation. The effect of such a reaction would be to render the 'spare' catechol useless for later catalysis. The simple dicatechols (196) and (207) were more or less free of this problem because of the greater flexibility that is inherent in their structures.

To examine whether a bischelated complex is capable of hydroxylation, 4-t-butylcatechol (125) was used at pH 6, where the bischelate should be the predominant species in solution. No phenol was obtained from this reaction but it is possible that the pH dependant hydrogen peroxide disproportionation was dominating all other reactions in this less acidic medium.

At this point it was evident that the paracyclophane dicatechol was not performing the desired hydroxylation at pH 4.2. Whether this was due to a lack of bischelation, or for some other reason, was unclear. Moving to higher pH values completely stopped the production of phenol and it was becoming increasingly obvious that the paracyclophane system could never really develop into a useful catalyst. The aim now was to optimise the conditions of the procedure, such as it was, to maximise phenol production.

During the course of the hydroxylation studies at pH 4.2 some interesting and distinct trends emerged, involved with the rate of phenol production. In all cases, the formation of phenol was slow to start with, speeded up after an induction period, and then levelled off as maximum phenol production was achieved.

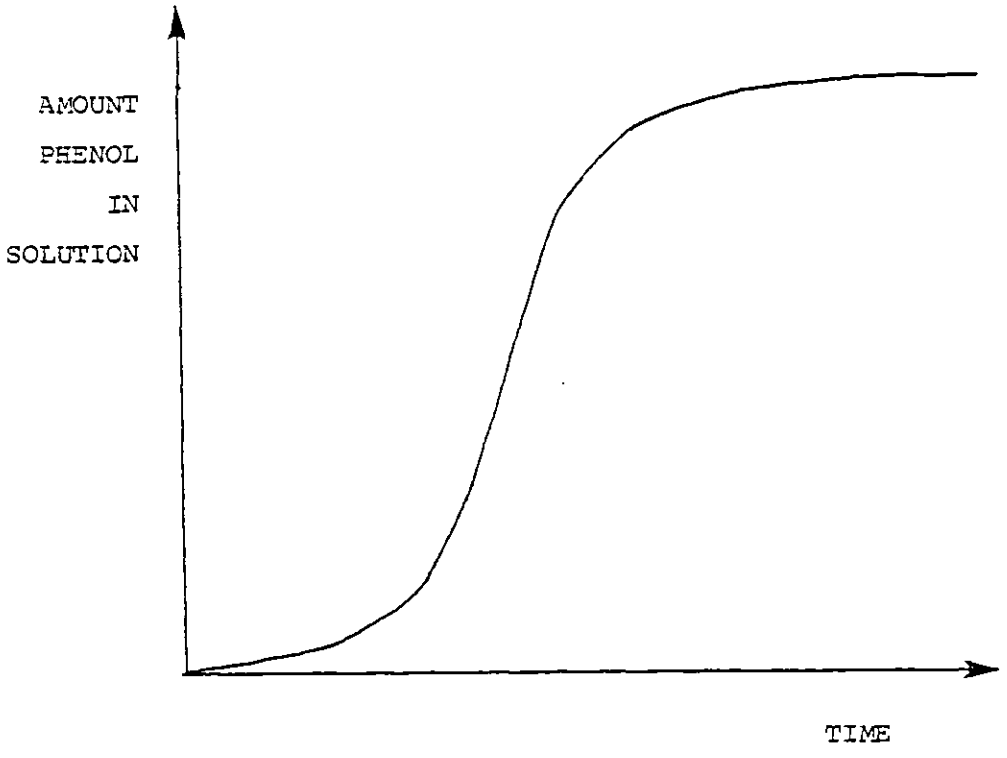


FIGURE 1

The reason for this behaviour became clear when the pH of the solution was measured at the end of the reaction. It had fallen to a value of 3.45 during the course of the hydroxylation. Thus the buffer used was not capable of absorbing the acid generated during the course of the reaction. It should be pointed out that the Japanese workers[127], whose conditions were being followed quite closely, used a considerably less concentrated buffer and so would have experienced the same shortcomings.

TABLE 2

BUFFER USED	STARTING pH	END pH	DURATION OF REACTION/MIN.	PHENOL FORMED/μmole
5M ACETATE (pH 4.2)	4.15	3.45	110	35
1M FORMATE (pH 2.6)	2.60	2.60	60	93
1M ACETATE, 0.1M FERRIC CHLORIDE (pH 4.25)	4.25	2.95	>120	51[a]
1M ACETATE (pH 4.2)	3.30[b]	2.65	60	96
NO BUFFER	3.30	2.40	70	78
NO BUFFER	6.0[c] 7.6	6.0- 7.6	-	-

a. reaction not complete

b. pH of acetate buffer adjusted before the addition of ferric chloride

c. reaction done with periodic additions of sodium hydroxide to keep pH above 6.0

Whatever the source of the acid, its appearance turned out to be valuable. As the reaction medium became more acidic, the rate determining step in the hydroxylation procedure, the loss of hydroxide ion from the iron(III)-peroxide-catechol complex, became more rapid. Prompted by this finding, several different buffers were tried and the results are shown in Table 2. In all cases 4-t-butylcatechol was used as catalyst and 100 equivalents of hydrogen peroxide were introduced. All the buffers contained 0.1M ferric chloride solution.

Of the buffers examined it was eventually decided to complete investigations into the system in a formate buffer at pH 2.6. The reactions at this lower pH were characterised by a much more rapid and steady reaction than at pH 4.2, and by the production of more phenol. Table 3 shows the yields of phenol produced at pH 2.60, with 10 μmoles of each catalyst and 100 equivalents of peroxide.

In all cases addition of further hydrogen peroxide did not restart the reaction. Looking at the yields for this lower pH, the dicatechols did not produce significantly more phenol than their mono- counterparts. This indicates that the 'spare' catechol moieties were being hydroxylated more quickly. No significant improvements were noted however, when in an attempt to utilise both catechols on the dicatechol (196) simultaneously, twice the normal amount of ferric ion was added. Slightly more phenol was observed in this case but not enough to make this aspect worthy of further investigation.

TABLE 3

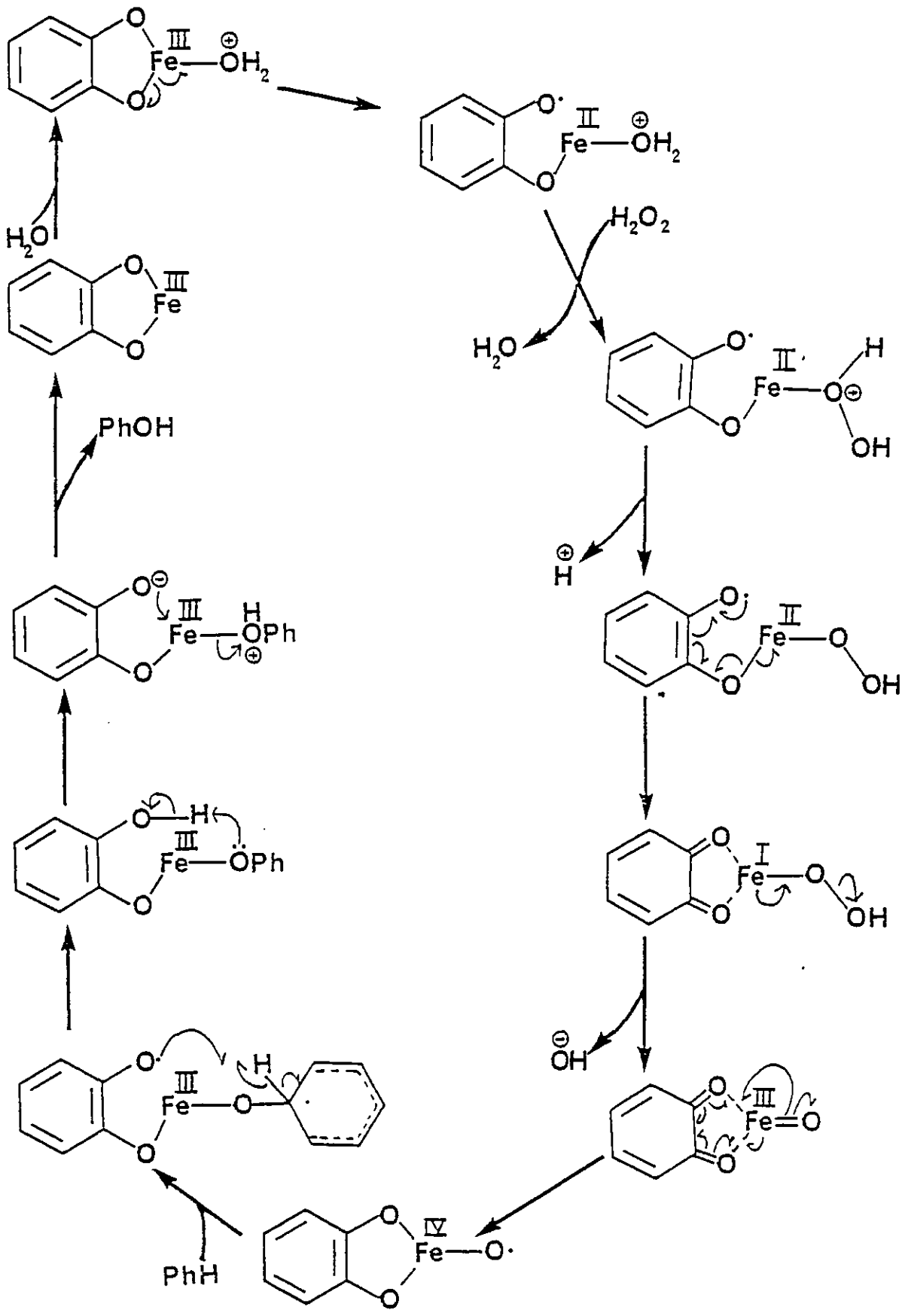
CATECHOL USED	POSITION OF COMPLEX	PHENOL FORMED /umole	DURATION OF REACTION /MIN
(216)	SOLUBLE AQUEOUS	61	70
(215)	SOLUBLE BENZENE	93	60
(195)	SOLUBLE AQUEOUS	76	50
(196)	SOLUBLE AQUEOUS	87	25
(207)	INSOLUBLE	78	40
(210)	INSOLUBLE	70	60
(211)	INSOLUBLE	75	60

The yields we could now report were considerably better than the best Japanese yields[127]. The move to lower pH values was beneficial for two main reasons. Firstly, as already noted, the rate-determining step of the process was speeded up. Secondly some of the disproportionation of the hydrogen peroxide was suppressed, thus allowing the catechol-iron(III) complex a greater opportunity to

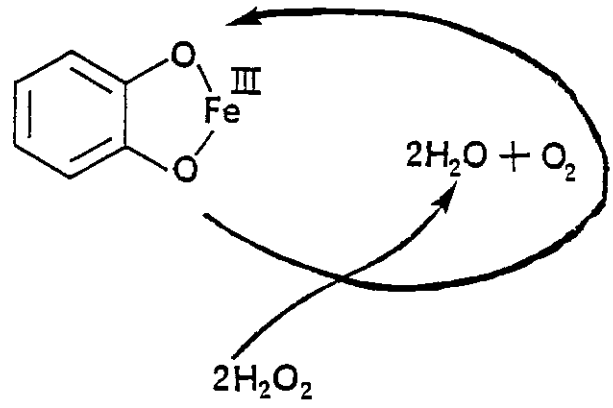
hydroxylate benzene, before it was destroyed.

It would be instructive to turn to the mechanism of the whole hydroxylation process. Hamilton in 1966[105] proposed a mechanism for the procedure that is still basically sound, although one or two details do need some revision in view of more recent findings. The most important of these concerns the oxidation state of the initial iron-catechol species, which Mössbauer studies have recently shown[136], at pH 4.5 or less, has iron in a ferrous oxidation level.

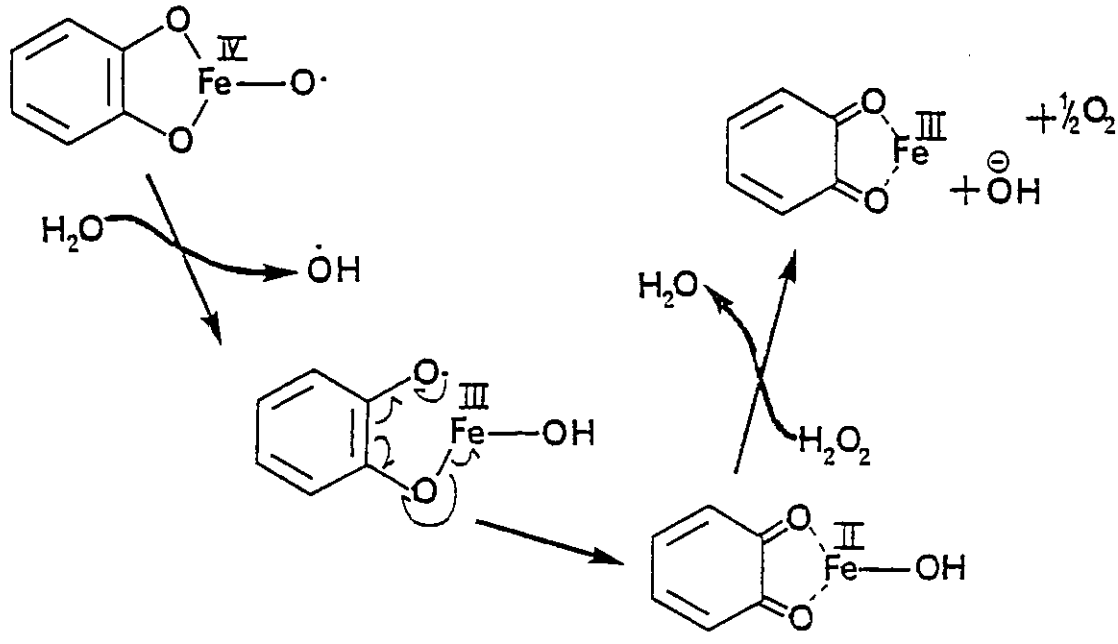
An omission from Hamilton's proposal[105] is mention of the way the catalytic system becomes deactivated. This is believed to occur by attack of the hydroxylating species on water. The resulting ferrous-quinone moiety is oxidised to a ferric-quinone species which is catalytically inactive and from which a useful catechol species cannot be generated. Scheme 33 shows the most acceptable rationalisation of the mechanism for the hydroxylation process. It also includes one of the modes of catalyst destruction as discussed. It should be noted that the attack of water onto the active iron(IV) species also leads to the formation of the hydroxyl radical which would be capable of destroying the catalyst. One interesting reaction tried, in an attempt to suppress attack by water, was to do the reaction in absence, as far as is possible, of water. Thus, the 4-t-butylcatechol complex was formed in the benzene layer and the aqueous phase removed. Addition of hydrogen peroxide solution at this stage, produced no phenol after a prolonged period of reaction. Thus paradoxically, the reaction it seems has to take place in the


III
Fe
OH2
H2O
H2O2
II
PhOH
H
OPh
OH
I
PhH
IV

Hydrogen Peroxide Disproportionation Route



One Possible Mode of Catalyst Deactivation



SCHEME 33

aqueous phase, in which, it is thought catalyst destruction occurs.

The disproportionation of hydrogen peroxide is also incorporated into Scheme 33, and this probably occurs at the stage of the catalytic cycle when the ferric ion is present, and hydroxylation is not in progress, as shown.

To see if any further improvements in the hydroxylation could occur by use of a different metal, reactions with ruthenium(III) were attempted. These totally failed to give any phenol but from the evident gaseous evolution, a rapid disproportionation of peroxide was still occurring.

Some experiments were attempted using different catalysts to see if these could be persuaded to hydroxylate benzene. Unfortunately ferrous ion and oxygen in the presence of both 2-aminothiophenol[108] and 2-mercaptobenzoic acid[107] gave no detectable amounts of phenol.

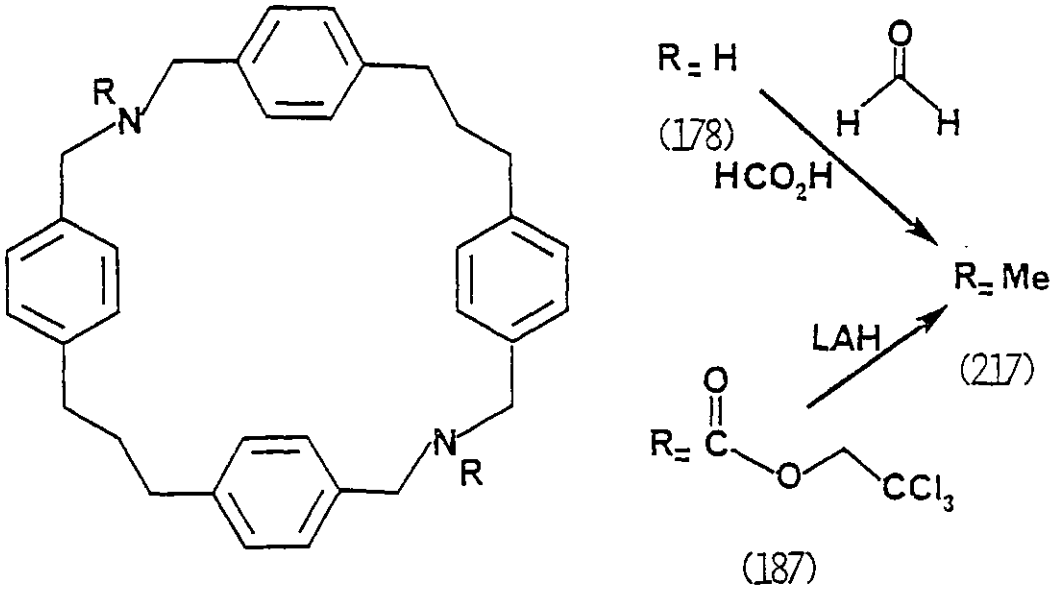
Thus it can be concluded that the catechol-iron(III)-hydrogen peroxide system can be made to convert benzene to phenol in quite respectable yields, but mounting two catechols onto a di-azaparacyclophane molecule is of no discernable advantage to the process.

3.6 Further Complexation Studies on the Di-aza[3.3.3.3]-paracyclophane System

After the very disappointing hydroxylation results with the di-azaparacyclophane dicatechol(211) it was decided to examine further the complexation properties of the di-aza[3.3.3.3]paracyclophane system.

The di-azaparacyclophane (178), as already discussed, had not given a useful X-ray crystallographic picture. ^{1}H nmr studies were not possible with this material due to its insolubility in aqueous acid, a solvent where any significant binding would have been apparent. Thus it was converted to its di-N-methylated derivative (217), a procedure that could be performed in two ways. The first involved the direct methylation of the di-NH compound (178) with formaldehyde and formic acid leaving the required compound (217) in 68% yield after column chromatography. Lithium aluminium hydride reduction of the dicarbamate (187) also led to the di-N-methylated compound (217) but in much poorer yield.

Compound (217) was a highly crystalline compound and on recrystallisation from benzene produced needles that were stable and suitable for an X-ray crystallographic study. The final picture provided a major surprise. Rather than observing the expected inclusion complex between the paracyclophane (217) and benzene, no guest was observed at all. The conformation of the azaparacyclophane (217) was such that no cavity existed in the centre of the molecule (see appendix II).



SCHEME 34

Two of the benzene rings in the molecule had folded in such a way as to fill the intramolecular space. To examine whether this was a phenomenon in just the solid phase, or whether this was the prevalent conformation in solution as well, a ^{1}H nmr study was designed. Previous work by Koga[11] indicated that a DCl/D_2O solution at pD 1.2 was a suitable solvent for the study, and 2,7-dihydroxynaphthalene an ideal guest. In addition to the di-N-methyl compound (217), the tetra-N-methyl-paracyclophane (12) was also available[18,137], a compound that is known to form inclusion complexes in both solid phase[19] and in solution[16].

TABLE 4

COMPOUND (217)/Eq.	2,7-DIHYDR-OXY-NAPHTH-ALENE/Eq.	REMARKS ON STATE OF SOLUTION
1	0	CLEAR
1	0.5	INSOLUBLE
1	1	INSOLUBLE

COMPOUND (12) /Eq.	2,7-DIHYDR-OXY-NAPETH-ALENE/Eq.	REMARKS ON STATE OF SOLUTION
1	0	HAZE
1	0.5	CLEAR
1	1	CLEAR

Initial Concentration Guest 2.5×10^{-2}M Host 5×10^{-2}M in DCl/D_2O pD 1.2 at 35°

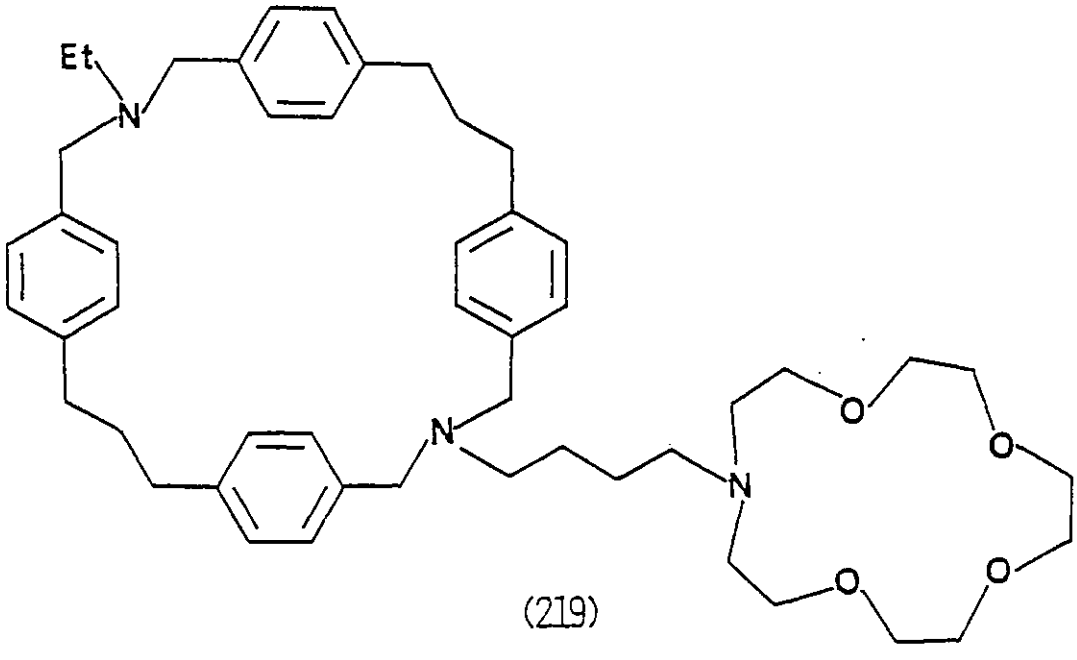
The di-N-methyl compound (217) was soluble enough in the deuterated acid to obtain a reasonable spectrum. However as soon any 2,7-dihydroxynaphthalene was added to the solution an insoluble white precipitate was formed and no sensible proton spectrum could be obtained. No polar solvent could be found to solubilise this precipitate, and no real conclusions could be drawn from this result.

In contrast, the tetra-N-methyl compound (12), although not completely soluble on its own in the aqueous acid, was completely solubilised in the presence of the guest molecule. Moreover, a 0.2 ppm upfield shift was noted in the positions of the 2,7-dihydroxynaphthalene aromatic protons. This shielding effect is consistent with the results of Koga's[11] studies, but the magnitude of the movement is considerably smaller, and unlike Koga's findings, it is the same for all the aromatic protons in the guest. This suggests that the compound (12) binds to the naphthalene relatively weakly, and this feature is in agreement with the X-ray crystallographic study carried out on this molecule with 1,4-dioxan[19] which showed the guest only sitting in the entrance to the cavity, rather than being buried deeply inside it.

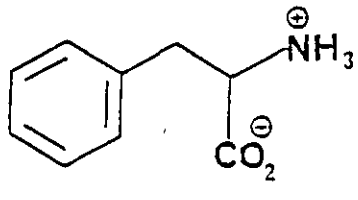
However the original question, concerning the intramolecular complexation abilities of the di-N-methyl compound (217), remained unanswered. The fact that an insoluble complex was being formed with the 2,7-dihydroxynaphthalene did not provide definitive evidence either way for whatever process was occurring.

A piece of firm evidence has subsequently emerged. The paracyclophane (178) was successfully monofunctionalised[122] and linked with an azacrown ether[138]. In order to demonstrate bifunctional complexation ability for this new host (219), an nmr study using phenylalanine (218) as guest was initiated, in deuterated methanol solutuon. The results[138] demonstrated the expected strong complexation between the ammonium group on the

guest and the crown portion of the host, but the aromatic ring on the phenylalanine was clearly not shielded, and hence not incorporated, by the azaparacyclophane moiety. In a situation where complexation should have occurred, none was observed. This finding dispelled any lingering hope that a substituted di-aza [3.3.3.3] paracyclophane such as compound (217) would form an intramolecular complex with a suitable guest. It also illustrated the subtelties of this area of chemistry, whereby the di-NH paracyclophane (178) seemed to exist in the right conformation for complexation as judged by its X-ray structure, whereas the di-N-substituted compounds (217) and (219) clearly did not. Another apparently minor change from the tetra-aza-series to the di-aza compounds also had a profound effect on complexation abilities.

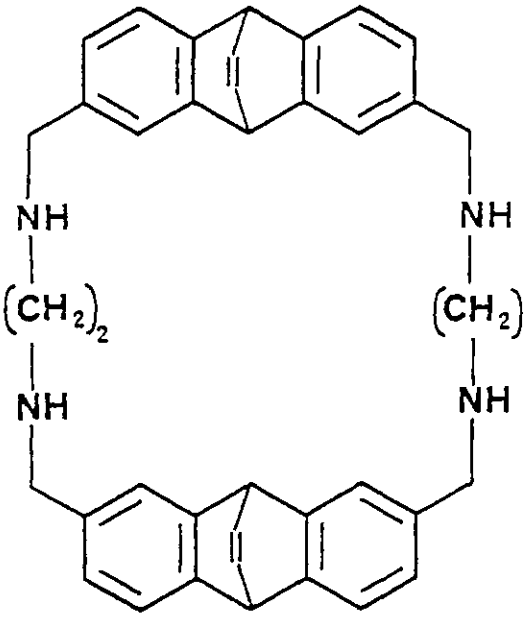


(219)

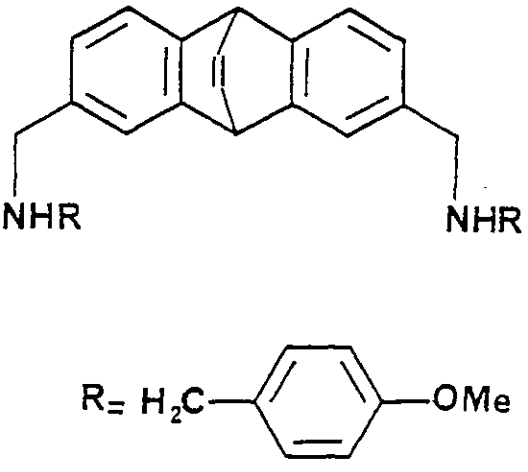


(218)

In an attempt to make an azaparacyclophane that was in a more rigid conformation, and hence more receptive to intramolecular bonding, a new molecule (220) was designed. Space-filling models



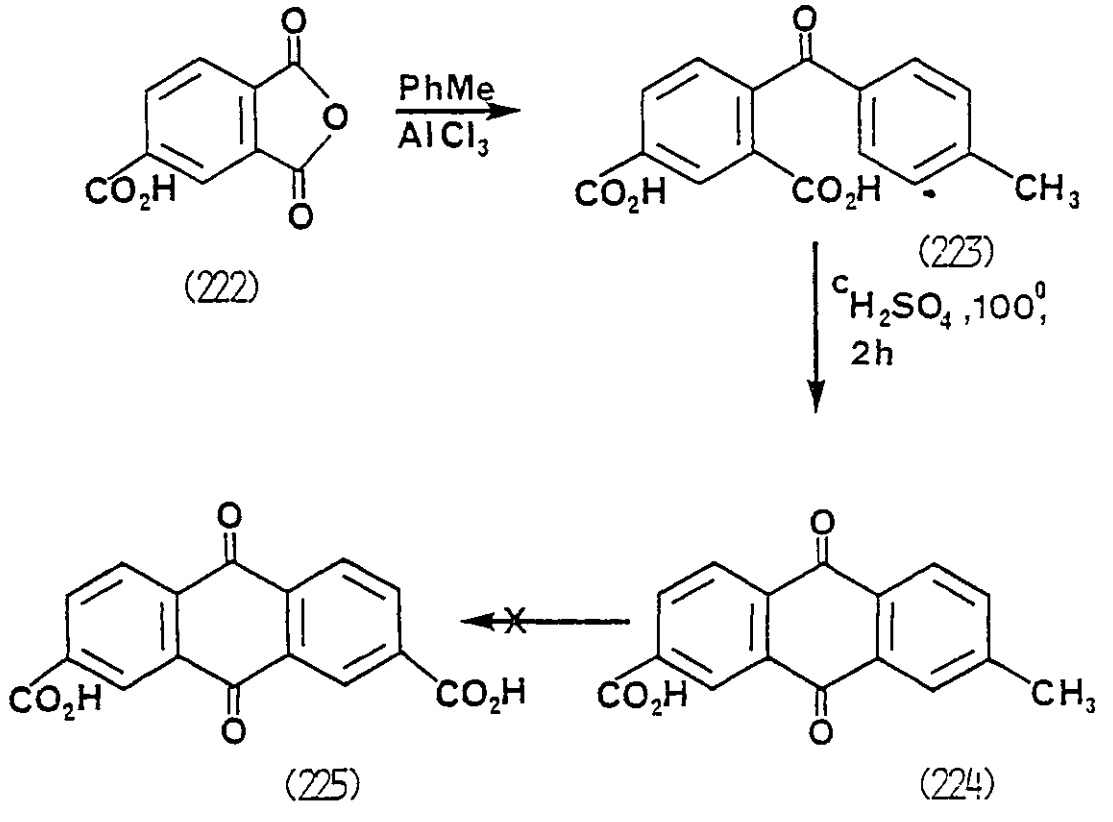
(220)



(221)

indicated that this compound (220) had an enforced cavity, one that would be unaltered in shape and size, whatever the conformation of the molecule. The route to this attractive compound was by way of an intermediate diamine (221), which on a high-dilution reaction with oxalyl chloride should have led to the macrocyclic ring system. Problems came in the synthesis of compound (221). As 2,7-disubstituted anthracenes and anthraquinones were not easily available commercially, they had to be made.

The route started with a Friedel-Crafts reaction between toluene and 4-hydroxycarbonylphthalic anhydride (222). This led to a single isomer, the substituted benzophenone (223) in 70% yield, with a ^{13}C nmr demonstrating that this was indeed a single compound. It was gratifying to note the powerful effect the presence of the aromatic carboxylic acid had on the electrophilic nature of the two anhydride carbonyl groups, with one of these, in position 4 relative to the acid, taking part exclusively in the electrophilic substitution process.



SCHEME 35

Unfortunately this was the only really clean reaction of the synthetic scheme. Sulphuric acid dehydration at 100° of compound (223) did take place, but the resulting anthraquinone (224) proved very difficult to purify due to the insoluble nature of the material. Attempts at

oxidation of the methyl side chain of the crude product with various powerful oxidants such as potassium permanganate and chromic acid led to the formation of some of the dicarboxylic acid (225) but as this was also very insoluble and the reactions almost impossible to follow, these reactions were never preparitively useful. After a considerable effort had been expended on this system with no useful results, attempts to make the new paracyclophane (220) ceased.

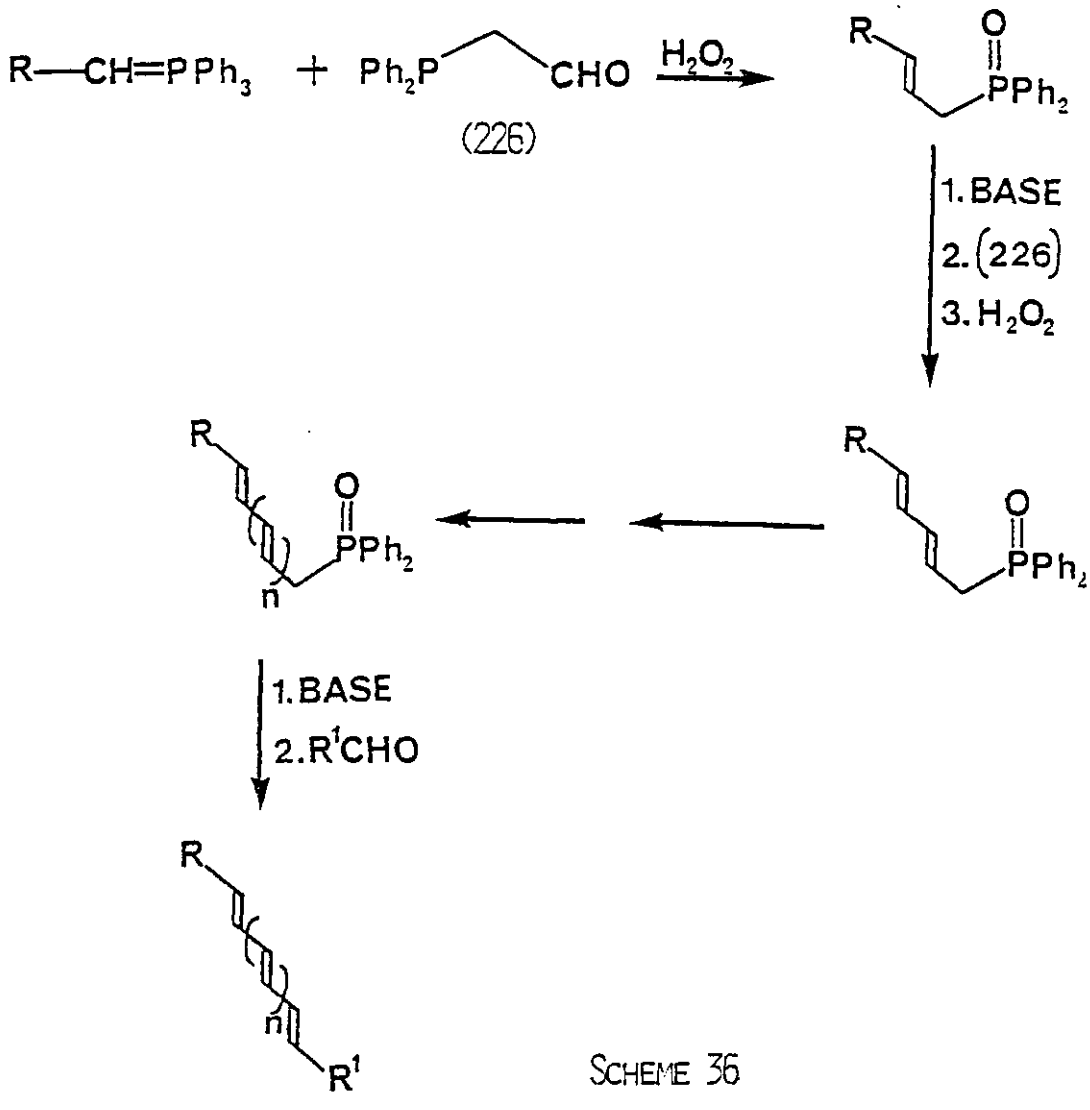
CHAPTER 4

ASPECTS OF THE CHEMISTRY OF AN ITERATIVE WITTIG CONDENSATION REAGENT

The Wittig reaction has been known for many years and provides a method of converting an aldehyde or a ketone into part of a carbon-carbon double bond. The reaction has been utilised in countless syntheses and synthetic schemes, and has found much usage in almost all aspects of synthetic organic chemistry. A vast range of phosphine ylides have been developed, each one with its own particular uses. Modification to the basic procedure such as that of Wadsworth and Emmons[139] has led to the production of many phosphonate ylides as well.

We were interested in diphenylphosphinoacetaldehyde (226) first described in 1977[140], as a potential reagent for performing a sequence of iterative Wittig type reactions to build up chains of trans double-bonds (Scheme 36).

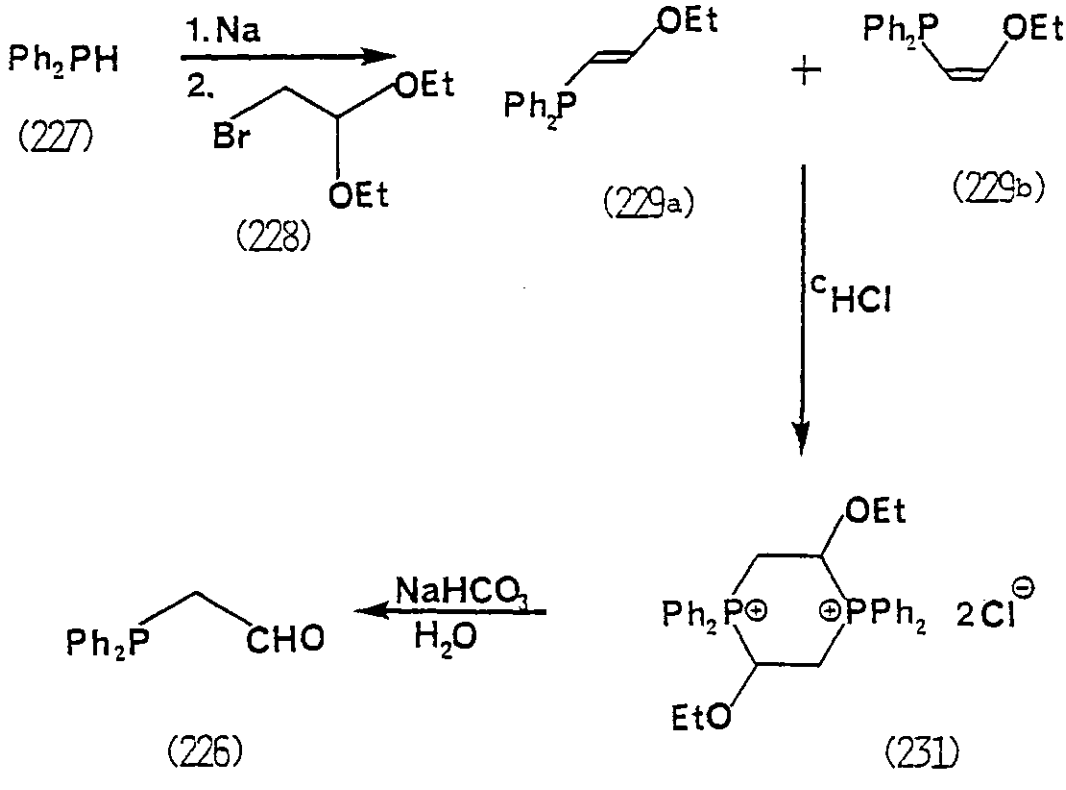
The work described here will focus onto the initial investigations into the utility of this system. Diphenylphosphinoacetaldehyde (226) was synthesised in three steps from diphenylphosphine (227). Treatment of compound (227) with sodium, followed by quenching of the anion formed with the diethylacetal of bromoacetaldehyde (228) led to a cis/trans mixture of the vinyl ether (229). The product obtained however differs from the literature[140] in that it has lost a molecule of ethanol. The authors claim analytical data for their compound (230) but structural proof for our molecule has also been obtained. The boiling



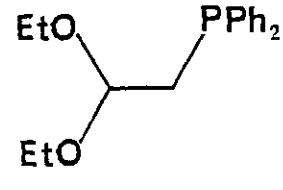
SCHEME 36

points of the two compounds (229) and (230) are in close agreement. Treatment of the isomers (229) with concentrated hydrochloric acid produces the salt (231). Diphenylphosphinoacetaldehyde (226) may be generated from this compound using a dilute sodium hydrogen carbonate solution. When literature[140] conditions were used in this final step, the potassium hydroxide employed led to extensive polymerisation of the

aldehyde, and only a very poor yield of the required compound was obtained.



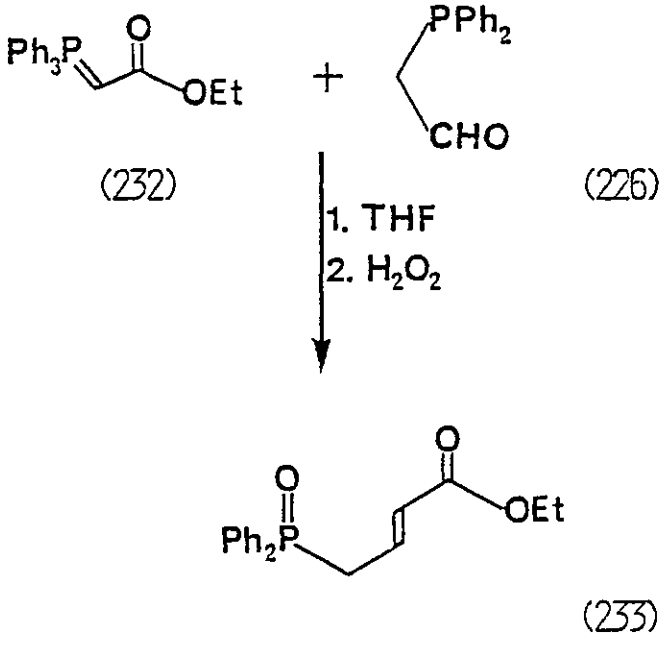
SCHEME 37



(230)

With the required aldehyde (226) now available, a condensation reaction was attempted. The stabilised ylide (232) was dissolved in dichloromethane and the aldehyde (226) was added. After five days, first at room temperature, and later at the reflux, the reaction had gone to completion. During the course of work up the phosphine was

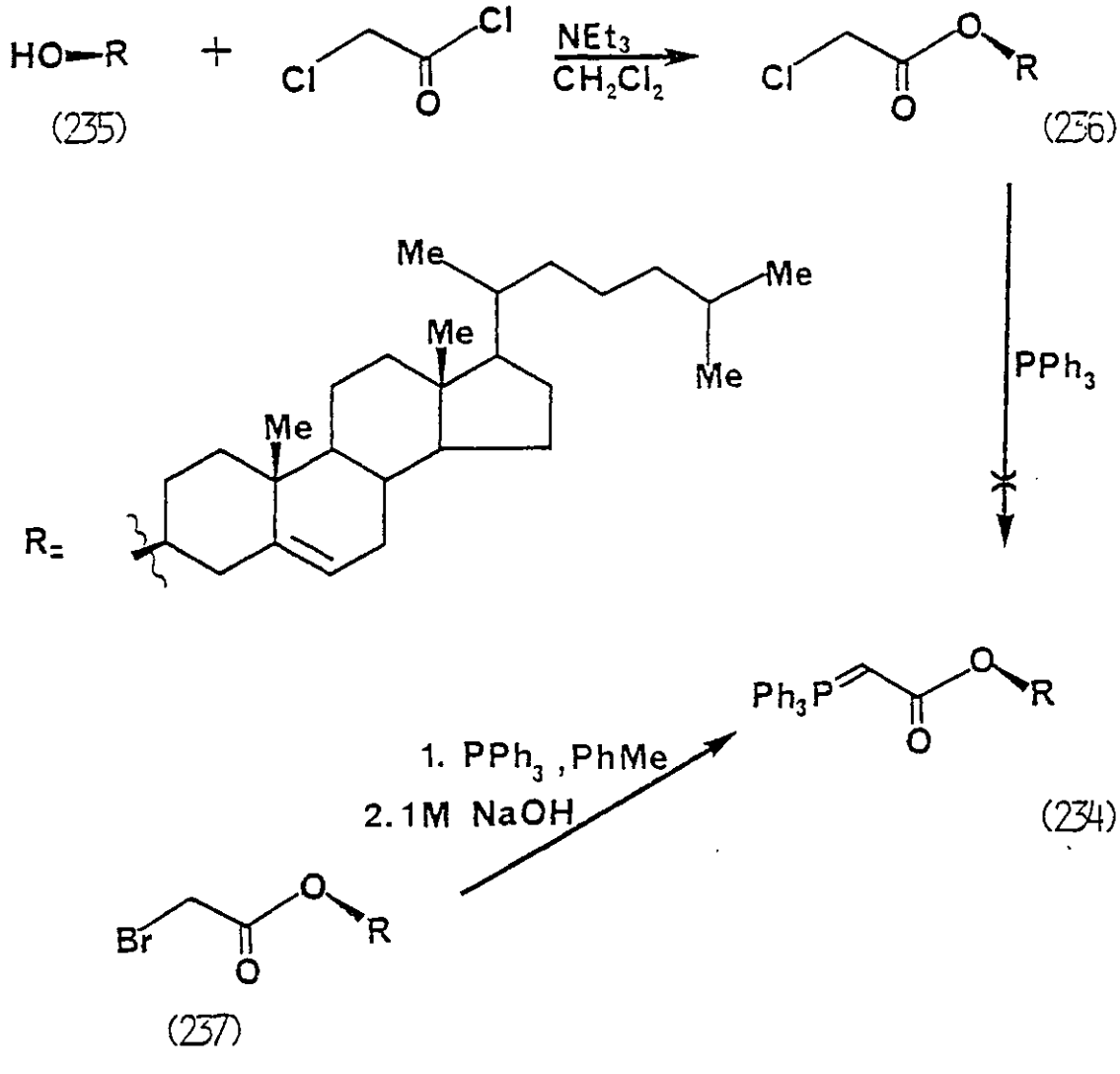
oxidised, with hydrogen peroxide, to the phosphine oxide (233) which on isolation was shown to be contaminated with triphenylphosphine oxide. The crude ^1H nmr indicated, as hoped, that only the desired trans double-bond had been formed in the reaction, justifying the choice of the stabilised ylide (232) as one of the reactants. Use of THF as solvent in the reaction speeded up the process considerably and the trans selectivity was retained. Unfortunately, the newly synthesised phosphine oxide (233) could not be separated from the triphenylphosphine oxide by chromatography, on either silica or alumina.



SCHEME 38

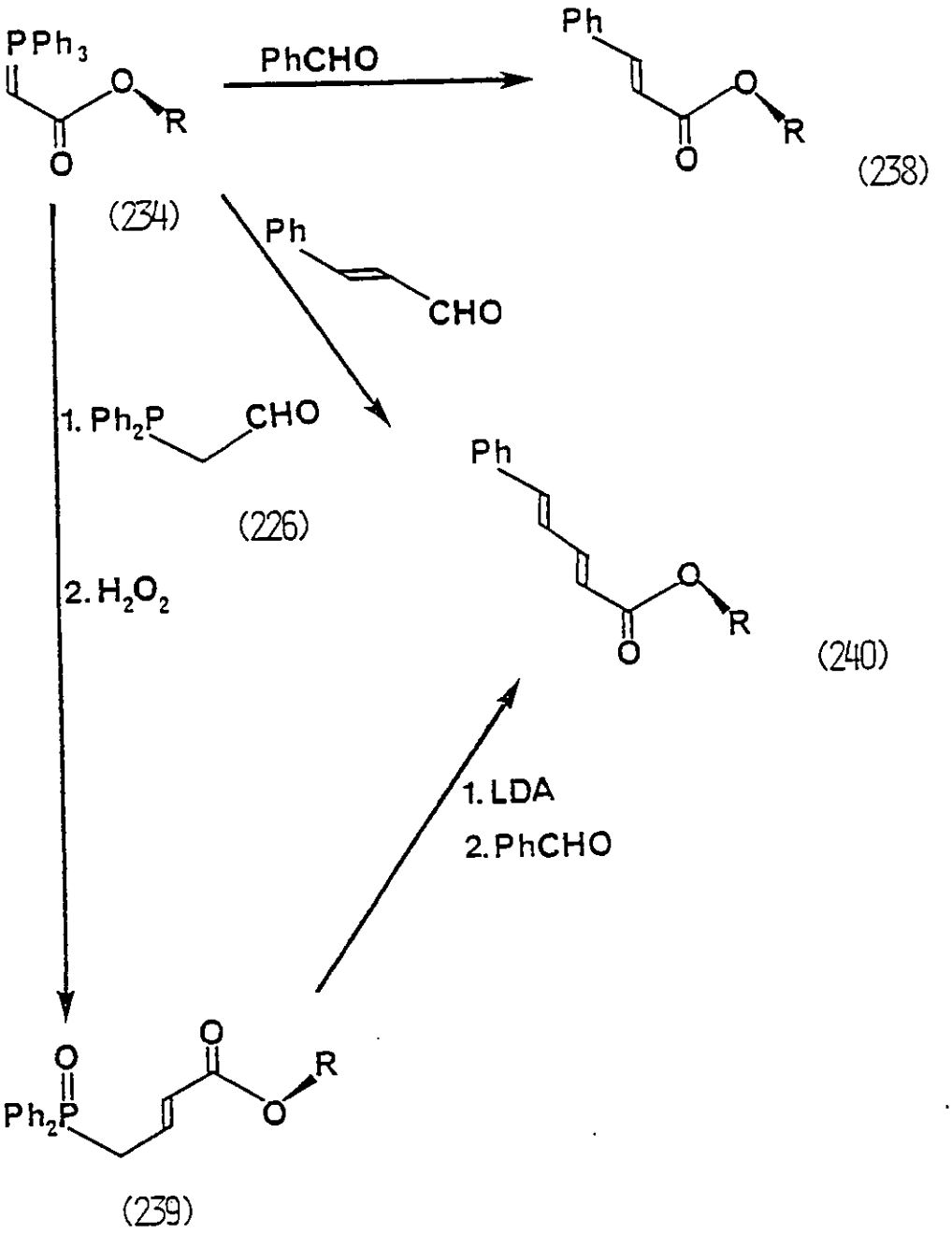
In order to obviate this problem of purification, it was decided to make a stabilised ylide of a cholesteryl ester (234). Thus cholesterol (235) was condensed with chloroacetyl chloride and the resulting ester (236) was treated with triphenylphosphine. However, regardless of solvent or reaction temperature, no displacement of the

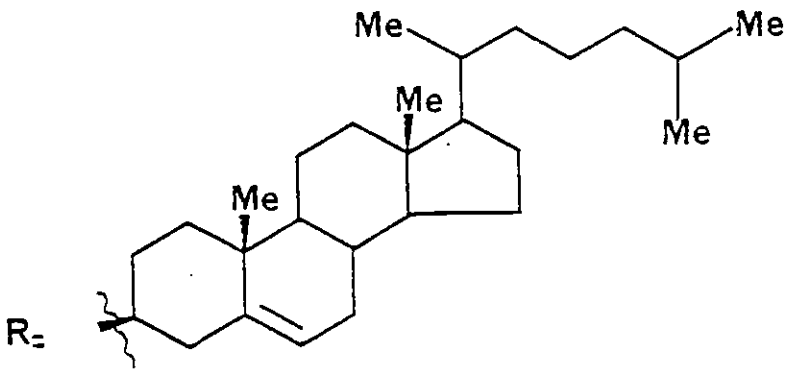
chlorine atom could be observed. Hence cholesteryl bromoacetate (237) was made from bromoacetyl bromide and cholesterol (235) and reacted with triphenylphosphine in refluxing toluene for 15 hours. All toluene was then removed, and a dichloromethane solution of the residual solid was treated with an aqueous solution of sodium hydroxide to give the stabilised ylide (234) directly.



SCHEME 39

In order to establish that the ylide (234) did have the structure shown, it was reacted with benzaldehyde in refluxing THF to lead, after


PPh3
PhCHO
Ph
O
R
(234)
(238)
Ph
CHO
1. Ph2P
CHO
(226)
2. H2O2
Ph
(240)
1. LDA
2. PhCHO
Ph2P
(239)


Me
Me
Me
Me
Me
R=

SCHEME 40

chromatography, to the cinnamate ester (238) in a 60% yield. Condensation with diphenylphosphinoacetaldehyde (226) in refluxing THF gave the required phosphine oxide (239) pure after column chromatography, but the yield of 32% was rather low. The product isolated was exclusively the trans isomer. When the reaction was performed in acetonitrile a slightly larger yield of the phosphine oxide (239) was isolated but this appeared to be a mixture of cis and trans isomers. All that was required now was to deprotonate the phosphine oxide in the α position. Similar deprotonations in the past have been performed with n-butyllithium[141] or lithium diisopropylamide (LDA)[142] and of these the latter seemed to be more compatible with the ester function also present in the molecule. Treatment of the phosphine oxide (239) with LDA at -78° followed by warming to 0° for half an hour, and then the removal of any hexane present in the solution, at reduced pressure, at -78°, gave an anion that was quenched with benzaldehyde. Chromatography led to the all trans diene ester (240) in poor yield. None of the reactions described above have been optimised in any way, and it is anticipated that when greater amounts of the various materials become available, significant improvements will occur to all the isolated yields. When the ylide (234) was quenched with trans cinnamaldehyde the diene ester (240) was again isolated, and the compounds from the two different reactions proved to be identical in all respects.

With the purification and deprotonation of the exclusive trans phosphine oxide (239) established, the basis of a useful synthetic method has been demonstrated. One may envisage long chains of double bonds being built up in a solely trans relationship. The use of the cholesteryl ester ylide (234) was necessary to make purification of the diphenylphosphine oxide (239) possible, but the cholesterol may, of course, by hydrolysed off at the end of any sequence to reveal an acid functionality, which can be elaborated further.

CHAPTER 5

CONCLUSION

A di-aza [3.3.3.3] paracyclophane catechol containing compound (211) was made and the hydroxylation of benzene was studied using it, and a series of other substituted catechols. The results obtained were disappointing with the presence of the di-azaparacyclophane making no significant difference to the process. This, it was later found, was due to the fact that the paracyclophane (217) did not incorporate molecules of benzene into its structure, as the expected cavity in the macrocycle was absent. There was also some doubt about the nature of the iron(III)-catechol complex attached to the di-azaparacyclophane, which may have been a monochelate at the pH used in the hydroxylation, rather than the hoped for bischelate.

Investigations were performed in the attempt to make a suitably disubstituted tetra-aza [3.3.3.3] paracyclophane, and although this led to the elaboration of a method for the dynamic protection of primary amines no useful molecules could be made.

The synthetic utility of diphenylphosphinoacetaldehyde (226) has been examined and it is hoped that the initial investigations reported here will lead to a general synthetic method for the construction of long chains of trans double bonds using Wittig type reaction conditions.

CHAPTER 6

EXPERIMENTAL

Melting points were determined using a Kofler hot stage apparatus and are uncorrected. Infrared spectra were recorded on a Perkin Elmer 298 or 257 grating infrared spectrophotometer. NMR spectra were recorded on a Varian EM 360A (60 MHZ), a Bruker WM 250 (250 MHz) or a Perkin Elmer R32 (90 MHz) spectrometer using tetramethylsilane as an internal reference. Optical rotations were performed on a Perkin Elmer 141 polarimeter. Analytical thin layer chromatography (tlc) was performed on Merck precoated GF_{254} silica. Column chromatography was carried out on Merck Kieselgel 60 H silica with the eluant solvent given in parentheses.

Solvents were purified as follows: Benzene, toluene - redistilled, sodium dried. Chloroform, carbon tetrachloride, dichloromethane - redistilled, dried if necessary over phosphorous pentoxide. Diethyl ether redistilled, dried if necessary over sodium wire. Ethyl acetate, 1,4-dioxan, petroleum ether 40-60^{o}. fraction - redistilled. Tetrahydrofuran (THF) - redistilled from potassium/benzophenone ketyl. Ethanol, methanol - AnalaR reagents, dried if necessary over magnesium. N,N-Dimethylformamide - redistilled at reduced pressure from 4Å molecular sieves. Dimethoxy-ethane (DME) - redistilled from 4Å molecular sieves on to 4Å molecular sieves. Pyridine - redistilled from potassium hydroxide and stored over 4Å molecular sieves. Triethylamine - redistilled from sodium wire and stored over sodium wire.

Methylamine in ethanol refers to a 33% w/v solution. Hydrogen bromide in glacial acetic acid refers to a 48% w/v solution and hydrogen iodide in water is a 57% commercially available solution.

Solvents were evaporated at reduced pressure using a rotary evaporator at or below 40° unless otherwise stated.

Microanalyses, mass spectral measurements, and X-ray crystallographic determinations were carried out by the respective laboratories at Imperial College.

The following abbreviations are used in the assignment of nmr spectra: s - singlet, d - doublet, t - triplet, q - quartet, p - quintet, dd - doublet of doublets, br - broad, and m - multiplet.

Preparation of 4,4′-Dimethoxybenzhydrylamine (137)

This material was prepared by the procedure of Trost[1], in several steps from 4,4′-dimethoxybenzophenone, mp 57-9° (*lit.*[109] 58-9°), ν_{max} (Nujol) 3370, 3300, 1610, 1585, 1505, 1240, 1170, 1030, and 830 cm^{-1}; ^1H nmr ($CDCl_3$) δ 7.25 (4H, d, J 8 Hz, aryl-H), 6.80 (4H, d, J 8 Hz, aryl-H), 5.12 (1H, s, $-CHNH_2$), 3.76 (6H, s, OMe), and 1.72 (2H, s, $-NH_2$); m/e 243 (M^+), 227, 212, 136, 109, and 93. The amine was further characterised as its *hydrochloride salt*, mp 199-203° (from aqueous methanol) (Found: C, 64.47; H, 6.51; N, 4.80. $C_{15}H_{17}NO_2.HCl$ requires C, 64.38; H, 6.50; N, 5.01%).

Preparation of Methyl Terephthalate (136)

The method used by Godfrey was employed[5]. Dimethyl terephthalate (134) (40.0 g, 0.21 mole) was heated in toluene (340 ml) to produce a clear solution. After this was allowed to cool slightly, a solution of potassium hydroxide (13.64 g, 0.21 mole) in methanol (200 ml) was added slowly over a period of fifteen min. The mixture was stirred at the reflux for a further fifteen min whereupon it was allowed to cool. The white precipitate formed was filtered and the powder obtained was washed with a little warm toluene and methanol. The material was dissolved in water (300 ml) yielding a clear solution and 2 M hydrochloric acid (300 ml) was added with vigorous stirring and ice-cooling being maintained. The title compound (136) was isolated by filtration, washing with cold water and drying *in vacuo* overnight (35.6 g, 95%), mp 221-2°(*lit.*[143] 222°), ν_{max} (Nujol) 3300-2300, 2650, 2550, 1720, 1690, 1420, 1280, 1100, and 730 cm^{-1};

^{1}H nmr ($CDCl_3$/trace d^6-DMSO) δ 8.30 (4H, s, aryl-H), and 4.01 (3H, s, $-OCH_3$).

Preparation of 4-Methoxycarbonylbenzoyl Chloride (130)

The method described by Godfrey was employed[5]. Methyl terephthalate (136) was suspended in thionyl chloride and heated at the reflux until a clear solution was obtained. Evaporation of the thionyl chloride left the desired acid chloride (130) pure enough for use, ν_{max} (Nujol) 1770, 1740, 1720, 1280, and 690 cm^{-1}.

Preparation of N-(4,4′-Dimethoxybenzhydryl)-4-methoxycarbonylbenzamide (138)

The monoamide (138) was prepared as described by Simpson[110] by treatment of 4,4′-dimethoxybenzhydrylamine (137) with 4-methoxycarbonylbenzoyl chloride (130) in dry dichloromethane using triethylamine as base. The material obtained (138) was identical with an authentic sample, mp 199-202° (from methanol) (*lit.* [110] 203-4°), ν_{max} ($CHCl_3$) 3440, 1720, 1660, 1610, 1480, and 910 cm^{-1}; ^{1}H nmr ($CDCl_3$) δ 8.07 (2H, d, J 8 Hz, aryl-H), 7.84 (2H, d, J 8 Hz, aryl-H), 7.22 [4H, d, J 8 Hz, (aryl$(OMe)_2$-H)], 6.88 [4H, d, J 8 Hz, (aryl$(OMe)_2$-H)], 6.65 (1H, br s -NH-), 6.36 (1H, d, J 6 Hz, -CH-), 3.95 (3H, s, $-CO_2CH_3$), and 3.80 (6H, s, aryl-OMe).

Preparation of N-(4,4′-Dimethoxybenzhydryl)-N′-methyl-terephthalamide (139)

The bisamide (139) was prepared by the method of Simpson[110] by treatment of the monoamide (138) with methylamine in ethanol. The product isolated was identical with an authentic sample of the material, mp 248-9° (*lit.*[110] 246-8°), ν_{max} (Nujol) 3280, 1630, 1548, 1500, 1240, 1169, 1025, and 810 cm^{-1}; ^1H nmr ($CDCl_3$) δ 6.73-7.80 (14H, m, aryl-H and NH), 6.60 (1H, d, J 10 Hz, -CH-), 3.80 (6H, s, -OMe), and 2.95 (3H, d, J 5Hz,-NMe).

Attempted Preparation of N-(4,4′-Dimethoxybenzhydryl)-N′-methyl-1,4-xylylenediamine (133)

To the bisamide (139) (0.52 g, 1.29 mmole) suspended in dry, redistilled THF (30 ml) was added a solution of diborane in THF (1.25 M, 3 ml , 18 hydride equivalents) whilst the reaction flask was cooled in ice. The solution on heating became clear and heating was continued at the reflux for 6 h, during which time a precipitate again formed. On cooling the reaction was quenched with acetic acid (1 M, 5 ml) and water (15 ml). Solid sodium bicarbonate was added until the solution became slightly basic. The THF was removed at reduced pressure and the remaining aqueous suspension was extracted with diethyl ether (3 x 25 ml). The organic layer was dried over sodium sulphate, filtered and concentrated to yield a green coloured oil which probably contained the title compound (133) as judged from the ^1H nmr spectrum in which protons had appeared at δ 3.75 as expected for the reduced benzylic positions, the loss of carbonyl absorbances in the infrared

spectrum and a parent ion at m/e 376 in the mass spectrum. Unfortunately boron containing residues could also be observed in the ^{1}H nmr and the infrared. Attempted purification by column chromatography failed, and attempted distillation of the oil yielded only a white crystalline material mp 47-9° which turned out to be bis(4-methoxyphenyl)methane (140) (*lit.*[144] mp 44-6°). An attempt to make the di-4-toluene-sulphonic acid salt of the impure material also failed, no crystalline material becoming evident.

Attempted Benzoylation of the Diamine (133)

The crude diamine (133) (85 mg) was dissolved in dichloromethane (5 ml) and benzoyl chloride (64.5 mg) was added followed by triethylamine (0.5 ml). The reaction was stirred at room temperature and monitored by tlc (50% dichloromethane/50% petrol). The reaction was stopped after 20 h and the organic solution was washed with water (2 x 10 ml), dried (sodium sulphate), filtered and evaporated to yield the impure bis-benzoylated compound as an oil (89 mg). The compound could not be purified further as it proved to be unstable to column chromatography on alumina.

Preparation of Ethyl 4-Cyanobenzoate (143)

Ethyl 4-aminobenzoate (142) (50 g, 0.30 mole) was dissolved in 2 M hydrochloric acid (450 ml) and the resulting solution cooled to 5°, some colourless crystals slowly appearing. Then a solution of sodium nitrite (27 g, 0.39 mole) in water (200 ml) was added with vigorous stirring. The temperature of the resulting yellow solution was maintained between 0° and 5°. A freshly prepared aqueous

solution of copper(I) cyanide[145] from sodium cyanide (80 g) was heated to 90° and the yellow diazonium salt was added to it, slowly. A vigorous evolution of nitrogen was observed, and the tarry, strong smelling product was formed almost immediately. The reaction mixture was allowed to cool and was extracted with diethyl ether (3 x 300 ml). The ethereal solution was filtered, evaporated and the residual tar was steam-distilled. The distillate on cooling to 4° overnight produced a pale yellow solid which was isolated by filtration. Recrystallisation from aqueous methanol led to the title compound (143) (25.3 g, 47%), mp 51.5 -52.5° (*lit.*[112] 52°), ν_{max} (Nujol) 2300, 1715, 870, and 770 cm^{-1}; ^1H nmr ($CDCl_3$) δ 8.15 (2H, d, J 9 Hz, aryl-H), 7.75 (2H, d, J 9 Hz, aryl-H), 4.45 (2H, q, J 7 Hz, $-OCH_2-CH_3$), and 1.45 (3H, t, J 7 Hz, $-OCH_2CH_3$).

Preparation of N-Methyl-4-cyanobenzamide (144)

Ethyl 4-cyanobenzoate (143) (7.30 g, 0.05 mole) was stirred with a 33% solution of methylamine in ethanol (20 ml, excess) for 2 h at room temperature. A white precipitate was formed. The volatile components were removed by evaporation at reduced pressure, and the solid recrystallised from aqueous methanol to yield the *title compound* (144) as white needles (7.10 g, 91%), mp 201-2°, ν_{max} (Nujol) 3340, 2220, 1640, 1550, 1300, 1160, 860, 765, and 620 cm^{-1}; ^1H nmr ($CDCl_3$, trace d^6-DMSO) δ 8.20 (1H, br s, NH), 7.92 (2H, d, J 9 Hz, aryl-H) 7.65 (2H, d, J 9 Hz, aryl-H), and 2.90 (3H, d, J 4.5 Hz, NMe); m/e 160 (M^+), 159, 130, 129, 101, 77, and 76 (Found: C, 67.52; H, 4.93; N, 17.45. $C_9H_8N_2O$ requires C, 67.49; H, 5.03; N, 17.49%).

Preparation of N-Methyl-1,4-xylylenediamine (141)

To a suspension of lithium aluminium hydride (4.2 g, excess) in dry (THF) (50 ml) was added finely powdered N-methyl-4-cyanobenzamide (144) (8.0 g, 50 mmole) suspended in THF (120 ml). The mixture was vigorously stirred and heated at the reflux under an atmosphere of dry nitrogen for 5 days. On cooling the reaction was quenched with a saturated solution of sodium sulphate, cautiously, until evolution of hydrogen gas ceased. The mixture was filtered and the residue extracted with boiling dichloromethane. The extract and original filtrate were evaporated to leave a wet, orange oil, which was dissoved in dichloromethane and dried (sodium sulphate). Evaporation of the solvent followed by distillation gave the title compound (141) as a colourless liquid (5.0 g, 68%), bp 82° at 0.3 mm Hg (*lit.*[146] 130-1° at 0.3 mm Hg), ν_{max} (film) 3360, 3300, 1590, and 800 cm^{-1}; ^1H nmr ($CDCl_3$) δ 7.25 (4H, s, aryl-H), 3.80 (2H, s, $-CH_2NH_2$), 3.70 (2H, s, $-CH_2NMe$), 2.45 (3H, s, -NMe), and 1.45 (3H, s, NH).

Preparation of N-Methyl-1,4-xylylenediammonium Di-toluene-4-sulphonate (161)

N-methyl-1,4-xylylenediamine (141) (2.25 g, 15 mmole) was dissolved in ethanol (2 ml). To this was added a solution of 4-toluenesulphonic acid monohydrate (5.70 g, 30 mmole), dissolved in ethanol. The two solutions were mixed and diethyl ether added until a cloudiness appeared. The salt was allowed to crystallise and filtered at the pump, the white solid *title compound* (161) being washed with diethyl ether (6.60 g, 89%), mp 199-203° (from ethanol/diethyl ether), ν_{max} (Nujol) 3400-2500, 1640, 1600, 1060, 1020, 820,

and 680 cm^{-1}; ^{1}H nmr (d^{6}-DMSO) δ 8.3 (5H, br s, $-N\underline{H}_2^+$ and $-N\underline{H}_3^+$), 7.05-7.50 (12H, m, aryl-$\underline{H}$), 4.1 (4H, br s, aryl-$C\underline{H}_2$-N), 2.5 (3H, br s, N-$C\underline{H}_3$), and 2.3 (6H, s, aryl-$C\underline{H}_3$) (Found: C, 55.63; H, 6.10; N, 5.59. $C_9H_{14}N_2.2\ C_7H_8SO_3$ requires C, 55.84; H, 6.13; N, 5.66%).

Preparation of N-(4-Methoxycarbonylbenzoyl)-N-methyl-N′-benzoyl-1,4-xylylenediamine (145) Entry 1

N-methyl-1,4-xylylenediamine (141) (75 mg, 0.5 mmole) was dissolved in dry dichloromethane (10 ml) and dry trifluoroacetic acid (38.5 µl, 57 mg, 0.5 mmole) was added. The solution went cloudy. Addition of dry 18-crown-6 (132 mg, 0.5 mmole) caused the precipitate to clear. Freshly prepared 4-methoxycarbonylbenzoyl chloride (130) (99 mg, 0.5 mmole) was added followed by dry triethylamine (51mg, 70 µl, 0.5 mmole). The reaction was stirred for 0.5 h. Potassium chloride (0.372 g, 2.5 mmole) was added, followed by triethylamine (255 mg, 0.35 ml, 2.5 mmole) and benzoyl chloride (70 mg, 58 µl 0.5 mmole). After a further period of 0.5 h, the reaction was terminated and the organic layer washed with water (2 x 10 ml) and dried (sodium sulphate). Filtration and evaporation yielded an oil which contained a major and several minor components. Column chromatography (80% dichloromethane/20% ethyl acetate) led to the isolation of the major product (88 mg, 42%) the *title compound* (145) a white crystalline material, mp 121-4° (from methanol), ν_{max} ($CHCl_3$) 3440, 1720, 1660, 1630, 1280, 1110, and 860 cm^{-1}; ^{1}H nmr ($CDCl_3$) δ 7.15-7.90 (13H, m, aryl-$\underline{H}$ + N-$\underline{H}$), 4.75 (2H, s, $-C\underline{H}_2-$), 4.65 (2H, s, $-C\underline{H}_2-$), 3.80 (3H, s, $-OC\underline{H}_3$), and 2.80 (3H, br s, N-$C\underline{H}_3$); ^{13}C nmr ($CDCl_3$) δ 43.80 ($-O\underline{C}H_3$), 51.18 ($-\underline{C}H_2$), 52.27 ($-N\underline{C}H_3$),

54.74 (-$\underline{C}H_2$), 126.96, 128.37, 128.63, 129.63, 129.81, 131.25, 131.60 134.46, 136.28, 137.95, 140.54, (all aryl-$\underline{C}$), 166.33, 167.36 (both -N-$\underline{C}$=O), and 170.71 (-$\underline{C}O_2Me$); m/e 295, 253, 237, 224, 223, 163 and 105 (Found: C, 71.95; H, 5.96; H, 6.56. $C_{25}H_{24}N_2O_4$ requires C, 72.09; H, 5.82; N, 6.73%).

Bis-acylation of N-Methyl-1,4-xylylenediamine (141). Blank Reaction

The reaction was performed as above on double the scale starting from N-methyl-1,4-xylylenediamine (141) (150 mg) and employing no 18-crown-6 in the procedure. The major component, a mixture of N-(4-methoxycarbonylbenzoyl)-N-methyl-N′-benzoyl-1,4-xylylenediamine (145) and N-benzoyl-N-methyl-N′-(4-methoxycarbonylbenzoyl)1,4-xylylenediamine (146), was isolated as a white solid (210 mg, 51%) after column chromatography (80% dichloromethane/20% ethyl acetate), mp 138-40° (from methanol), ν_{max} ^{1}H nmr identical with previous reaction above; ^{13}C nmr ($CDCl_3$) δ 43.86 (-$\underline{C}H_3$), 50.60 (-$\underline{C}H_2$-), 52.24 (-N$\underline{C}H_3$, 1 isomer), 52.33 (-N$\underline{C}H_3$, other isomer), 54.77 (-$\underline{C}H_2$), 126.84, 126.96, 127.05, 128.40, 128.58, 129.81, 131.22, 131.55, 132.87, 135.84, 136.21, 137.63, 138.25, 140.46 (all aryl-$\underline{C}$), 166.21, 166.27, 166.48 (all -N-$\underline{C}$=O), and 170.65 (-$\underline{C}O_2$Me); m/e 295, 279, 253, 237, 224, 223, 160, 130, and 105. A minor product was also isolated in a pure state and was identified as *N-methyl-N-trifluoromethylcarbonyl-N′-(4-methoxycarbonylbenzoyl)-1,4-xylylenediamine* (147) (45 mg, 11%) a white crystalline solid, mp 150-1° (from methanol), ν_{max} ($CHCl_3$) 3450, 1720, 1690, 1665, 1280, 1150, and 910 cm^{-1}; ^{1}H nmr ($CDCl_3$) δ 8.1 (2H, d, $\underline{J}$ 9 Hz, aryl-$\underline{H}$), 7.90 (2H, d, $\underline{J}$ 9 Hz, aryl-$\underline{H}$), 7.35 (4H, m, aryl-$\underline{H}$), 6.85 (1H, br s, -N$\underline{H}$), 4.65 (4H, br s, -$\underline{C}H_2$-),

3.95 (3H, s, -OMe), and 3.00 (3H, d, J 15 Hz -NMe); m/e 408 (M^+), 377, 281, 229, and 163 (Found: C, 58.73; H, 4.67; N, 6.81. $C_{20}H_{19}N_2O_4F_3$ requires C, 58.85; H, 4.70; N, 6.87%).

Factors Determining the Selectivity of Acylation - Monoacylation Studies on N-Methyl-1,4-xylylenediamine (141)

a No Protection

N-Methyl-1,4-xylylenediamine (141) (75 mg, 0.5 mmole) was dissolved in dry dichloromethane (15 ml) under nitrogen and freshly prepared 4-methoxycarbonylbenzoyl chloride (130) (99 mg, 0.5 mmole) was added, followed by triethylamine (51 mg, 70 µl, 0.5 mmole). After 1 h, more triethylamine (255 mg, 350 µl, 2.5 mmole) was added. The organic layer was washed with saturated potassium chloride solution (2 x 10 ml), dried (sodium sulphate), and evaporated to leave a yellow oil (110 mg, 67%). This was clearly a 50-50 mixture of the two possible amides from the condensation, namely N-(4-methoxycarbonylbenzoyl)-N-methyl-1,4-xylylenediamine (148), and N-(4-methoxycarbonylbenzoyl)-N'-methyl-1,4-xylylenediamine (149) ν_{max} ($CHCl_3$) 3450, 1725, 1672, (C=O str sec. amide), 1640 (C=O str tert. amide), 1515, and 1110 cm^{-1}; ^1H nmr ($CDCl_3$) δ 7.20-8.00 (8H, m, aryl-H), 4.40-4.80 (2H, m, $-CH_2NR-C=O$, R=H and Me), 3.92 (3H, s, $-CO_2Me$), 3.85 (1H, s, $-CH_2NH_2$), 3.73 (1H, s, $-CH_2NHMe$), 2.90 (1.5H, br s, -NMeCO Ar), 2.40 (1.5H, s, -NHMe), and 1.60 (1.5H, br s, $-NH_2$ and -NHMe). Two minor products possibly trifluoroacetamides could not be isolated, and could not be detected in the ^1H nmr study.

b Addition of one Equivalent of Acid

The reaction was performed exactly as above with the exception that dry trifluoroacetic acid (57 mg, 38 µl, 0.5 mmole) was added to the stirred diamine solution. The product mixture was isolated in the same ratio as before, and identical spectral data was obtained.

c Addition of one Equivalent of Acid and one Equivalent of 18-Crown-6. The Selective Preparation of N-(4-Methoxycarbonylbenzoyl)-N-methyl-1,4-xylylenediamine (148)

N-Methyl-1,4-xylylenediamine (141) (150 mg, 1 mmole) was dissolved in dry dichloromethane (30 ml) under an atmosphere of nitrogen and dry trifluoroacetic acid (114 mg, 77 µl, 1 mmole) was added. Dry 18-crown-6 (264 mg, 1mmole) was introduced followed by freshly prepared 4-methoxycarbonylbenzoyl chloride (130) (198 mg, 1 mmole) and triethylamine (101 mg, 140 µl, 1 mmole). The reaction was stirred for 1 h whereupon it was quenched with triethylamine (505 mg, 700 µl, 5 mmole) and washed with saturated potassium chloride solution (4 x 20 ml). The dichloromethane layer was dried (sodium sulphate), filtered and evaporated to give a yellow oil (148) which slowly solidified on standing (245 mg, 75%), mp 114-7°, ν_{max} ($CHCl_3$) 3200, 1725, 1637, 1355, 1102, 963, 895, and 835 cm^{-1}; ^1H nmr ($CDCl_3$) δ 7.98 (2H, d, J 10 Hz, aryl-H), 7.45 (2H, d, J 10 Hz, aryl-H), 7.25 (4H, m, aryl-H), 4.60 (2H, m, $-CH_2NC=O$), 3.90 (3H, s, $-OCH_3$), 3.83 (2H, s, $-CH_2NH_2$), 2.95 (3H, br d, J 15 Hz, $-NCH_3$), and 1.77 (2H, br s, $-NH_2$); m/e 312 (M^+), 311, 295, 163, 149, 135, 119, 118, 91, and 77. The compound was further characterised as the

4-toluenesulphonic acid salt, mp 228-32° (from ethanol/diethyl ether) (Found: C, 61.83; H, 5.81; N, 5.78. $C_{18}H_{20}N_2O_3 \cdot C_7H_8SO_3$ requires C, 61.96; H, 5.85; N, 5.78%).

Preparation of 2,2-Dimethyl-1,3-benzo-[d]-dioxole (151)[116]

Catechol (216) (25 g, 0.23 mole) was heated in dry acetone (25 ml) to 55°. Phosphorus pentoxide (40 g, 0.28 mole) was slowly added and the reaction temperature rose to 90°. The flask was periodically cooled in water to slow down the reaction. After addition was complete (approximately 15 min) the crude title compound was decanted away from the acetone condensation products and an aqueous solution of sodium hydroxide (3M, 20 ml) was added. This solution was subjected to steam distillation. The aqueous distillate (500 ml) was extracted with diethyl ether (2 x 100 ml). The ethereal layer was dried over sodium sulphate, filtered, evaporated and distilled to furnish the title compound (151) (15.4 g, 45%, *lit.*[116] 26%), bp 72-3° at 15 mm Hg (*lit.*[116] 182° at 760 mm Hg), ν_{max} (thin film), 3060, 1625, 1605, 1490, 1230, 840, 820, and 740 cm^{-1}; ^1H nmr ($CDCl_3$) δ 6.70 (3H, s, aryl-H), and 1.65 (6H, -C-CH_3).

Preparation of 2,2-Dimethyl-1,3-benzo-[d]-dioxole-4-carboxylic Acid (152)[73]

2,2-Dimethyl-1,3-benzo-[d]-dioxole (151) (10.0 g, 0.07 mole) was dissolved in dry hexane (200 ml) under nitrogen and tetramethylethylenediamine (10 ml, 0.07 mole) was added. The solution was cooled to -78° and n-butyllithium in hexane (53 ml, 1.38 M, 0.077 mole) was slowly added. The reaction was warmed to 0°C and maintained at this

temperature for 6 h whilst a green colour developed in the solution and a precipitate appeared. The mixture was again cooled to -78° and a stream of carbon dioxide gas was bubbled through the suspension - the green colour disappearing very rapidly. After 0.5 h the flow of gas was stopped and a 10% aqueous solution of sodium hydrogen carbonate (250 ml) was added. The aqueous layer was washed with dichloromethane (2 x 100 ml) and then acidified with concentrated hydrochloric acid. The precipitated acid was extracted with dichloromethane (2 x 100 ml), and the organic layer dried (sodium sulphate), filtered and evaporated to give the white crystalline title compound (152) (4.5 g, 35 %), mp 154-6° (*lit.*[73] 156°), ν_{max} (Nujol) 3300-2500, 1710, 840, and 740 cm^{-1}; ^1H nmr ($CDCl_3$) δ 9.4 (1H, br s, $-CO_2\underline{H}$), 6.8-7.4 (3H, m, aryl-$\underline{H}$), and 1.8 (6H, s, $C\underline{H}_3$); m/e 194 (M^+), 179, and 136.

Preparation of 2,2-Dimethyl-1,3-benzo-[d]-dioxole-4-carbonyl Chloride (67)[73]

2,2-Dimethyl-1,3-benzo-[d]-dioxole-4-carboxylic acid (152) (75 mg, 0.39 mmole) was dissolved in dry dichloromethane (5 ml) and N,N-dimethylformamide (1 drop) was added. Thionyl chloride (51 mg, 31 µl, 0.43 mmole) was added followed by triethylamine (47 mg, 65 µl, 0.43 mmole). The mixture was stirred at 0° for 4 h. The solvent was removed and the acid chloride extracted from the orange residue with petroleum ether to yield the white crystalline title compound (67) on evaporation (70 mg, 85%), mp 93-4° (*lit.*[73] 90-1°), ν_{max} (CH_2Cl_2) 1755, 1625, 1412, 1245, 1025, 970, and 885 cm^{-1}; ^1H nmr ($CDCl_3$) δ 6.80-7.60 (3H, m, aryl-$\underline{H}$), and 1.45 (6H, s, $-C\underline{H}_3$); m/e 214, 212, (both M^+), 199, 197, 177, and 137.

Preparation of N-(4-Methoxycarbonylbenzoyl)-N-methyl-N′-(2,2-dimethyl-1,3-benzo-[d]-dioxole-4-carbonyl)-1,4-xylylenediamine (154)

N-Methyl-1,4-xylylenediamine (141) (450 mg, 3 mmole) was dissolved in dry dichloromethane (40 ml) under an atmosphere of nitrogen and dry trifluoroacetic acid (342 mg, 231 µl, 3 mmole) was added, followed by dry 18-crown-6 (792 mg, 3 mmole), 4-methoxycarbonylbenzoyl chloride (130) (594 mg, 3 mmole) and triethylamine (303 mg, 420 µL, 3 mmole). The reaction was stirred for 1 h and more triethylamine (1.51 g, 2.1 ml, 15 mmole) was added followed by 2,2-dimethyl-benzo-[d]-dioxole-4-carbonyl chloride (67) (637 mg, 3 mmole). Finally potassium chloride (2.3 g, 31 mmole) was introduced and the mixture was stirred for a further hour. The dichloromethane solution was washed with a saturated solution of potassium chloride (3 x 50 ml) and water (2 x 50 ml). The organic layer was dried (sodium sulphate), filtered and evaporated to leave a brown oil which by tlc (silica, ethyl acetate 20%/ dichloromethane 80%) was shown to contain at least four products. Column chromatography (same solvents) led to the isolation of three single spot materials. The least polar product was isolated as an oil (56 mg), that could not be fully characterised, ν_{max} (CH_2Cl_2) 3430 (secondary amide N-H_{str}), 1725 (C=O_{str}, ester), 1690, 1660 (sec. amide C=O_{str}), and 1630 cm^{-1} (tert. amide C=O_{str}); ^1H nmr ($CDCl_3$) δ 6.70-7.50 (8H,m,aryl-H), 4.73 (1H, s), 4.58 (3H, s), 3.0 (2H, s), 2.91 (1H, s), and 1.71 (6H, s); m/e 342, 277, 249, 234, 229, 216, 205, 177, 137, and 110. The second compound by tlc, could not be obtained pure but had the same rf value as N-methyl--N-trifluoromethylcarbonyl-N′-(4-methoxycarbonylbenzoyl)-1,4-

xylylenediamine (147) isolated in a previous acylation. The third product, *the title compound* (154), was obtained as a colourless gum (611 mg, 43%), ν_{max} (CH_2Cl_2) 3430, 1720, 1665, 1635, 1597, 1539, 1423, 1250, and 890 cm^{-1}; ^1H nmr ($CDCl_3$) δ 8.12 (2H, d, J 8 Hz, aryl-H), 6.93-7.65 (10H, m, aryl-H + N-H), 4.5-4.8 (4H, m, 2 x Ar-CH_2), 3.95 (3H, s, -CO_2Me), 2.92 (3H, br s, N-Me), and 1.72 (6H, s, -C-CH_3); m/e 488 (M^+), 295, 245, 177, and 163 (M^+ 488.1960. $C_{28}H_{28}N_2O_6$ requires 488.1947). The fourth component, the most polar was a white solid believed to be N,N′-*dimethoxycarbonylbenzoyl*-N-*methyl*-1,4-*xylylenediamine* (159) (65 mg, 5%) mp 128-31° (from aqueous methanol) (*lit.*[110] 168-9°), ν_{max} (CH_2Cl_2) 3450, 3350, 1715, 1665, 1630, 1560, 1520, 1110, and 900 cm^{-1}; ^1H nmr ($CDCl_3$) δ 6.9-8.1 (13H, m, aryl-H + N-H), 4.45-4.75 (4H, m, 2 x -CH_2N), 3.95 (6H, s, CO_2Me), and 3.05-2.85 (3H, m, N-Me); m/e 472 (M^+-2), 443, 311, 295, 281, 173, and 134 (Found: C, 68.22; H, 5.55; N, 5.85. $C_{27}H_{26}N_2O_6$ requires C, 68.34; H, 5.52; N, 5.90%).

Attempted Preparation of N-(4-Methoxycarbonylbenzyl)-N-methyl-N′-(2,2-dimethyl-1,3-benzo-[d]-dioxole-4-methylene)-1,4-xylylenediamine (155)

The bisamide (154) (100 mg, 0.20 mmole) was dissolved in dry THF (25 ml) and cooled to 0° under nitrogen. Diborane in THF (2.5 M BH_3, 0.3 ml, 0.75 mmole) was added and the mixture heated to reflux for 6 h. Cyclohexene (2 ml, a large excess) was added and the solution was allowed to reflux overnight. On cooling acetic acid (0.3 M, 30 ml) was added and stirred for 30 min whereupon sodium hydrogen carbonate was used to basify the reaction mixture. The THF

was removed at reduced pressure and water (15 ml) was added. The product was extracted with dichloromethane (2 x 15 ml) which was dried (sodium sulphate), filtered and evaporated to leave a brown oil (170 mg, >100% due to boron-containing impurities) which turned out to be the half reduced compound, with just the tertiary amide reduced, ν_{max} (CH_2Cl_2) 3420, 1720, 1660, 1610, 1590, and 1550 cm^{-1}; ^1H nmr ($CDCl_3$) δ 6.9-8.1 (11H, m, aryl-H), 4.30-4.80 (6H, m, 2 x CH_2NMe + $CH_2NHC{=}O$), 3.92 (3H, s, CO_2Me), 2.40 (3H, s, -NMe), 1.72 (6H, s, CCH_3), and 1.20-2.0 (broad humps, impurity peaks); m/e 474 (M^+), 442, 394, 363, 326, 297, 282, 259, 245, 216, 192, 178, 166, 149, 135, and 107. The compound could not be fully characterised.

Attempted Preparation of N-(4-Hydroxymethylenebenzyl)-N-methyl-N'-(2,2-dimethyl-1,3-benzo-[d]-dioxole-4-methylene)-1,4-xylylenediamine (157)

The bisamide (154) (265 mg, 0.54 mmole), was dissolved in THF (50 ml) and the solution was vigorously stirred under nitrogen. Lithium aluminium hydride (200 mg, 5.7 mmole) suspended in THF (30 ml) was added to the reaction mixture which was heated at the reflux for 24 h, during which time a violet coloured precipitate was formed. On cooling, the reaction was quenched with a saturated, aqueous sodium sulphate solution. The salts formed were filtered off and the filtrate evaporated to yield a wet oil. This was dissolved in dichloromethane, dried (sodium sulphate), filtered and evaporated to yield the impure title compound (157) (130 mg), ν_{max} (CH_2Cl_2) 3610, 3420, 1660 ($C{=}O_{str}$ secondary amide from an impurity), 1590, 1525, 1512, 1460, 1210, 1020, and 900 cm^{-1}; ^1H nmr ($CDCl_3$) δ 6.61-7.27 (11H, m, aryl-H), 4.62 (2H, s, $-CH_2OH$), 3.11-3.89 (10H, m, aryl-CH_2

+ N-H + O-H), 2.15 (3H, s, -NMe), and 1.63 (3H, s, -O-C-CH_3 low integration due to some decomposition). The product could not be purified or characterised any further.

Preparation of N-Methyl-N-trifluoromethylcarbonyl-N'-(4-methoxycarbonylbenzoyl-1,4-xylylenediamine (147)

N-Methyl-1,4-xylylenediamine (141) (150 mg, 1 mmole) was dissolved in dry dichloromethane under an atmosphere of nitrogen. Dry trifluoroacetic acid (114 mg, 77 µl, 1 mmole) and 18-crown-6 (264 mg, 1 mmole) were added followed by trifluoroacetic anhydride (246 mg, 141 µl, 1 mmole) and triethylamine (101 mg, 140 µl, 1 mmole). The reaction was stirred for 1 h at 0° and then warmed to room temperature. More triethylamine (505 mg, 0.7 ml, 5 mmole) was added followed by 4-methoxycarbonylbenzoyl chloride (130) (198 mg, 1 mmole). Finally potassium chloride (744 mg, 10 mmole) was introduced. The solution was stirred for a further hour and washed with saturated potassium chloride solution (3 x 25 ml), dried (sodium sulphate), filtered and evaporated to leave a material that contained three major, and one minor product, by tlc (silica, 20% ethyl acetate/80% dichloromethane). Column chromatography in the same solvent system led to the isolation of each of the major products. The least polar turned out to be the *title compound* (147) as a white, crystalline solid (47 mg, 12%) identical with an authentic sample described earlier. The second compound, an isomer of the first, was *N-(4-methoxycarbonylbenzoyl)-N-methyl-N'-trifluoromethylcarbonyl-1,4-xylylenediamine* (158) (39 mg, 10%), mp 168-71° (from methanol), ν_{max} ($CHCl_3$) 3440, 1720, 1630, 1400, 1280, 1170, and 910 cm^{-1}; ^1H nmr ($CDCl_3$) δ 8.0 (2H, d,

J 7 Hz, aryl-H), 7.45 (2H, d, J 7 Hz, aryl-H), 7.3 (4H, m, aryl-H), 4.5 (4H, m, aryl-CH_2), 3.9 (3H, s, $-CO_2Me$), and 2.9 (3H, br s, -NMe); m/e 408 (M^+), 295, 215, and 163 (Found: C, 58.95; H, 4.69; H, 6.83. $C_{20}H_{19}N_2O_4F_3$ requires C, 58.85; H, 4.70; N, 6.87%). The most polar compound turned out to be identical with an authentic sample of N,N'-dimethoxycarbonylbenzoyl-N-methyl-1,4-xylylenediamine (159) (37 mg, 8%) in all respects.

Preparation of N-(4-Methoxycarbonylbenzoyl)-N-methyl-N'-benzoyl-1,4-xylylenediamine (145). Entry 2

N-Methyl-1,4-xylylenediammonium di-toluene-4-sulphonate (161) (247 mg, 0.5 mmole) was added to dry dichloromethane (15 ml) under a nitrogen atmosphere. Triethylamine (50 mg, 70 µl, 0.5 mmole) was added followed by 18-crown-6 (132 mg, 0.5 mmole). After a clear solution had formed,4-methoxycarbonylbenzoyl chloride (130) (99 mg, 0.5 mmole) was added and then more triethylamine (50 mg, 70 µl, 0.5 mmole) was introduced. The solution was allowed to stir for 1 h and an infrared spectrum of the reaction mixture showed formation of a tertiary amide only ν_{max} (CH_2Cl_2) 1638 cm^{-1}. Triethylamine (255 mg, 350 µl, 2.5 mmole) was added followed by benzoyl chloride (70 mg, 59 µl, 0.5 mmole) and potassium chloride (0.37 g, 5 mmole). After stirring for a further hour reaction was stopped by washing the organic layer with a saturated potassium chloride solution (3 x 25 ml). The dichloromethane solution was dried (sodium sulphate), filtered and evaporated to yield an oil, containing only one product that moved off the baseline by tlc (silica, 30% ethyl acetate/70% dichloromethane).

The baseline material was removed by column chromatography (same solvent) and the oil obtained which crystallised on standing (130 mg, 63%) was identical in every respect with an authentic sample of the title compound (145).

Preparation of N-(4-Methoxycarbonylbenzoyl)-N-methyl-1,4-xylylenediamine (148). Entry 2

N-Methyl-1,4-xylylenediammonium di-toluene-4-sulphonate (161) (5.93 g, 12 mmole) was added to dry dichloromethane (150 ml) under nitrogen. Triethylamine (1.21 g, 1.68 ml, 12 mmole), 18-crown-6 (3.17 g, 12 mmole), 4-methoxycarbonylbenzoyl chloride (130) (2.38 g, 12 mmole) and more triethylamine (1.21 g, 1.68 ml, 12 mmole) were added sequentially. The solution was allowed to stir for 1 h and quenched with triethylamine (5.0 ml). The organic layer was washed with saturated potassium chloride solution (10 x 50 ml), dried (sodium sulphate), filtered and evaporated to leave the title compound (148), identical in all respects with authentic material isolated earlier (3.28 g, 88%).

Preparation of N-(4-Hydroxycarbonylbenzoyl)-N-methyl-1,4-xylylenediamine (162)

The amino-ester (148) (1.41 g, 4.52 mmole) was dissolved in methanol (70 ml) and an aqueous sodium hydroxide solution (0.5 M, 9.1 ml, 4.52 mmole) was added. The solution was heated at the reflux for 6 h until tlc analysis (silica, 80% dichloromethane/20% methanol) had shown the disappearance of the starting ester. The reaction

mixture was cooled and hydrochloric acid (0.1 M, 45.5 ml, 4.55 mmole) was added. The solvent was all removed and the residue was taken up in a minimum amount of 10% aqueous sodium hydrogen carbonate. A 1 M hydrochloric acid solution was added until a small amount of a gum appeared. This solution after standing for several days produced a white, amorphous solid (860 mg) which was isolated by filtration. Although this solid could not be fully characterised it almost certainly contained some of the title compound (162) mp >300°, ν_{max} (Nujol) 3280, 2400-3200, 2660, 2540, 1680, 1625, 1575, 1535, 1280, 1070, and 840 cm^{-1}; ^1H nmr (d^6-DMSO) δ 7.25-7.95 (11H, m, aryl-H and $-NH_3$), 4.35-4.65 (4H, m, aryl-CH_2), and 2.80 (3H, br s, -NMe); m/e too involatile to be measured.

Preparation of N-(4-Chlorocarbonylbenzoyl)-N-methyl-1,4-xylylenediammonium Chloride (163)

The crude amino-acid (162) (50 mg, 0.17 mmole) was suspended in thionyl chloride (5 ml) and the mixture stirred at the reflux for 6 h. The solution became homogeneous during the course of the reaction. On cooling, the thionyl chloride was removed at reduced pressure to leave the title compound (163) as a white solid (54 mg), ν_{max} (CH_2Cl_2) 2600-3000, 1775, 1745, 1635, 1200, and 860 cm^{-1}. The identity of this compound was confirmed by conversion back to the methyl ester (see below).

Preparation of N-(4-Methoxycarbonylbenzoyl)-N-methyl-1,4-xylylenediamine (148). Entry 3

The amino-acid chloride (163) (54 mg) was dissolved in dry

methanol (20 ml) and the mixture stirred at room temperature for 20 min. The methanol was removed *in vacuo* to leave the hydrochloride salt of the title compound (148) (45 mg), ν_{max} (CH_2Cl_2) 2600-3000, 1725, 1635, and 1115 cm^{-1}. The oil was taken up in 10% aqueous sodium hydrogen carbonate (5 ml) and extracted with dichloromethane (2 x 5 ml). The organic layer was dried (sodium sulphate), filtered and evaporated to leave the amino-ester title compound (148) (35 mg), identical with an authentic sample of the material.

Preparation of 1,4-Xylylenediamine (164)

1,4-Dicyanobenzene (36.0 g, 0.29 mole) in THF (400 ml) was slowly added to a stirred suspension of lithium aluminium hydride (20 g, 0.53 mole) in THF (200 ml) under nitrogen. The mixture was heated at the reflux for 15 h during which time the dark green precipitate formed discharged its colour to become much more pale. ^1H nmr analysis after this time showed that the reaction had gone to completion, whereupon the mixture was cooled in ice to 0°. The reaction was quenched with a solution of saturated sodium sulphate (approximately 100 ml). The solution was then filtered and the filtrate evaporated to leave a wet, orange oil. This was dissolved in dichloromethane and dried over sodium sulphate. Meanwhile, the salts produced from the original reaction were extracted with hot dichloromethane and again filtered. The combined dichloromethane layers were dried, filtered and evaporated to give the title compound (164) as an orange, waxy solid (32.1 g, 82%), mp 33-4° (*Lit.*[147] 35°), ν_{max} (Nujol), 3360, 3280, 1640, 1600, 1510, 1165, 1065, and 710 cm^{-1}; ^1H nmr ($CDCl_3$) δ 7.25 (4H, s, aryl-$\underline{H}$), 3.81 (4H, s, aryl-$C\underline{H}_2$), and 1.48 (4H, s, $-N\underline{H}_2$).

Preparation of 1,4-Xylylenediammonium Di-toluene-4-sulphonate (165)

1,4-Xylylenediamine (164) (5.0 g, 37 mmole) was dissolved in methanol (5 ml) and a solution of 4-toluenesulphonic acid monohydrate (14.8 g, 74 mmole) in methanol (20 ml) was added. The yellow crystalline salt, *the title compound* (165), precipitated immediately (12.54 g, 67%), mp 296-9° (from water), ν_{max} (Nujol), 2400-3300, 1640, 1600, 1240, 1150, 820, and 685 cm^{-1}; ^1H nmr (d^6-DMSO) δ 8.1 (6H, br s, $-NH_3$), 7.40 (8H, m, aryl-H), 7.0 (4H, d, J 8 Hz, aryl-H), 3.92 (4H, q, J 5 Hz, aryl-CH_2), and 2.19 (6H, s, aryl-CH_3) (Found: C, 55.22; H, 5.87; N, 5.82. $C_8H_{12}N_2.2\ C_7H_8SO_3$ requires C, 54.97; H, 5.88; N, 5.83%).

Preparation of N-(4-Methoxycarbonylbenzoyl)-N′-trifluoromethylcarbonyl-1,4-xylylenediamine (166)

1,4-Xylylenediammonium di-toluene-4-sulphonate (165) (480 mg, 1 mmole) was suspended in dichloromethane under an atmosphere of nitrogen. Triethylamine (101 mg, 140 µl, 1 mmole) and 18-crown-6 (264 mg, 1 mmole) were both added. After stirring for 30 min to allow equilibration, 4-methoxycarbonylbenzoyl chloride (130) (198 mg, 1 mmole) was added followed by more triethylamine (101 mg, 140 µl, 1 mmole). After 1 h the suspension was cooled to -78° and a third portion of triethylamine (505 mg, 0.7 ml, 5 mmole) was introduced followed by trifluoroacetic anhydride (210 mg, 141 µl, 1 mmole) and potassium chloride (0.75 g, 10 mmole). The suspension was allowed to reach room temperature and after a further hour was washed with saturated potassium chloride solution (4 x 25 ml). After drying (sodium sulphate), the organic layer was filtered and evaporated

to leave a white solid which by tlc (silica, ethyl acetate 20%/ dichloromethane 80%) showed 2 major products. Column chromatography (same solvents) led to the isolation of single spot material of both major components. The first proved to be *the title compound* (166) (61 mg, 16%), mp 211-214° (from methanol), ν_{max} ($CHCl_3$) 3430, 1725, 1675, 1600, 1285, 1150, and 925 cm^{-1}; ^1H nmr ($CDCl_3$) δ 6.85-7.70 (10H, m, aryl-H + N-H), 4.15 (2H, d, J 7 Hz, aryl-CH_2), 4.05 (2H, d, J 7 Hz, aryl-CH_2), and 3.50 (3H, s, CO_2Me); m/e 394 (M^+), 362, 297, 281, 216, 215, 163, and 135 (Found: C, 57.66; H, 4.27; N, 7.10. $C_{19}H_{17}N_2O_4F_3$ requires C, 57.87; H, 4.35; N, 7.10%). The more polar major component (54 mg), a white solid, could not be characterised at all due to its insolubility and involatility.

Preparation of N,N'-Bis-(trifluoromethylcarbonyl)-1,4-xylylene-diamine (167)

1,4-Xylylenediammonium di-toluene-4-sulphonate (165) (480 mg, 1 mmole) was suspended in dichloromethane and triethylamine (202 mg, 280µl, 2 mmole) was added. The solution was stirred under nitrogen and cooled to -78° and trifluoroacetic anhydride (420 mg, 282 µl, 2 mmole) was introduced followed by triethylamine (202 mg, 280 µl, 2 mmole). A pale orange suspension appeared, the colour discharging as the reaction warmed up. The reaction was left to stir for 2 h and more triethylamine (1 ml, an excess) was added. The reaction mixture was diluted with dichloromethane (50 ml) and was washed with a saturated potassium chloride solution (2 x 50 ml). The organic layer was dried (sodium sulphate), filtered and evaporated to yield the white crystalline *title compound* (167) (127 mg, 39%), mp 202-3°

(from dichloromethane and methanol), ν_{max} ($CHCl_3$) 3420, 1722, 1160, 1010, and 910 cm^{-1}; ^1H nmr ($CDCl_3$) δ 7.30 (4H, s, aryl-H), 4.90 (2H, s, -NHCO), and 4.60 (4H, br s, aryl-CH_2); m/e 328 (M^+), 216, 215, and 202 (Found: C, 43.78; H, 3.05; N, 8.37. $C_{12}H_{10}N_2O_2F_6$ requires C, 43.91; H, 3.21; N, 8.67%).

Preparation of N,N′-Di-(4-methoxybenzoyl)-1,4-xylylenediamine (169)

4-Methoxybenzoyl chloride (170) (80.25 g, 0.47 mole) was dissolved in dichloromethane (200 ml) under an atmosphere of nitrogen. To the vigorously stirred mixture, cooled to 0°, was slowly added a solution of 1,4-xylylenediamine (164) (32.1 g, 0.235 mole) and triethylamine (150 ml, an excess) in dichloromethane (250 ml). During addition a white precipitate appeared. The mixture was left for 1 h and the white solid amide filtered off. This was washed with dichloromethane (1000 ml) and hot methanol (500 ml) and dried *in vacuo* overnight to yield the *title compound* (169) (73.05 g, 77%), mp 251-2° (from trifluoroacetic acid, methanol), ν_{max} (Nujol) 3330, 1632, 1610, 1550, 1500, 1295, 1255, 1191, 1025, 983, 840, and 772 cm^{-1}; ^1H nmr (CF_3CO_2H and $CDCl_3$) δ 7.73 (4H, d, J 9 Hz, aryl-H), 7.32 (4H, s, aryl-H), 7.01 (4H, d, J 9 Hz, aryl-H), 4.75 (4H, s, aryl-CH_2), and 3.90 (6H, s, -OMe); m/e 404 (M^+), 268, 253, 135, and 77 (Found: C, 71.15; H, 5.98; N, 6.89. $C_{24}H_{24}N_2O_4$ requires C, 71.27; H, 5.98; N, 6.93%).

Preparation of N,N′-Di-(4-methoxybenzyl)-1,4-xylylenediamine (171)

To a vigorously stirred suspension of the bisamide (169) (12.5 g,

31 mmole) in dry THF (150 ml) under a nitrogen atmosphere was added a slurry of lithium aluminium hydride (4.1 g, 108 mmole) in THF (300 ml). The suspension was heated to reflux for 18 h during which time it assumed a red colouration. The mixture was then cooled and in doing so it turned green. Saturated sodium sulphate solution was added cautiously to the ice-cooled mixture, and the salts formed during the quench were filtered off and extracted with hot dichloromethane. The filtrate was concentrated to leave a wet yellow oil which was dissolved in dichloromethane. The two dichloromethane solutions were combined and dried (sodium sulphate). Filtration and evaporation yielded the title compound (171) as a yellow oil which solidified on standing (11.28 g, 97%), mp 73-5°, ν_{max} (Nujol) 3320, 1610, 1580, 1510, 1245, 1030, 820, and 730 cm^{-1}; ^1H nmr ($CDCl_3$) δ 7.30 (4H, s, aryl-H), 7.22 (4H, d, J 9 Hz, aryl-H) 6.85 (4H, d, J 9 Hz, aryl-H), 3.80 (8H, s, aryl-CH_2), 3.75 (6H, s, aryl-OMe), and 1.66 (2H, br s, -NH). The spectra were identical with an authentic sample of the material[5].

Preparation of N,N′,N″, N‴ ,-Tetra-(4-methoxybenzyl)-2,11,20,29-tetra-aza-[3.3.3.3]paracyclophane (173)

The compound was prepared in a similar manner to that of Godfrey[5]. To a rapidly stirred solution of dichloromethane (3 L) under an atmosphere of nitrogen in special high-dilution apparatus (see appendix I), was added two reagent solutions simultaneously over 16 h. The first consisted of freshly prepared terephthaloyl chloride (172), (5.40 g, 26.60 mmole) in dry dichloromethane (48 ml), and the second of N, N′-di-(4-methoxybenzyl)-1,4-xylylenediamine (171) (10.0 g, 26.60

mmole) and triethylamine (18 ml, an excess) made up to 48 ml with dichloromethane. A reflux was maintained to recycle the solvent around the apparatus throughout the reaction period. After the reaction was complete the solution was removed from the apparatus, reduced in volume to approximately 500 ml and washed with dilute hydrochloric acid (500 ml). The aqueous layer was re-extracted with dichloromethane (300 ml) and the combined organic layers were dried over sodium sulphate. Filtration and evaporation left a brown amorphous material, the crude tetra-amide (14.4 g), ν_{max} (Nujol) 1635 cm^{-1}. This material (14.4 g) was suspended in dry THF (200 ml), and the solution was vigorously stirred under an atmosphere of dry nitrogen. A suspension of lithium aluminium hydride (2.65 g, 70 mmole) in THF (150 ml) was added whereupon the mixture was heated at the reflux for 48 h. After cooling, the reaction was quenched with saturated sodium sulphate solution. Filtration and evaporation of the THF solution led to a wet oil which was dissolved in dichloromethane and dried (sodium sulphate). The salts produced during the quench were extracted with hot dichloromethane. The combined organic layers, were filtered and evaporated to yield a white foam (12.2 g). Purification was achieved after repeated chromatography (dichloromethane) to leave a white crystalline material (173) (1.93 g, 15%), mp 205-8° (*lit.*[5] 207-8°), ν_{max} (CH_2Cl_2) 2920, 2800, 1612, 1510, 1370, 1040, and 900 cm^{-1}; ^1H nmr ($CDCl_3$) δ 7.35 (16H, s, aryl-H paracyclophane ring), 7.30 (8H, d, J 9 Hz, aryl-H), 6.87 (8H, d, J 9 Hz, aryl-H), 3.77 (12H, s, aryl-OMe), 3.51 (8H, s, N-CH_2-aryl-OMe), and 3.39 (16H, s, N-CH_2-aryl).

Preparation of N,N′,N″,N‴ -Tetra-(2,2,2-trichloroethoxycarbonyl)-2,11,20,29-tetra-aza[3.3.3.3]paracyclophane (174)

The compound was prepared by the method of Godfrey[5] by treatment of the tetra-(4-methoxybenzyl)paracyclophane (173) with an excess of 2,2,2-trichloroethyl chloroformate in refluxing carbon tetrachloride for 18 h. The compound (174) was isolated by chromatography as a white foam in 68% yield, ν_{max} (CH_2Cl_2) 1710, 1215, and 1125 cm^{-1}; ^1H nmr ($CDCl_3$) δ 6.95 (16H, s, aryl-H), 4.85 (8H, s, $-OCH_2-CCl_3$), and 4.38 (16H, s, aryl-CH_2).

Preparation of 2,11,20,29-Tetra-aza[3.3.3.3]paracyclophane (168)

The procedure of Godfrey[5] was used. The tetra-carbamate (174) was treated with an excess of potassium hydroxide in a dioxan-water mixture. The mixture was heated to reflux under nitrogen for 7 days. The title compound (168) was isolated as a yellow crystalline compound in 88% yield, mp 140-2° (*lit.*[5] 142-3°), ν_{max} ($CHCl_3$), 3320, 1612, 1455, and 1090 cm^{-1}; ^1H nmr ($CDCl_3$) δ 7.07 (16H, s, aryl-H), 3.70 (16H, s, aryl-CH_2-), and 1.60 (4H, s, NH).

Reaction of 2,11,20,29-Tetra-aza[3.3.3.3]paracyclophane (168) with Isophthaloyl Dichloride (175)

A solution of the tetra-azaparacyclophane (168) (165 mg, 0.35 mmole), in dichloromethane (250 ml) was added to vigorously stirred dichloromethane (2000 ml) containing triethylamine (5 ml) at the same time as a solution of isophthaloyl dichloride (175) (71 mg, 0.35 mmole) in dichloromethane (250 ml). The reaction was

performed under an atmosphere of nitrogen. After addition was complete (approximately 9 h) the dichloromethane solution was concentrated to a volume of about 50 ml and washed with a solution of saturated sodium sulphate (2 x 30 ml). After drying (sodium sulphate), the organic layer was filtered and evaporated. The residue (256 mg) was chromatographed (alumina, dichloromethane) and both non-polar products were isolated. The first less-polar fraction was a white compound (42 mg), mp >300°, ν_{max} (CH_2Cl_2) 3440, 1625, 1400, 1095, and 1020 cm^{-1}; ^1H nmr ($CDCl_3$) δ 6.7-7.6 (m, aryl-H), 4.2-4.5 (m, aryl-CH_2), and 3.4-3.75 (m, aryl-CH_2), ratio aromatic:benzylic protons 4:3; m/e 251, 231, and 132. The compound could not be positively identified. The more polar component was also a white, amorphous solid after recrystallisation from chloroform, petroleum ether, and may have been the desired 2-20 bridged bis-amide (176) (61 mg), mp >300°, ν_{max} (CH_2Cl_2) 3440, 1625, 1400, 1325, and 895 cm^{-1}; ^1H nmr ($CDCl_3$) δ 6.9-7.5 (24H, m, aryl-H), 5.9-6.6 (10H, m, aryl-H), and 3.5-4.3 (16H, m, aryl-CH_2); m/e 606 (M^+), 474, 251, 231, and 132. This compound however could not be fully characterised.

Preparation of 1,3-Diphenylpropane (179)

1,3-Diphenylpropane was prepared by a Wolff-Kishner reduction employing a Huang-Minlon modification on 1,3-diphenylacetone as described by Cram and Steinberg[120]. The compound was obtained in 89% yield, bp 163° at 25 mm Hg (*lit.*[120] 165° at 25 mm Hg), ν_{max} (thin film) 3080, 3060, 3020, 2930, 2850, 1602, 1493, 1451, 1081, 1027, 740, and 700 cm^{-1}; ^1H nmr ($CDCl_3$) δ 7.2 (10H, br s, aryl-H), 2.60 (4H, t, J 8 Hz, aryl-CH_2), and 1.85 (2H, p, J 8 Hz, $-CH_2-CH_2-CH_2$).

Preparation of Di-1,3-(4-methylcarbonylphenyl)propane (180)

A solution of 1,3-diphenylpropane (179) (37.0 g, 0.19 mole) and acetyl chloride (75 g, 68 ml, 0.96 mole) in dichloromethane (100 ml) was added dropwise over 1 h to a vigorously stirred suspension of aluminium chloride (126 g, 0.88 mole) in dichloromethane (100 ml) cooled in an ice-salt bath. An atmosphere of dry nitrogen was maintained in the reaction vessel. After addition was complete the mixture was heated at the reflux for 2 h whereupon the volatile materials were allowed to distill off leaving a brown, tarry sludge. After cooling, the mixture was carefully introduced into a stirred mixture of concentrated hydrochloric acid (250 ml) and ice (500 g). The resulting brown tar was filtered off, washed copiously with water and dissolved in hot methanol (300 ml). Treatment with activated charcoal followed by filtration through celite and evaporation left the title compound (180) as a yellow solid (46.02 g, 88%), mp 83-6° (*lit.*[121] 84-6°), ν_{max} (Nujol) 1668, 1598, 1561, 1405, 1262, 1176, 953, and 832 cm^{-1}; ^1H nmr ($CDCl_3$) δ 7.90 (4H, d, J 7 Hz, aryl-H), 7.27 (4H, d, J 7 Hz, aryl-H), 2.57-2.79 (10H, m, aryl-CH_2 and COMe), and 2.01 (2H, p, J 6 Hz, CH_2-CH_2-CH_2); m/e 280 (M^+), 265, 147, 133, and 43.

Preparation of Di-1,3-(4-hydroxycarbonylphenyl)propane (181)

The diacetyl compound (180) (9.5 g, 34 mmole) was suspended in methanol (400 ml) and stirred. An aqueous sodium hypochlorite solution (10-14%, 400 ml, 500-700 mmole) was added and the mixture was heated so that the temperature remained between 65° and 75° for 4 h. After

cooling, acetone (100 ml) was added to quench excess hypochlorite and any residual undissolved solid was removed by filtration. The aqueous solution was acidified cautiously with concentrated hydrochloric acid (until acid to congo red indicator paper). The precipitated solid was either filtered or centrifugated away from the solution and the white solid was washed thoroughly with hot water to remove almost all the precipitated sodium chloride. Thorough drying *in vacuo* produced the title compound (181) pure enough for subsequent use (7.63 g, 79%), ν_{max} (Nujol) 2400-3300, 1685, 1612, 1573, 1428, 1320, 1290, 1180, 1020, 950, and 765 cm^{-1}; ^{1}H nmr ($CDCl_3$, d^6-DMSO) δ 7.90 (4H, d, J 7 Hz, aryl-H), 7.31 (4H, d, J 7 Hz, aryl-H), 2.67 (4H, t, J 6 Hz, aryl-CH_2), and 1.92 (2H, p, J 6 Hz, $-CH_2-CH_2-CH_2$); m/e 285 ($M^+ + 1$), 268, 149, and 136.

Preparation of Di-1,3-(4-chlorocarbonylphenyl)propane (182)

The diacid (181) (6.50 g, 23 mmole) was suspended in thionyl chloride (100 ml) and heated to reflux. N,N-dimethylformamide (2 drops) was added and heating continued for 2 h in which time an almost clear solution was obtained. The thionyl chloride was removed at reduced pressure and dry dichloromethane (50 ml) was added. Rapid filtration of the dichloromethane solution removed the small amounts of insoluble material. Evaporation led to the title compound (182) as a white solid (6.88 g, 94%), ν_{max} (CH_2Cl_2) 2940, 2850, 1772, 1735, 1602, 1410, 1230, 1170, and 878 cm^{-1}. The compound was further characterised by the subsequent chemical transformations.

Preparation of Di-1,3-[4-(4-methoxybenzylamino)-carbonylphenyl]-propane (184)

The acid chloride (182) (33.21 g, 0.103 mole) was dissolved in dry dichloromethane (500 ml) under an atmosphere of dry nitrogen. The reaction was cooled in an ice-bath whilst a solution of 4-methoxybenzylamine (28.33 g, 27 ml, 0.206 mole) and triethylamine (29 g, 40 ml, 0.287 mole) in dichloromethane (200 ml) was added. The reaction was allowed to stir overnight during which time a light green coloured precipitate was noted. Dilution of the reaction mixture with more dichloromethane (500 ml) led to the dissolution of the precipitate. The organic layer was sequentially washed with 10% aqueous sodium hydrogen carbonate solution (400 ml), 2 M hydrochloric acid (400 ml) and saturated aqueous sodium sulphate solution (2 x 400 ml). Drying (sodium sulphate) followed by filtration and evaporation led to the slightly brown coloured *title compound* (184) (50.49 g, 93%), mp 158-9° (from methanol), ν_{max} (CH_2Cl_2) 3450, 2930, 1658, 1612, 1512, 1492, 1410, 1175, 1035, and 830 cm^{-1}; ^1H nmr ($CDCl_3$) δ 7.66 (4H, d, J 9 Hz, aryl-H), 7.18 (8H, t, J 8 Hz, aryl-H), 6.83 (4H, d, J 9 Hz, aryl-H), 6.50 (2H, t, J 5 Hz, -NH), 4.52 (4H, d, J 5 Hz, aryl-CH_2-NH), 3.74 (6H, s, aryl-OMe), 2.62 (4H, t, J 7 Hz, aryl-CH_2-CH_2), and 1,89 (2H, p, J 7 Hz, CH_2-CH_2-CH_2); m/e 522 (M^+), 487, 459, 431, 266, 251, 223, and 136 (Found: C, 75.59; H, 6.54; N, 5.39. $C_{33}H_{34}N_2O_4$ requires C, 75.48; H, 6.56; N, 5.36%).

Preparation of Di-1,3-[4-(4-methoxybenzylamino)-methylenephenyl]-propane (185)

To a stirred suspension of lithium aluminium hydride (5.0 g, 0.13 mole) in tetrahydrofuran (200 ml) under an atmosphere of nitrogen was added a solution of the bisamide (184) (6.92 g, 13.2 mmole) in tetrahydrofuran (150 ml). The resulting mixture was heated at the reflux producing a purple colour which faded to a light green as the reaction proceeded. After 16 h the reaction was allowed to cool in an ice-bath and a saturated aqueous solution of sodium sulphate (100 ml) was added. Filtration followed by evaporation gave a wet yellow oil that was dissolved in dichloromethane. Meanwhile the salts produced during the quench were extracted with hot dichloromethane. The two organic solutions were combined and dried (sodium sulphate), filtered and evaporated to give a yellow oil (6.45 g, 99%), the title compound (185), ν_{max} (CH_2Cl_2) 3440, 2900, 1620, 1410, 1170, 1050, and 880 cm^{-1}; ^1H nmr ($CDCl_3$) δ 6.81-7.29 (16H, m, aryl-H), 3.78 (14H, br s, aryl-CH_2N + aryl-OMe), 2.62 (4H, t, J 8 Hz, aryl-CH_2-C), 1.86 (2H, br s, CH_2-CH_2-CH_2), and 1.81 (2H, s, N-H); m/e 494 (M^+), 388, 371, 357, 137, and 121. The compound was further characterised as its *dihydrochloride salt*, mp 242-3° (from water) (Found: C, 69.98; H, 7.08; N, 4.75. $C_{33}H_{38}N_2O_2 \cdot 2HCl$ requires C, 69.83; H, 7.10; N, 4.94%).

Preparation of Di-1,3-(4-aminocarbonylphenyl)propane (190)

To a solution of diacid chloride (182) (323 mg, 1 mmole) in dichloromethane (10 ml) was added 0.88 ammonia solution (5 ml) with

vigorous stirring. A white solid formed immediately and this was filtered and washed thoroughly with both dichloromethane and water. Drying *in vacuo* left the title compound (190) as a white amorphous powder (205 mg, 72%), mp 241-2° (from trifluoroacetic acid and methanol), ν_{max} (Nujol) 3400, 3160, 1655, 1620, 1570, 1411, and 720 cm^{-1}; ^1H nmr ($CDCl_3$, d^6-DMSO) δ 7.75 (4H, d, J 9 Hz, aryl-H), 7.20 (4H, d, J 9 Hz, aryl-H), 2.65 (4H, t, J 7 Hz, aryl-CH_2), and 1.90 (2H, p, J 8 Hz, $-CH_2-CH_2-CH_2$); m/e 282 (M^+), 267, 148, and 134. Although pure by all spectral criteria the compound could not be obtained microanalytically pure possibly due to the presence of some inorganic impurities.

Preparation of Di-1,3-(4-aminoethylenephenyl)propane (189)

The crude bisamide (190) (150 mg, 0.53 mmole) was suspended in THF (50 ml) and to this vigorously stirred slurry was added a suspension of lithium aluminium hydride (250 mg, 6.6 mmole) in THF (100 ml). The mixture was heated at the reflux under nitrogen for 24 h after which it was cooled and quenched with saturated sodium sulphate solution (10 ml). Filtration and evaporation left a moist oil which was dissolved in dichloromethane (50 ml) and dried (sodium sulphate). Further filtration and evaporation yielded the title compound (189) as a brown oil (96 mg, 71%), ν_{max} (thin film) 3340, 3290, 1640, 1608, 1510, 1415, 1382, 1050, and 800 cm^{-1}; ^1H nmr ($CDCl_3$) δ 7.15 (8H, m, aryl-H), 3.80 (4H, s, aryl-CH_2-N), 2.61 (4H, t, J 8 Hz, aryl-CH_2-C), and 1.72 (6H, m, $-CH_2-CH_2-CH_2$ + NH); m/e 237 (M^+-NH_3), 149, 136, and 132. The compound was further characterised by conversion to the *di-toluene-4-sulphonic acid salt* mp 198-205° (from methanol and diethyl ether) (Found: C, 62.13; H, 6.42; H, 4.39. $C_{17}H_{22}N_2 \cdot 2C_7H_8SO_3$ requires C, 62.18; H, 6.40; N, 4.68%).

Preparation of N,N'-Di-(4-methoxybenzyl)-2,20-di-aza[3.3.3.3]-paracyclophane (186)

To vigorously stirred dichloromethane (2.5 l) in a special high-dilution apparatus (see appendix I) was added over 48 h two solutions simultaneously. The first consisted of the diacid chloride (182) (11.4 g, 36 mmole) dissolved in dichloromethane (150 ml) and the second, the diamine (185) (17.75 g, 36 mmole) in triethylamine (15.25 g, 21 ml, an excess) in dichloromethane (129 ml). After addition was complete the dichloromethane solution was concentrated to about 800 ml and washed with 2 M hydrochloric acid (800 ml). The aqueous layer was re-extracted with dichloromethane (500 ml), and combined organic layers were dried (sodium sulphate), filtered and evaporated to yield a brown foam (25 g), ν_{max} (CH_2Cl_2) 1623 cm^{-1} clearly a complex mixture of polyamides. The crude mixture (25 g) was dissolved in THF (500 ml) and added to a vigorously stirred suspension of lithium aluminium hydride (14 g) in THF (300ml). The mixture was heated at the reflux for 40 h under an inert atmosphere and cooled. The reaction mixture was quenched with saturated sodium sulphate solution, filtered and evaporated to leave a wet oil. This was dissolved in dichloromethane and combined with hot dichloromethane with which the salts generated on quenching had been extracted. The organic layer was dried (sodium sulphate), filtered and evaporated to leave a white crystalline material which by tlc (silica, 1% ethyl acetate/ 99% dichloromethane) showed two non-polar spots. Column chromatography (dichloromethane) isolated the less polar of these products as the white crystalline *title compound*

(186) (6.00 g, 23.5%), mp 201-2° (from chloroform and methanol), ν_{max} (CH_2Cl_2) 2990, 2920, 2790, 1611, 1507, 1365, 1030, and 835 cm^{-1}; ^1H nmr (250 MHz) ($CDCl_3$) δ 7.33 (4H, d, J 8 Hz, MeO-aryl-H), 7.15 (8H, d, J 8 Hz, NCH_2-aryl-H), 7.00 (8H, d, J 8 Hz, NCH_2-aryl-H), 6.86 (4H, d, J 8 Hz, MeO-aryl-H), 3.81 (6H, s, aryl-OMe), 3.60 (4H, s, MeO-aryl-CH_2), 3.39 (8H, s, aryl-CH_2-N), 2.54 (8H, t, J 8 Hz, aryl-CH_2-C), and 1.76 (4H, p, J 8 Hz, $-CH_2-CH_2-CH_2$); ^{13}C nmr ($CDCl_3$) δ 34.58, 34.92, 55.31, 57.41, 58.98, 113,74, 128.07, 128.71, 130.15, 131.91, 137.89, 141.03, and 158.79; m/e 714 (M^+), 594, 464, 356, 265, 218, 170, and 133 (Found: C, 83.77; H, 7.64; N, 3.88. $C_{50}H_{54}N_2O_2$ requires C, 83.99; H, 7.61; N, 3.92%).

Preparation of N,N'-Di-(2,2,2-trichloroethoxycarbonyl-2.20-di-aza-[3.3.3.3]paracyclophane (187)

To a stirred suspension of the di-(4-methoxybenzyl)-paracyclophane (186) (5.96 g, 8.35 mmole) in dry carbon tetrachloride (150 ml) at room temperature under an atmosphere of dry nitrogen was added 2,2,2-trichloroethyl chloroformate (9.40 g, 6.11 ml, 44 mmole). The mixture was heated to the reflux whereupon it became homogeneous. After 18 h ^1H nmr analysis revealed that the reaction had gone to completion. The solution was allowed to cool and the solvent removed by evaporation at reduced pressure. Baseline material formed during the reaction was removed by column chromatography (dichloromethane) and 4-methoxybenzyl chloride was evaporated off under a hard vacuum. This left the *title compound* (187) as a white, crystalline material (6.16 g, 89%), mp 194-5° (from chloroform and methanol), ν_{max} (CH_2Cl_2) 2920, 1705, 1505, 1405, 1120, and 675 cm^{-1}; ^1H nmr (250 MHz) ($CDCl_3$) δ 6.84

(16H, m, aryl-H), 4.84 (4H, s, $-CH_2CCl_3$), 4.59 (8H, d, J 9 Hz, aryl-CH_2-N), 2.42 (8H, br s, aryl-CH_2-C), and 1.81 (4H, p, J 6 Hz $-CH_2-CH_2-CH_2$); ^{13}C nmr ($CDCl_3$) δ 32.73, 34.28, 52.83, 53.48, 75.47, 128.16, 128.38, 128.69, 134.67, 141.09, and 154.92; m/e 822-828 (all M^+), 499, 474, 264, and 132 (Found: C, 58.20; H, 4.90; N, 3.46. $C_{40}H_{40}N_2O_4Cl_6$ requires C, 58.20; H, 4.88; N, 3.39%).

Preparation of 2,20-Di-aza[3.3.3.3]paracyclophane (178)

The di-carbamate (187) (3.0 g, 3.63 mmole) was suspended in 1,4-dioxan (150 ml) and a solution of potassium hydroxide (12.0 g) in water (45 ml) was added. The solution was heated at the reflux with vigorous stirring under nitrogen for 4.5 days. On cooling the solution was evaporated almost to dryness and partioned between dichloromethane (150 ml) and water (150 ml). The organic layer was dried (sodium sulphate), filtered and evaporated to leave a yellow solid, the title compound (178) (1.69 g, 98%), mp 138-40° (from chloroform and hexane), ν_{max} (CH_2Cl_2) 3350, 3000, 2930, 2860, 1512, 1430, 1345, 1090, 910, and 820 cm^{-1}; ^1H nmr ($CDCl_3$) (250 MHz) δ 7.02 (8H, d, J 6.5 Hz, aryl-H), 6.93 (8H, d, J 6.5 Hz, aryl-H), 3.71 (8H, s, aryl-CH_2-N), 2.52 (8H, t, J 8 Hz, aryl-CH_2-C), 1.84 (4H, p, J 8 Hz, $-CH_2-CH_2-CH_2-$), and 1.70 (2H, br s, N-H); ^{13}C nmr ($CDCl_3$)δ 33.14, 34.45, 52.87, 128.20, 128.45, 138.08, and 140.95; m/e 474 (M^+), 251, 237, 203, 121, and 84 (M^+ 474.3038, $C_{34}H_{38}N_2$ requires 474.3035). The structure of the compound was further characterised by X-ray crystallography and by preparation of the *di-toluene-4-sulphonic acid derivative* mp 268-73° (from methanol

and diethyl ether) (Found: C, 70.55; H, 6.78; N, 3.44. $C_{34}H_{38}N_2 \cdot 2C_7H_8SO_3$ requires C, 70.39; H, 6.65; N, 3.42%).

Preparation of N,N'-Di-methyl-2,20-di-aza[3.3.3.3]paracyclophane (217)

To the di-azaparacyclophane (178) (75 mg, 0.158 mmole) was added formic acid (4 ml) and 37% aqueous formalin (0.3 ml, 3.7 mmole). The mixture was heated to reflux under a nitrogen atmosphere for 24 h whereupon the formic acid was removed and water (5 ml) was added. The solution was basified with 10% sodium hydrogen carbonate solution and then extracted with dichloromethane (3 x 5 ml) which was dried (sodium sulphate), filtered and evaporated to yield the crude di-N methylated compound. Column chromatography (95% dichloromethane and 5% methanol) led to the *title compound* (217) a white crystalline material (54 mg, 68%) mp 182-4° (from dichloromethane and hexane), ν_{max} (CH_2Cl_2) 2940, 2860, 1590, 1420, and 840 cm^{-1}; ^1H nmr ($CDCl_3$) δ 6.95 (16H, m, aryl-H), 3.32 (8H, s, aryl-CH_2-N), 2.35-2.65 (14H, m, aryl-CH_2-C and N-CH_3), and 1.85 (4H, m, $-CH_2-CH_2-CH_2$); m/e 502 (M^+), 487, 472, and 278 (Found: C, 86.03; H, 8.47; N, 5.46. $C_{36}H_{42}N_2$ requires C, 86.01; H, 8.42; N, 5.57%). The structure was further confirmed by X-ray crystallography.

Preparation of 2,3-Dihydroxybenzoic acid (191)

The acid was prepared by the method of Dallacher, Thiemann and Uddrich[124] by heating a mixture of 3-methoxysalicaldehyde (192) and potassium hydroxide to 250° in a nickel crucible. The material mp 201-3° (*lit.*[124] 204°), was isolated in 68% yield and used without

further purification, ν_{max} (Nujol) 3360, 2500-3300, 1680, 1660, 842, and 740 cm^{-1}; ^1H nmr ($CDCl_3$) δ 8.5 (3H, br s, -OH), and 6.45-7.40 (3H, m, aryl-H).

Preparation of Methyl 2,3-Dihydroxybenzoate (194)

2,3-Dihydroxybenzoic acid (191) (4.50 g, 29 mmole) was suspended in thionyl chloride (70 ml) and heated at the reflux for 5 h. The thionyl chloride was removed firstly by distillation and finally under vacuum to give a crude acid chloride (126) (4.8 g), ν_{max} ($CHCl_3$) 1750, 1620, and 1230 cm^{-1}. The brown gum was added to cold, dry methanol (30 ml) and stirred for 10 min. Methanol was removed by evaporation and the residue twice sublimed (110° at 0.07 mm Hg) to yield the title, yellow, methyl ester (194) (2.30 g, 62%), mp 69-73° (*lit.*[148] 73°), ν_{max} (Nujol) 3580, 3450, 1675, 1615, 1605, 840, and 760 cm^{-1}; ^1H nmr ($CDCl_3$) δ 10.9 (1H, s, 2-aryl-OH), 6.8-7.4 (3H, m, aryl-H), 5.8 (1H, br s, 3-aryl-OH), and 4.0 (3H, s, -OMe).

Preparation of N-Methyl-2,3-dihydroxybenzamide (195)

Methyl 2,3-dihydroxybenzoate (194) (1.5 g, 8.93 mmole) was suspended in a solution of methylamine in ethanol (20 ml). The mixture was stirred and the solid slowly dissolved. TLC analysis (silica, ethyl acetate) after 16 h showed the disappearance of the starting ester which had been replaced by a more polar material. The solvent was removed at reduced pressure, and the *title compound* (195) was isolated by filtration through a pad of silica (eluant ethyl acetate) as its monohydrate (1.20 g, 73%), mp 133-4° (from methanol and water), ν_{max} (Nujol) 2400-3500 (br), 1590 (br C=O str, lowered

due to hydrogen bonding), 1250, 930, 845, and 745 cm^{-1}; ^1H nmr ($CDCl_3$) 6.62-7.25 (5H, m, aryl-H + aryl-OH, 2H disappear on D_2O exchange), 6.35 (1H, br s, N-H, disappears on D_2O exchange), 3.05 and 2.97 (5H, s, NMe, and H_2O, 2 H disappear on D_2O exchange); m/e 167 (M^+), 149, 136, and 108 (Found: C, 52.21; H, 5.81; N, 7.56: $C_8H_9NO_3 \cdot H_2O$ requires C, 51.89; H, 5.99; N, 7.56%).

Attempted Preparation of N,N'-Di-(2,3-dihydroxybenzoyl)1,5-diaminopentane (196). Entry 1

Methyl 2,3-dihydroxybenzoate (194) (336 mg, 2 mmole) was dissolved in dry methanol(5 ml) and 1,5-diaminopentane (102 mg, 117 µl, 1 mmole) was added. The mixture was heated to 120° in a sealed glass tube for one week after which time tlc indicated the presence of large amounts of the methyl ester (194) in addition to polymeric baseline material. No amide was observed.

Attempted Preparation of N,N'-Di-(2,2-dimethyl-1,3-benzo-[d]-dioxole-4-carbonyl)-1,5-diaminopentane (198)

To a solution of 2,2-dimethyl-1,3-benzo-[d]-dioxole-4-carboxylic acid (152) (475 mg, 2.4 mmole) in THF (50 ml) was added 1,5-diaminopentane (122 mg, 143 µl, 1.2 mmole) and N-ethoxycarbonyl-2-ethoxy-1,2-dihydroquinoline (EEDQ) (197) (620 mg, 2.50 mmole). The solution was stirred for 4 days at room temperature under an atmosphere of nitrogen. When the reaction seemed complete by tlc the white crystalline material formed during the preparation was filtered and dried. The material (480 mg) was impure and could not be purified or

fully characterised, ν_{max} (Nujol) 3320, 1645, 1575, 1250, 1205, 800 and 750 cm^{-1}; ^1H nmr ($CDCl_3$) δ 6.6-7.5 (9H, m, aryl-H), 3.2 (3H, m), and 1.75 (12H, m).

Preparation of N,N'-Di-(2,2-dimethyl-1,3-benzo-[d]-dioxole-4-carbonyl)-1,5-diaminopentane (198)

To the freshly prepared 2,2-dimethyl-1,3-benzo-[d]-dioxole-4-carbonyl chloride (67) (427 mg, 2 mmole) in dry dichloromethane (25 ml) was added 1,5-diaminopentane (102 mg, 117 µl, 1 mmole) and triethylamine (218 mg, 300 µl, 2.2 mmole). The solution was kept at room temperature under an atmosphere of nitrogen for an overnight period. The dichloromethane solution was washed with 0.1 M aqueous hydrochloric acid solution (20 ml), a 10% aqueous sodium hydrogen carbonate solution (20 ml), and finally with a saturated aqueous sodium sulphate solution (2 x 20 ml). The dichloromethane layer was dried (sodium sulphate), filtered and evaporated. The resulting brown material was further purified by filtration through a pad of silica (eluant ethyl acetate). Evaporation yielded the white, crystalline *title compound* (198) (383 mg, 84%), mp 135-7° (from methanol and water), ν_{max} (CH_2Cl_2), 3420, 1665, 1595, 1535, 1460, 1375, 1215, 1105, 1050, and 835 cm^{-1}; ^1H nmr ($CDCl_3$) δ 6.7-7.55 (8H, m, aryl-H + N-H), 3.48 (4H, q, J 6 Hz, CH_2NH), and 1.3-1.9 (18H, m, $NCH_2-CH_2-CH_2-CH_2-CH_2-N$ + Me); m/e 454 (M^+), 262, 177, 137, 136, and 85. (Found: C, 66.18; H, 6.84; N, 5.88. $C_{25}H_{30}N_2O_6$ requires C, 66.06; H, 6.65; N, 6.16%).

Attempted Preparation of N,N'-Di-(2,3-dihydroxybenzoyl)-1,5-diaminopentane (196). Entry 2

The bisacetonide (198) (173 mg, 0.38 mmole) was heated to 100° in a 4:1 mixture or glacial acetic acid and water (10 ml). TLC of the reaction mixture (silica, ethyl acetate) showed the appearance of two products with the more polar one increasing in intensity as time went on. After 48 h the reaction seemed to be proceeding no further and the heating was stopped. The solution was evaporated and the residue passed through a pad of silica (eluant ethyl acetate) to yield the two components. Recrystallisation (methanol and water) yielded pure crystals of the less polar material (10 mg) m/e 414, 374, and 238, this probably being the monoacetonide (201). Column chromatography (ethyl acetate) gave the more polar material as a single spot compound (72 mg), ^{1}H nmr ($CDCl_3$, d^6-DMSO) δ 8.70 (4H, br s, aryl-OH), 6.4-7.3 (8H, m, aryl-H + N-H), and 4.42 (2H, s); m/e 154. Spectral data indicated that this material was mainly 2,3-dihydroxybenzoic acid (191).

Preparation of 2,3-Diacetoxybenzoic Acid (204)

The material was prepared in 91% yield by treatment of 2,3-dihydroxybenzoic acid (191) with acetic anhydride and a catalytic amount of concentrated sulphuric acid by the method of Bergeron *et. al.*[92]. The white crystalline material had a mp 156-8° (*lit.*[92] 157-8°), ν_{max} (Nujol) 2700, 2570, 1770, 1680, 1603, 1580, 1300, 1200, 1045, 1005, 908, and 745 cm^{-1}; ^{1}H nmr ($CDCl_3$ and trace d^6-DMSO) δ 9.1 (1H, br s, CO_2H), 7.9 (1H, m, aryl-H), 7.3 (2H, m,

aryl-H), and 2.3 (6H, s, CH_3); m/e 238 (M^+), 196, 154, 152, 136, 109, and 43.

Preparation of 2,3-Diacetoxybenzoyl Chloride (205)

This material was prepared by the method of Bergeron *et. al.*[92]. Treatment of 2,3-diacetoxybenzoic acid (204) with phosphorus pentachloride led to the white, crystalline title compound (205) (72%), mp 76-7° (*lit.*[92] 76-7°), ν_{max} (Nujol) 1760, 1600, 1585, 1255, 1235, 1200, 1160, 995, 885, 805, 769, and 720 cm^{-1}; ^1H nmr ($CDCl_3$) δ 7.65 (3H, m, aryl-H), and 2.32 (6H, s, CH_3); m/e 258, 256, (both M^+), 221, 178, 172, 136, 108, and 43.

Preparation of N,N'-Di-(2,3-diacetoxybenzoyl)-1,5-diaminopentane (206)

2,3-Diacetoxybenzoyl chloride (205) (115 mg, 0.45 mmole) was dissolved in dry dichloromethane (10 ml) under nitrogen. To this was added a solution of 1,5-diaminopentane (24 mg, 27 µl, 0.225 mmole) and triethylamine (73 mg, 100 µl, 0.72 mmole) in dichloromethane (10 ml). After stirring overnight the reaction solution was washed successively with 5% sodium hydrogen carbonate solution (5 ml), 2 M hydrochloric acid (5 ml) and saturated aqueous sodium sulphate solution. The organic layer was dried (sodium sulphate), filtered and evaporated to leave the *title compound* (206) as an analytically pure foam (115 mg, 95%), mp 40-6°, ν_{max} (CH_2Cl_2) 3440, 2920, 1770, 1665, 1580, 1520, 1365, and 1195 cm^{-1}; ^1H nmr ($CDCl_3$) δ 7.30 (6H, m, aryl-H), 6.35 (2H, br s, NH), 3.35 (4H, q, J 7 Hz, $HN-CH_2$), 2.25 (12H, s, COMe), and 1.50 (6H, br s, $-CH_2-CH_2-CH_2-CH_2-CH_2-$); m/e 542 ($M^+$), 500, 459,

374, 281, 209, 179, 136, 86, and 84 (Found: C, 59.86; H, 5.80; N, 5.13. $C_{27}H_{30}N_2O_{10}$ requires C, 59.77; H, 5.57; N, 5.16%).

Preparation of N,N'-Di-(2,3-dihydroxybenzoyl)-1,5-diaminopentane (196). Entry 3

The tetraacetate (206) (115 mg, 0.21 mmole) was dissolved in dry methanol (5 ml) and nitrogen was bubbled through the solution for 0.5 h. The solution was kept under nitrogen and a solution of sodium methoxide[from sodium (20 mg, 0.87 mmole)] in methanol (1 ml) was added. After stirring for one hour, tlc (silica, ethyl acetate) showed that one material had formed, less polar than the starting material. 2M Hydrochloric acid (5 ml) was added followed by water until a buff precipitate was formed. The quenched reaction mixture was extracted with ethyl acetate (2 x 20 ml) and the solution was dried (magnesium sulphate). Filtration, followed by evaporation furnished the *title compound* (196) as its monohydrate (70 mg, 85%), mp 166-8° (from methanol and water) (*lit.*[100] 174-6°), ν_{max} (diethyl ether) 2500-3360, 1640, 1600, and 730 cm^{-1}; ^1H nmr (d^6-acetone) δ 7.90 (2H, br s, 3-aryl-OH), 6.3-7.1 (8H, m, aryl-H and N-H), 3.2 (4H, br s, N-CH_2-), and 1.4 (6H, br s, $-CH_2-CH_2-CH_2-CH_2-CH_2$); m/e 374 ($M^+$) 238 and 137 [M(374)= 374.1469. $C_{19}H_{22}N_2O_6$ requires 374.1478] (Found: C, 58.20; H, 6.12; N, 6.91. $C_{19}H_{22}O_6N_2.H_2O$ requires C, 58.15 ; H, 6.16; N, 7.13%).

Preparation of N,N′-Di-(2,3-diacetoxybenzoyl)-2,20-di-aza[3.3.3.3]-paracyclophane (209)

To a solution of 2,3-diacetoxybenzoyl chloride (205) (173 mg, 0.67 mmole) in dichloromethane (10 ml) stirred under nitrogen was added a solution of the di-azaparacyclophane (178) (160 mg, 0.33 mmole) and triethylamine (108.9 mg, 150 µl, 1.08 mmole) in dichloromethane (5 ml). The mixture was stirred at room temperature overnight whereupon infrared analysis showed reaction to be complete. The mixture was washed successively with 5% sodium hydrogen carbonate solution (10 ml), 2M hydrochloric acid (10 ml) and finally with saturated sodium sulphate solution (2 x 10 ml). The organic layer was dried (sodium sulphate) and evaporated to yield the *title compound* (209), as its monohydrate (315 mg, 99%), mp 208-12° (from methanol), ν_{max} (CH_2Cl_2) 2930, 2860, 1780, 1638, 1510, 1420, 1370, 1190, 1160, and 1005 cm^{-1}; ^1H nmr (250 MHz) ($CDCl_3$) δ 6.6-7.4 (22H, m, aryl-H), 4.63 (4H, br s, aryl-CH_2-N), 4.50 (4H, br s, aryl-CH_2-N), 3.80 (2H, s, H_2O), 2.45 (8H, t, J 7.5 Hz, aryl-CH_2-C), 2.29 (12H, s, $COCH_3$), and 1.85 (4H, p, J 7.5 Hz, -CH_2-CH_2-CH_2-); compound too involatile for mass spectrum (Found: C, 71.91; H, 5.92; N, 2.68. $C_{56}H_{54}N_2O_{10}.H_2O$ requires C, 72.08; H, 6.04; N, 3.00%).

Preparation of N,N′-Di-(2,3-dihydroxybenzoyl)-2,20-di-aza-[3.3.3.3]-paracyclophane (210)

The paracyclophane tetra-acetate (209) (45 mg, 0.05 mmole) was suspended in dry methanol (10 ml) and nitrogen was passed through the solution for 0.5 h. Then a solution of sodium methoxide [from sodium

(5 mg, 0.21 mmole) in methanol (300 µl) was added, a nitrogen atmosphere being maintained throughout the reaction. The light green solution was stirred for 1 h, until tlc (silica, ethyl acetate) showed no more starting material to be present. 2M Hydrochloric acid (2 ml) was added, followed by enough water to form a white precipitate, The aqueous phase was extracted with ethyl acetate (2 x 20 ml) which was then dried (sodium sulphate), filtered and evaporated to give a compound (26 mg) which could not be fully characterised, but spectral data indicated that this was mainly the title compound (210) ν_{max} (Nujol), 3380, 1640, 1010, 920, 825, and 730 cm^{-1}; ^{1}H nmr (d^{6}-DMSO) δ 6.8-7.3 (22H, m, aryl-H), 4.70 (8H, br s, aryl-CH_2-N), 2.50 (8H, br s, aryl-CH_2-C), and 1.80 (4H, br s, -CH_2-CH_2-CH_2-); m/e 610 (M^{+}-2,3-dihydroxybenzoyl), 472, and 110.

Preparation of N,N'-Di-(2,3-dihydroxybenzyl)-2,20-di-aza-[3.3.3]-paracyclophane (211)

The paracyclophane tetra-acetate (209) (218 mg, 0.23 mmole) was suspended in THF (15 ml) and diborane in THF (1.25 M, 2.2 ml, 72 hydride equivalents - an excess) was added. The resulting mixture was stirred under nitrogen at the reflux for 15 h and on cooling, methanol (10 ml) was added. The solvent was evaporated to leave a white solid which was again taken up in methanol (10 ml) and heated at a gentle reflux for 24 h. Evaporation left a violet coloured salt (250 mg) which after column chromatography (eluant dichloromethane: ethyl acetate, 1:0→0:1) yielded the *title compound* (211), a white, analytically pure material (95 mg, 57%), mp 195-202° dec. (from column), ν_{max} (CH_2Cl_2) 3520, 2910, 2820, 1604, 1505, 1475, 1370

1180, 1070, 955, 905, and 840 cm^{-1}; ^1H nmr ($CDCl_3$) δ 6.60-7.25 (26H, m, aryl-H + aryl-OH), 3.85 (4H, s, N-CH_2-aryl-OH), 3.45 (8H, s, aryl-CH_2-N), 2.48 (8H, t, J 8 Hz, aryl-CH_2C), and 1.90 (4H, br s, -CH_2-CH_2-CH_2-); m/e 595 (M^+-2,3-dihydroxybenzoyl), 546, 472, 457, 352, 252, 222, 132, 131, 121, 119, 118, 117, 110, and 105 (Found: C, 80.08; H, 7.18; N, 3.85. $C_{48}H_{50}N_2O_4$ requires C, 80.19; H, 7.01, n, 3.90%).

Preparation of Di-1,3-[4-(2,3-diacetoxybenzamido)-methylenephenyl]-propane (208)

To a stirred solution of 2,3-diacetoxybenzoyl chloride (205) (403 mg, 1.57 mmole) in dichloromethane (10 ml) under an atmosphere of nitrogen was added a solution of di-1,3-(4-aminomethylenephenyl)-propane (189) (200 mg, 0.79 mmole) and triethylamine (218 mg, 300 µl, 2.15 mmole) in dichloromethane (15 ml). After stirring overnight the solution was washed with 5% sodium hydrogen carbonate solution (5 ml), 2M hydrochloric acid (5 ml) and saturated sodium sulphate (2 x 5 ml). Drying (sodium sulphate), filtration and evaporation led to the *title compound* (208) (479 mg, 87%), mp 169-71° (from methanol), ν_{max} (CH_2Cl_2) 3430, 1777, 1668, 1512, 1365, and 1195 cm^{-1}; ^1H nmr ($CDCl_3$) δ 7.10-7.65 (14H, m, aryl-H), 6.50 (2H, br s, N-H), 4.52 (4H, d, J 6 Hz, aryl-CH_2-N), 2.63 (4H, t, J 8 Hz, aryl-CH_2-C), 2.23 (6H, s, 2-aryl-OCOCH_3), and 2.05 (8H, m, 3-aryl-OCOCH_3 + -CH_2-CH_2-CH_2-); m/e 498, 473, (M^+-2,3-diacetoxybenzoyl), 432, 373, 295, 154, 136, and 110 (Found: C, 67.48; H, 5.47; N, 4.03. $C_{39}H_{38}N_2O_{10}$ requires C, 67.43; H, 5.51; N, 4.03%).

Preparation of Di-1,3-[4-(2,3-dihydroxybenzamido)-methylenephenyl]-propane (207)

The bisamido tetra-acetate (208) (150 mg, 0.22 mmole) was dissolved in methanol (5 ml) and nitrogen was bubbled through the solution for 0.5 h. Then a solution of sodium methoxide[from sodium (22 mg, 0.96 mmole)] in methanol (1 ml) was added. The light green solution was stirred for 2 h under nitrogen until tlc (silica, ethyl acetate) showed that no starting material remained. Quenching the reaction with 2M hydrochloric acid (15 ml) led to the formation of a buff coloured precipitate which was extracted with ethyl acetate (2 x 15 ml). Drying (sodium sulphate) followed by filtration and evaporation gave a gum which was purified by column chromatography (eluant dichloromethane:ethyl acetate 1:0→0:1) to furnish the *title compound* (207) as its monohydrate (25 mg, 23%), mp 64-6° (from chromatography), ν_{max} (Nujol) 2500-3400, 1640, 1590, 1535, 1260, 1170, and 725 cm^{-1}; ^1H nmr (d^6-acetone) δ 8.7 (2H, br s, N-H), 6.65-7.50 (14H, m, aryl-H), 4.64 (4H, d, J 7 Hz, aryl-CH_2-N), 2.65 (4H, 6, J 8 Hz, aryl-CH_2-C), and 2.05 (2H, m, -CH_2-CH_2-CH_2); m/e 526 (M^+), 432, 374, 296, 284, 238, 135, and 108 (Found: C, 68.45; H, 5.71; N, 5.05. $C_{31}H_{30}N_2O_6.H_2O$ requires C, 68.37; H, 5.92; N, 5.14%).

Preparation of 3,4-Dimethoxybenzhydryl Alcohol (213)

Magnesium turnings (0.73 g, 30.4 mmole) were suspended in dry diethyl ether (30 ml) and a few drops of a solution of bromobenzene (4.71 g, 3.16 ml, 30 mmole) in diethyl ether (25 ml) was added. A few crystals of iodine were also introduced until the reaction started. The

remainder of the bromobenzene solution was added dropwise and the reaction mixture was vigorously stirred under nitrogen. After the phenyl magnesium bromide had formed (approx. 1 h), a solution of 3,4-dimethoxybenzaldehyde (5.0 g, 30 mmole) in diethyl ether (50 ml) was added and the reaction mixture was heated at the reflux. After 4 h, when the reaction appeared to be proceeding no further, the mixture was cooled and quenched with 2M aqueous hydrochloric acid (50 ml), and extracted with diethyl ether (2 x 50 ml) to leave a mixture of product and starting aldehyde (5.31 g). Column chromatography (dichloromethane) afforded the pure title compound (213) (2.74 g, 38%), mp 96-8° (from dichloromethane and hexane) (*lit.*[149] 99°), ν_{max} (Nujol) 3470, 1590, 1260, 1230, 1130, 1015, 925, 730, and 705 cm^{-1}; ^1H nmr ($CDCl_3$) δ 7.22 (5H, s, aryl-H), 6.75 (3H, m, aryl-H), 5.65 (1H, s, aryl-CH-aryl), 3.80 (3H, s, aryl-OCH_3), 3.78 (3H, s, aryl-OCH_3), and 2.50 (1H, br s, O-H); m/e 244 (M^+), 227, 213, 167, 153, 139, 105, and 77 (Found: C, 73.56; H, 6.59. $C_{15}H_{16}O_3$ requires C, 73.75; H, 6.60%).

Preparation of (3,4-Dimethoxyphenyl)phenylmethane (214)

3,4-Dimethoxybenzhydryl alcohol (213) (1.63 g, 67 mmole) was dissolved in THF (40 ml) and trifluoroacetic acid (2 ml) was added followed by 10% palladium on charcoal catalyst. The mixture was subjected to hydrogenation, the reaction being followed by tlc. After completion of reaction the catalyst was removed by filtration and the volatile material was removed by evaporation. The oily residue was dissolved in dichloromethane (25 ml) and washed with 10% sodium hydrogen carbonate solution (20 ml), dried (sodium sulphate),

filtered, evaporated and distilled to produce the title compound (214) (788 mg, 53%) bp 158° at 0.8 mm Hg (*lit.*[149] 130° at 0.1 mm Hg), ν_{max} (thin film) 3040, 3005, 2980, 2920, 2815, 1590, 1580, 1500, 1450, 1405, 1250, 1130, 1040, 785, 760, and 705 cm^{-1}; ^1H nmr ($CDCl_3$) δ 7.18 (5H, s, aryl-H), 6.68 (3H, m, aryl-H), 3.95 (2H, s, aryl-CH_2), 3.82 (3H, s, aryl-OCH_3), and 3.80 (3H, s, aryl-OCH_3); m/e 228 (M^+), 213, 197, 151, and 91.

Attempted Deprotection of (3,4-Dimethoxyphenyl)phenylmethane (214). Entry 1

A solution of chlorotrimethylsilane (95 mg, 111 µl, 0.87 mmole) and sodium iodide (131 mg, 0.87 mmole) in dry acetonitrile (5 ml) was stirred for one hour under nitrogen at room temperature. Then a solution of 3,4-dimethoxydiphenylmethane (214) (100 mg, 0.435 mmole) in acetonitrile (2 ml) was added to the solution. The reaction vessel was maintained in the dark throughout the operation. No reaction occurred to give deprotection after 48 h at room temperature, and even when allowed to reflux for several days, no reaction could be noted.

Attempted Deprotection of (3,4-Dimethoxyphenyl)phenylmethane (214). Entry 2

The dimethoxy compound (214) (100 mg, 0.435 mmole) was dissolved in acetic acid (2 ml) and a solution of hydrogen bromide in acetic acid (157 µl, 0.93 mmole) was added. The resultant solution was stirred at room temperature under a nitrogen atmosphere for 40 h. TLC indicated that some deprotection had occurred and so more of the

hydrogen bromide solution (0.2 ml, 1.18 mmole) was added, but no further reaction could be observed.

Attempted Deprotection of (3,4-Dimethoxyphenyl)phenylmethane (214). Entry 3

The dimethoxy compound (214) (50 mg, 0.22 mmole) was dissolved in acetic acid (10 ml) under an atmosphere of nitrogen. A solution of hydrogen iodide in water (200 µl, 0.88 mmole) was added. The solution was heated to 100° for 3 h whereupon tlc indicated that no starting material was left. On cooling, water (20 ml) was added and the aqueous phase extracted with dichloromethane (2 x 20 ml). The organic layer was washed with sodium thiosulphate solution (1 x 10 ml), dried filtered and evaporated to yield a polymeric tar.

Hydroxylation Studies

General Points

All phenol concentrations were determined by high performance liquid chromatography (HPLC). The machine used was a Perkin Elmer series 3B liquid chromatograph, fitted with a reverse phase column (Phasesep 20 µ silica). The runs were conducted using a solvent programme of 1:3 methanol:5% aqueous formic acid for 3 min followed by 9:1 methanol:5% aqueous formic acid for 5 min at a solution flow rate of 2 ml min^{-1}. An LC 75 spectrophotometric detector was used at λ 272 nm, and phenol had a retention time of 250-280 seconds. Concentrations were determined by comparison of peak heights with peaks obtained from standard solutions of phenol. The hydrogen peroxide

used was a BDH reagent and was found to be a 7.69M solution. All reactions were performed in glass vials at 26.5° unless otherwise stated.

Hydroxylation of Benzene using 4-t-Butylcatechol (215) in a Single Phase Reaction System

A solution of 4-t-butylcatechol (215) (1.66 mg, 10 μmole) in benzene (1.0 ml), methanol (0.9 ml) and 0.1M ferric chloride solution in 5M acetate buffer (pH 4.2) (0.1 ml) was shaken vigorously. To this was added a 7.69M solution of hydrogen peroxide (13 μl, 100 μmole). Periodically aliquots were removed and assayed both for hydrogen peroxide content (a potassium permanganate titration) and phenol content. When all the peroxide had been consumed only 0.74 μmoles of phenol had been formed. The relevant blank experiments using a.ferric ion and hydrogen peroxide, b. 4-t-butylcatechol and hydrogen peroxide, c. hydrogen peroxide alone, d. 4-t-butylcatechol and ferric ion, all failed to produce any significant amounts of phenol.

Experiment to Determine Whether 4-t-Butylcatechol (215) is Destroyed in the Single Phase Hydroxylation of Benzene

Using identical conditions to above, hydrogen peroxide (7.69M, 13 μl, 100 μmole) was added and the sample shaken for 2 h. The flask was analysed for phenol, and a second aliquot of hydrogen peroxide (13 μl, 100 μmole) was added. After a further period of 2 h, analysis was followed by a third injection.

TABLE 5

Injection No	Amount Phenol in Flask After Each Two Hour Period/μmole
1	0.82
2	1.90
3	2.78

Experiment for Two Phase Hydroxylation of Benzene Using Ten Equivalents of Hydrogen Peroxide

To 4-t-butylcatechol (215) (1.66 mg, 10 μmole) was added 0.1M Ferric chloride solution in 5M acetate buffer (pH 4.2) (0.1 ml) followed by water (0.9 ml). Benzene (1.0 ml) was introduced. After shaking for a few minutes 7.69M hydrogen peroxide (13 μl, 100 μmole) was added. The amount of phenol formed was assayed periodically and after 75 min a total of 9.5 μmoles had been formed, a figure that did not change significantly over the next 0.5 h. A second injection of hydrogen peroxide (13 μl, 100 μmole) led to the formation of more phenol, boosting the total amount converted to 13 μmoles, showing that the catalyst could survive more than one cycle.

Two Phase Hydroxylation of Benzene Using N-Methyl-2,3-dihydroxybenzamide (195) as Catalyst

The reaction conditions above were used but with N-methyl-2,3-dihydroxybenzamide monohydrate (195) (1.85 mg, 10 μmole) as catalyst. After the addition of hydrogen peroxide (13 μl, 100 μmole), phenol (12.5 μmole) was formed in 50 min, before the reaction stopped. After 1 h another aliquot of peroxide (100 μmole) was added, and the phenol content analysed. This process was taken through several cycles. The results are shown below.

TABLE 6

Injection No	Amount Phenol in Flask After Each One Hour Period/μmole
1	12.5
2	19.9
3	22.7
4	27.1
5	30.2
6	30.5

Experiments to Determine the Amount of Phenol Formed Using Various Catechols, Ferric Ion and 100 Equivalents of Hydrogen Peroxide

General Method

To the catechol X (10 μmole) was added 0.1M ferric chloride solution in 5M acetate buffer (pH 4.15) (0.1 ml). Benzene (1 ml) and water (0.77 ml) were added. Where necessary the reaction vessel was placed in an ultrasonic bath to aid complex formation. When this was complete, hydrogen peroxide (130 μl, 1 mmole) was added, and phenol formation was monitored by HPLC, 10 μl aliquots being removed from the benzene layer every 12 to 13 minutes. The results obtained are shown in table 1 in the discussion section. All reactions were allowed to equilibrate with vigorous shaking for 0.5 h, before peroxide was added. Zero readings for all the reactions indicated no production of phenol without hydrogen peroxide being present. Blank reactions with combinations of ferric ion, benzene and hydrogen peroxide and a variety of the catalysts indicated a very small formation of phenol but an insignificant amount with respect to the catalysed reaction. In all but one case, addition of more peroxide produced no further significant amounts of phenol.

To Examine the Effect of pH on the Hydroxylation of Benzene Using 100 Equivalents of Hydrogen Peroxide and 4-t-Butylcatechol (215)

Using the general method indicated above with 4-t-butylcatechol (1.66 mg, 10 μmole) as catalyst and a variety of buffers containing 0.1M ferric chloride, reactions were performed at a variety of pH conditions. The pH was measured before and after reaction. The

results are shown in table 2 in the discussion section.

To Examine the Effect of Repeated Additions of Hydrogen Peroxide at Low pH Using 4-t-Butylcatechol (215) as Catalyst

To 4-t-butylcatechol(215) (1.66 mg, 10 µmole) was added a solution of 0.1M ferric chloride in 1M formate buffer (pH 2.6) (0.1 ml), and water (0.9 ml) and benzene (1 ml) were added. The solution was shaken and hydrogen peroxide (6 x 13 µl) was added at hourly intervals. The results are noted below.

TABLE 7

Injection No	Amount Phenol Present at End of Each One Hour Period/µmole
1	6
2	32
3	44
4	64
5	63
6	63

To Examine the Effect of Repeated Additions of Hydrogen Peroxide at Low pH Using N-Methyl-2,3-dihydroxybenzamide (195) as Catalyst

Using the same method as above, but with N-methyl-2,3-dihydroxybenzamide monohydrate (195) the following results were obtained as shown in table 8.

TABLE 8

Injection No	Amount Phenol Present at end of Each One Hour Period/μmole
1	9
2	26
3	40
4	49
5	61
6	66

Experiment to Determine the Amount of Phenol Formed at pH 2.6 for a Range of Catechols

General Method

To the catechol X (10 μmole) was added 0.1 M ferric chloride solution in 1M formate buffer (pH 2.6) (0.1 ml). Benzene (1 ml) and water (0.77 ml) were added. Where necessary the reaction vial was placed in an ultrasonic bath to aid complex formation. The mixture was then shaken vigorously to ensure equilibration for at least 0.5 h. When complex formation was complete, hydrogen peroxide (130 μl, 1 mmole) was added and the phenol formation was followed by HPLC, 10 μl aliquots being removed every 12 to 13 minutes. Zero readings and blank reactions indicated that no significant amounts of phenol were formed without the presence of all the requitsite components. The results are presented in table 3 in the discussion section.

To Examine the Effect of Ferric Ion Concentration on the Hydroxylation of Benzene Using a Dicatechol

To N,N′-di-(2,3-dihydroxybenzoyl)-1,5-diaminopentane monohydrate (196) (3.92 mg, 10 µmole) was added 0.1M ferric chloride solution in 1M formate buffer (pH 2.6) (0.2 ml, 20 µmole ferric ion), followed by benzene (1 ml) and water (670 µl). This was sonicated unitl an insoluble indigo complex was formed. Then hydrogen peroxide (130 µl, 1 mmole) was added. Phenol (79 µmole) was formed in one hour after which reaction stopped. A second injection of peroxide (130 µl, 1mmole) led to the formation of some extra phenol, 96 µmoles being present at the end of the reaction.

To Examine the Effect of the Exclusion of Water from the Hydroxylation System

To 4-t-butylcatechol (215) (1.66 mg, 10 µmole) was added 0.1M ferric chloride in 5M acetate buffer (pH 4.15) (0.1 ml) followed by benzene (1 ml) and water (0.9 ml). The mixture was shaken and a deep blue coloured complex was formed and stayed in the benzene phase. As much of the aqueous phase as possible was removed and hydrogen peroxide (13 µl, 100 µmole)was added. After 6 h the colour of the solution had faded to a light yellow and phenol (1.3 µ mole) had been formed. A permanganate titration for residual peroxide indicated that some 43 µmoles of this still remained in solution.

To Determine the Relative Rates of Oxygen Evolution Under Various Reaction Conditions

(a) 0.1M ferric chloride solution in 5M acetate buffer (pH 4.2) (0.1 ml) was diluted with water (1.9 ml). Nitrogen gas was bubbled through the solution for several minutes and hydrogen peroxide (13 µl, 100 µmole) was added. Oxygen evolution was qualitatively measured using a Clark type oxygen measuring electrode (Rank Brothers, Cambridge).

(b) Water (2 ml) was degassed with nitrogen and hydrogen peroxide (13 µl, 100 µmole) was added. The evolution of oxygen was again determined.

(c) Using the conditions in part (a) with N-methyl-2,3-dihydroxybenzamide (1.85mg, 10 µmole) added, the oxygen evolution was measured.

Results: Parts (a) and (b) showed a steady evolution of oxygen which eventually levelled off. Part (c) showed an immediate very rapid evolution of oxygen after the hydrogen peroxide had been added, followed by a slight decrease and a levelling off as a bubble formed and was evolved.

Study of the Effect of a Ruthenium-Catechol Complex Under the Hydroxylation Conditions

To 4-t-butylcatechol (215) (1.66 mg, 10 µmole) was added a 0.1M solution of ruthenium trichloride in 1M formate buffer (pH 2.6) (0.1 ml), water (0.77 ml) and benzene (1 ml). A cherry red aqueous

layer was formed below a yellow benzene layer. Hydrogen peroxide (130 µl, 1 mmole) was added whereupon a vigorous and quite visible evolution of oxygen began. No phenol was formed.

Experiment to See Whether Ferrous Ion, 2-Aminobenzenethiol and Air Can Act as a Hydroxylation Catalyst for Benzene

To 2-aminobenzenethiol hydrochloride (16.2 mg, 100 µmole), was added a 10^{-2}M solution of ferrous sulphate heptahydrate (0.1 ml, 1 µmole of ferrous ion). Then a 1M solution of sodium hydroxide (1 ml) was added followed by acetone (10 ml) and benzene (1 ml). The solution was shaken for 90 min with periodic aliquots being analysed. No phenol was noted. Some hydrochloric acid was added to lower the pH to 5 but this had no effect on the reaction.

To Examine Whether Ferrous Ion and 2-Mercaptobenzoic Acid Act as Hydroxylation Catalysts for Benzene

To 2-mercaptobenzoic acid (15.4 mg, 100 µmole) was added a 10^{-2}M aqueous solution of ferrous sulphate heptahydrate (0.1 ml, 1 µmole) followed by 80% aqueous acetone (10 ml). The pH of the solution was adjusted to 4 and benzene (1 ml) was added. No trace of phenol could be observed after several hours shaking.

Preparation of 2,4-Dihydroxycarbonyl-4′-methylbenzophenone (223)

To 4-hydroxycarbonylphthalic anhydride (222) (5.0 g, 26 mmole) in toluene (30 ml) under an atmosphere of dry nitrogen was added aluminium chloride (12 g, 92 mmole). The suspension was vigorously

stirred at the reflux for 3 h, becoming a red coloured paste. The reaction was allowed to cool and crushed ice (50 g) was added slowly followed by concentrated hydrochloric acid (10 ml). This procedure led to the formation of a pale brown coloured solid in a clear solution. 10% aqueous sodium carbonate was cautiously added until the solution became alkaline. This was heated to boiling and activated charcoal was added. The solution was filtered through celite and allowed to cool. Cautious acidification with concentrated hydrochloric acid led to the precipitation of a white oil which solidified on standing. Isolated by filtration, this material was dried *in vacuo* and it turned out to be the *title compound* (223) (5.21 g, 70%), mp 235-8° (from acetone and hexane), ν_{max} (Nujol) 2400-3300, 1690, 1662, 1603, and 1290 cm^{-1}; ^{1}H nmr (d^{6}-acetone) δ 7.2-8.8 (9H, m, aryl-H + $CO_2\underline{H}$), and 2.35 (3H, s, aryl-$C\underline{H}_3$); ^{13}C nmr (d^{6}-acetone) δ21.60, 128.86, 129.29, 129.44, 130.02, 130.51, 130.86, 131.31, 132.12, 132.62, 134.14, 134.86, 135.72, 144.69, 166.42, and 166.73; m/e 284 (M^{+}), 219, 196, 194, 119, 105, and 91 (Found : C, 67.39; H, 4.27. $C_{16}H_{12}O_5$ requires C, 67.60; H, 4.25%).

Preparation of 2-Methylanthraquinone-7-carboxylic acid (224)

2,4-Dihydroxycarbonyl-4′-methylbenzophenone (223) (0.5 g, 1.76 mmole) was dissolved in concentrated sulphuric acid (5 ml) and an orange solution formed. This was heated to 100° for 2 h during which time it went black. On cooling water (10 ml) was added and the viscous, black suspension was extracted with ethyl acetate (2 x 25 ml). The organic layer was dried (sodium sulphate), filtered and evaporated to afford a mixture of the title compound

(224) and anthraquinone-2,7-dicarboxylic acid (225) (302 mg) ν_{max} (Nujol) 2300-3400, 1695, 1678, 1598, and 720 cm^{-1}; ^1H nmr (trifluoroacetic acid) δ 7.5-8.7 (6H, m, aryl-H), and 2.52 (2.5H, s, aryl-CH_3); m/e 266 (M^+ for title compound), 251, 249, 238, 221, and 165. The mixture could not be separated and was used as isolated for the following step.

Attempted Preparation of Anthraquinone-2,7-dicarboxylic acid (225) Entry 1

Crude 2-methylanthraquinone-7-carboxylic acid (224) (250 mg, 0.94 mmole) was added to water (5 ml). The mixture was heated to reflux and potassium permanganate (500 mg, 3.16 mmole) was added at intervals over 12 h. The mixture was allowed to reflux over a further 10 h and cooled. Manganese dioxide was filtered off and the aqueous solution was acidified. The white precipitate formed was extracted with ethyl acetate (2 x 10 ml), dried (sodium sulphate), filtered and evaporated to yield a brown powder (179 mg) which contained an inseparable mixture of the di- and mono- acids.

Attempted Preparation of Anthraquinone-2,7-dicarboxylic acid (225) Entry 2

2-Methylanthraquinone-7-carboxylic acid (224) (219 mg, 0.82 mmole) was suspended in water (2 ml) and sodium dichromate dihydrate (680 mg, 2.47 mmole) was added. Concentrated sulphuric acid (0.94 ml) was added and the mixture heated to 120° for 15 h. Water (50 ml) was added to the cooled green solution and the product was extracted with ethyl acetate (4 x 30 ml). The organic layer however again consisted of a

mixture of the mono- and di-acids.

Preparation of cis and trans Diphenylphosphino-2-ethoxyethylene (229)

Sodium (378 mg, 16.4 mmoles) was placed in THF (20 ml) and diphenylphosphine (3.20 g, 3.00 ml, 17.2 mmole) was added slowly. A deep orange-red solution of the anion ensued. When all the sodium had dissolved (approximately 18 h) the solution was cooled to -5° and 1,1-diethoxy-2-bromoethane (228) (3.20 g, 2.44 ml, 16.4 mmole) was added dropwise. The colour of the solution dissipated gradually. The mixture was left at -5° for 15 min and allowed to warm. Water (40 ml) was added and the organic phase thus formed was separated, concentrated and distilled to give the *title compounds* (229) (2.41 g, 57%), bp 150° at 0.1 mm Hg, ν_{max} (thin film), 3045, 2970, 2920, 2890, 1590, 1470, 1430, 1330, 1300, 1160, 730, and 690 cm^{-1}; ^1H nmr ($CDCl_3$) δ 7.30 (10H, s, aryl-H), 6.81 (1H, m, P-CH), 5.34 (0.5H, dd, J_{HH} 14 Hz, J_{HP} 4 Hz, P-C^{t}=CHOEt), 4.91 (0.5H, dd, J_{HH} 7 Hz, J_{HP} 3 Hz, P-C^{c}=CHOEt), 3.90 (2H, q, J 8 Hz, OCH_2-), and 1.32 (3H, overlapping t, J 8 Hz, OCH_2-CH_3); m/e 256 (M^+), 241, 200, 186, 108, and 107 (Found: C, 74.84; H, 6.80. $C_{16}H_{17}PO$ requires C, 74.99; H, 6.69%).

Preparation of P,P′-Tetraphenyl-2,5-dihydroxy-1,4-diphosphonium Dichloride (231)

To the mixture of the substituted ethyl vinyl ethers (229) prepared above (1.5 g, 5.86 mmole) was added concentrated hydrochloric acid (2.4 ml). The mixture was allowed to stand for 2 days at room temperature in which time white crystals appeared. These were filtered

off and washed with water, acetone, and finally ether. Drying *in vacuo* gave the title compound (231) (1.24 g, 80%), mp 144-7° (*lit.*[140] 145-7°).

Preparation of Diphenylphosphinoacetaldehyde (226)

The dichloride salt (231) prepared above (100 mg) was dissolved in water (10 ml) and this was treated with sodium hydrogen carbonate solution until a pH of 8 was obtained. The white precipitate obtained was extracted with chloroform (3 x 10 ml), which was dried (sodium sulphate), filtered and evaporated to give the title compound (226) as a colourless gum (74 mg, 86%), ν_{max} (CH_2Cl_2) 2920, 2840, 2730, 1718, 1592, 1380, 1185, 1115, 995, and 830 cm^{-1}; ^1H nmr ($CDCl_3$) δ 9.8 (1H, t, J 3 Hz, CHO), 7.6 (10H, m, aryl-H), and 3.7 (2H dd, J_{HH} 3 Hz, J_{PH} 15 Hz, CH_2CHO); m/e 228, 215, 200, 85, 83, and 47.

Attempted Preparation of Ethyl 4-Diphenylphosphinoyl-2-butenoate (233)

Diphenylphosphinoacetaldehyde (226) (87 mg, 0.38 mmole) and carbethoxymethylenetriphenylphosphorane (232) (133 mg, 0.38 mmole) were suspended in THF (5 ml). The solution was heated at the reflux for 15 h in which time the solution became clear. TLC (silica, 10% methanol and 90% chloroform) indicated a complex reaction mixture but clearly triphenylphosphine oxide had been formed. The reaction was cooled and evaporated. The yellow gum was dissolved in dichloromethane (10 ml) and washed with 3% hydrogen peroxide solution (10 ml). The organic layer was dried (sodium sulphate), filtered and evaporated to yield single spot material by tlc (154 mg) running at the same place

as triphenylphosphine oxide. This turned out to be an inseparable mixture of triphenylphosphine oxide and the desired compound (233). Chromatography on both silica and alumina led to no resolution at all. Spectral data indicated the presence of the title compound (233), ν_{max} (CH_2Cl_2) 2920, 1718, 1650, 1590, 1305, 1190, 1115, and 900 cm^{-1}; ^1H nmr ($CDCl_3$) δ 7.45 (19H, m, aryl-H and PPh_3O aryl-H), 6.70 (1H, m, CH_2-CH=CH), 5.80 (1H, dd, J_{HH} 16 Hz, J_{PH} 4 Hz, PCH_2-CH=CH), 4.05 (2H, q, J 7 Hz, OCH_2CH_3), 3.22 (2H, dd, J_{HH} 8 Hz, J_{PH} 16 Hz, P-CH_2-CH), and 1.20 (3H, t, J 7 Hz, $-OCH_2CH_3$); m/e 314, 278, 277, 201, and 77.

Attempted Preparation of Cholest-5-en-3β-yloxycarbonyltriphenylphosphorane (234). Entry 1

Cholesteryl chloroacetate (236) (50 mg, 0.11 mmole) and triphenylphosphine (27 mg, 0.11 mmole) were dissolved in DME (0.5 ml). The mixture was heated at the reflux under nitrogen for 6 days, after which time all triphenylphosphine had been consumed. Unfortunately a complex mixture of products was noted and the reaction discontinued.

Preparation of Cholesteryl Bromoacetate (237)

Bromoacetyl bromide (3.47 g, 1.50 ml, 17.23 mmole) was dissolved in toluene (50 ml) under nitrogen and the resultant solution was cooled to 0°. A solution of cholesterol (235) (6.0 g, 15.5 mmole) and pyridine (1.84 g, 1.88 ml, 23.2 mmole) in toluene (30 ml) was added dropwise to the stirred acid bromide. After addition was complete, the solution was stirred for 2 h at room temperature. The solution

was washed with 10% sodium hydrogen carbonate (100 ml) and saturated sodium sulphate solution (2 x 100 ml). After drying (sodium sulphate), the toluene was filtered and evaporated. The residue subjected to column chromatography (eluant 50% petroleum ether and 50% dichloromethane) gave the white crystalline title compound (237) (6.20 g, 79%), mp 156-7° (from chloroform and petroleum ether) (*lit.*[150] 156-156.5°), ν_{max} (CH_2Cl_2), 2900, 1730, 1260, 1160, 990, and 680 cm^{-1}; ^1H nmr ($CDCl_3$) δ 5.35 (1H, br s, C<u>H</u>=C), 4.65 (1H, br s, <u>H</u>C-OR), 3.75 (2H, s, C<u>H</u>$_2$Br), and 0.65-2.40 (43H, m, saturated cholesterol-<u>H</u>); m/e 506 and 508 (M^+), 369, 336, 262, 248, 144, and 81.

<u>Preparation of Cholest-5-en-3β-yloxycarbonyltriphenylphosphorane (234) Entry 2</u>

Cholesteryl bromoacetate (237) (4.23 g, 8.34 mmole) was dissolved in toluene (100 ml). Triphenylphosphine (2.19 g, 8.34 mmole) was added. The solution was stirred and heated to the reflux, and briefly a clear yellow solution was noted. On continued heating, however, a white precipitate appeared. After a period of fifteen hours the reaction seemed complete by tlc (silica, 50% petroluem ether and 50% dichloromethane) and the solvent was removed at reduced pressure. The residue was dissolved in dichloromethane (150 ml) and 1M sodium hydroxide solution (150 ml) was added. After vigorous shaking the two layers were separated and the organic layer dried (sodium sulphate) filtered and evaporated to leave the title compound (234) as a solid foam (5.71 g, 99%), ν_{max} (CH_2Cl_2) 2900, 1612, 1370, 1330, 1103, 1046, 950, and 880 cm^{-1}. The compound contained small amounts of impurity

but these could not be removed. The material was used crude in subsequent transformations with satisfactory results.

Preparation of (E)-Cholesteryl Cinnamate (238)

The ylide (234) (780 mg, 1.13 mmole was suspended in THF (50 ml) and benzaldehyde (120 mg, 115 µl, 1.13 mmole) was added. The mixture was heated to reflux under nitrogen for 15 h, and the initially clear solution becoming cloudy as heating was continued. TLC analysis after this time also indicated the presence of a new product that was uv active and less polar than benzaldehyde. The reaction was cooled and evaporated and the residue subjected to column chromatography (eluant 30% dichloromethane and 70% petroleum ether) to yield the title compound (238) as a white crystalline solid (347 mg, 60%), mp 161-2° (from dichloromethane and petroleum ether) (*lit.*[151] 161-2°), $[\alpha]_D^{23.5}$ + 43° (C 0.03 in benzene) (*lit.*[151] $[\alpha]_D^{25}$ + 44° in benzene), ν_{max} (CH_2Cl_2) 2938, 1700, 1637, 1493, 1170, and 1000 cm^{-1}; ^1H nmr ($CDCl_3$) δ 7.18-7.82 (6H, m, aryl-H + Ph-CH=C), 6.34 (1H, d, J 16 Hz, C=CHCO$_2$R), 5.35 (1H, br s, CH=CR$_2$), 4.65 (1H, br s, HC-O), and 0.65-2.45 (43H, m, saturated cholesterol-H); m/e 516 (M^+), 368, 354, 260, 247, 213, and 131.

Preparation of (E),(E) Cholesteryl 5-Phenyl-2,4-pentadienoate (240)

Entry 1

The ylide (234) (100 mg, 0.145 mmole) was dissolved in THF (5 ml) and (E)cinnamaldehyde (19 mg, 18.3 µl, 0.145 mmole) was added. The solution was heated at the reflux under an atmosphere of nitrogen

for 25 h when tlc indicated the reaction was proceeding no further. All volatile material was removed at reduced pressure and the residue subjected to column chromatography (eluant 30% dichloromethane and 70% petroleum ether) to yield the title compound (240) (26 mg, 33%), mp 147-9° (from dichloromethane and petroleum ether) (*lit.*[151] 149°), $[\alpha]_D^{23.5}$ + 18° (C 0.12 in benzene) (*lit.*[151] $[\alpha]_D^{25}$ + 21° in benzene) ν_{max} (CH_2Cl_2) 2900, 2840, 1699, 1624, 1126, and 999 cm^{-1}; ^1H nmr ($CDCl_3$) δ 7.70 (1H, m, PhC=C-C<u>H</u>), 7.40 (5H, m, aryl-<u>H</u>), 6.88 (2H, m, PhC<u>H</u>=C and PhCH=C<u>H</u>-), 5.94 (1H, d, <u>J</u> 15 Hz, PhCH=CH-CH=C<u>H</u>-), 5.40 (1H, br s, C<u>H</u>=CR_2), 4.70 (1H, br s, <u>H</u>C-OR), and 0.67-2.40 (43H, m, saturated cholesterol-<u>H</u>); m/e No M^+ 368, 353, 278, 248, and 128.

<u>Preparation of Cholesteryl 4-Diphenylphosphinoyl-2-butenoate (239)</u>

Diphenylphosphinoacetaldehyde (226) (125 mg, 0.55 mmole) was suspended in THF (10 ml). The ylide (234) (379 mg, 0.55 mmole) was added. The mixture was heated at the reflux under nitrogen and the initially clear solution went cloudly as time progressed. After 24 h the reaction was allowed to cool and evaporated to dryness. The residue was dissolved in dichloromethane (30 ml) and this was shaken thoroughly with 3% hydrogen peroxide solution (25 ml). The organic layer was dried (sodium sulphate), filtered and evaporated and the residue purified by chromatography (eluant 2% methanol and 98% dichloromethane) to give the *title compound* (239) (114 mg, 32%), mp 218-21° (from dichloromethane and petroleum ether), $[\alpha]_D^{23.5}$ + 42° (C 0.01 in $CHCl_3$), ν_{max} (CH_2Cl_2) 2930, 2870, 1712, 1651, 1190, and 890 cm^{-1};

^{1}H nmr ($CDCl_3$) δ 7.62 (10H, m, aryl-H), 6.85 (1H, m, -P-CH_2CH), 5.88 (1H, dd, J_{HH} 16 Hz, J_{PH} 4 Hz, -P-CH_2-CH=CH), 5.35 (1H, br s, CH=CR_2), 4.58 (1H, br s, HCOR), 3.25 (2H, dd, J_{HH} 6.5 Hz, J_{PH} 14 Hz, aryl-P-CH_2), and 0.65-2.31 (43H, m, saturated cholesterol-H); m/e 654 (M^+), 386, 368, 353, 288, 269, 219, 201, 145, 105, and 95 (Found: C, 78.71; H, 9.19. $C_{43}H_{59}PO_3$ requires C, 78.86; H, 9.08%).

Preparation of (E),(E)-Cholesteryl 5-Phenyl-2,4-pentadienoate (240) Entry 2

To di-isopropylamine (12.6 mg, 17.5 µl, 0.125 mmole) in THF (2 ml) was added a solution of n-butyllithium in hexane (1.60M, 78 µl, 0.125 mmole) at -78° under an atmosphere of dry nitrogen. The solution was warmed to 0° and left for 0.5 h. The mixture was cooled to -78° and the hexane was removed at reduced pressure. A solution of cholesteryl 4-diphenylphosphinoyl-2-butenoate (239) (74 mg, 0.113 mmole) in THF (2 ml) was introduced and the solution warmed to 0° for 15 min. A pale green solution resulted. On cooling to -78° benzaldehyde (14.1 mg, 13.5 µl, 0.133 mmole) was added. The resultant solution was warmed to room temperature which slowly became a yellow suspension. After five days the reaction mixture was evaporated and the residue was purified by chromatography (30% dichloromethane and 70% petroleum ether) to give the title compound (240) (14 mg, 23%) identical in every respect with authentic material.

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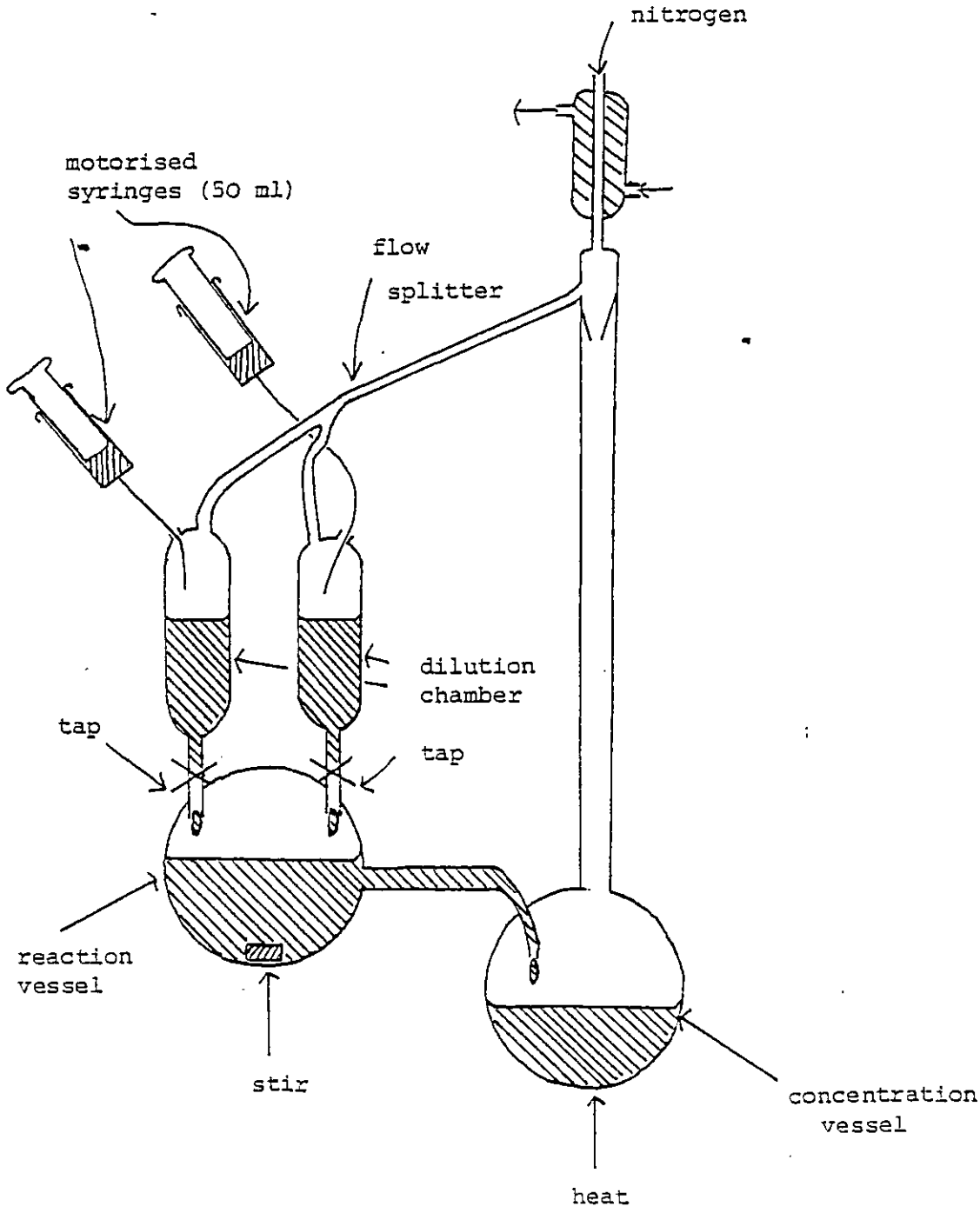
APPENDIX I

HIGH-DILUTION APPARATUS

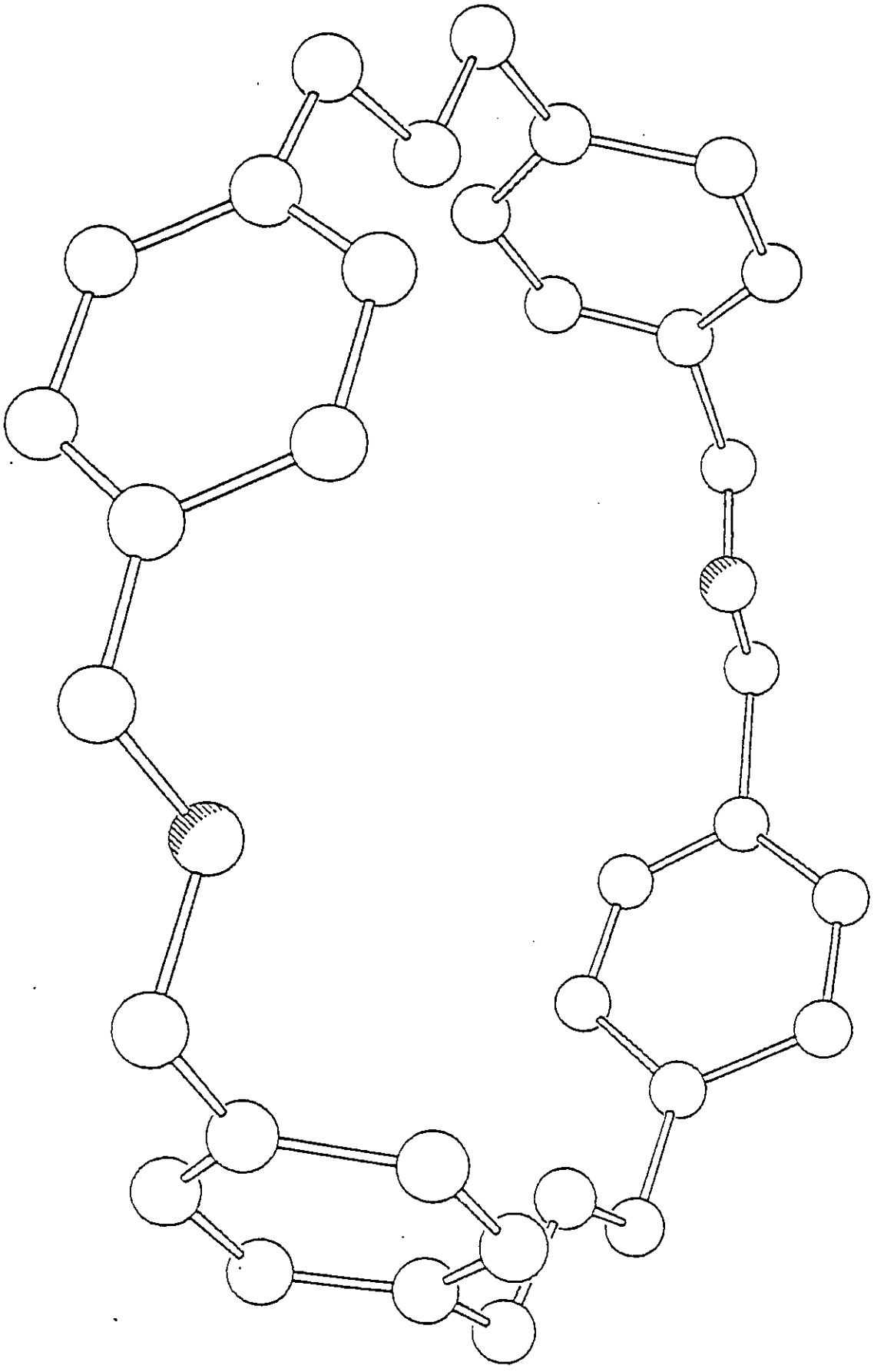
Approximately 15 mmole of each reactant is dissolved in 50 ml dichloromethane and added to the apparatus through the motorised syringes in 16 hours.



APPENDIX II

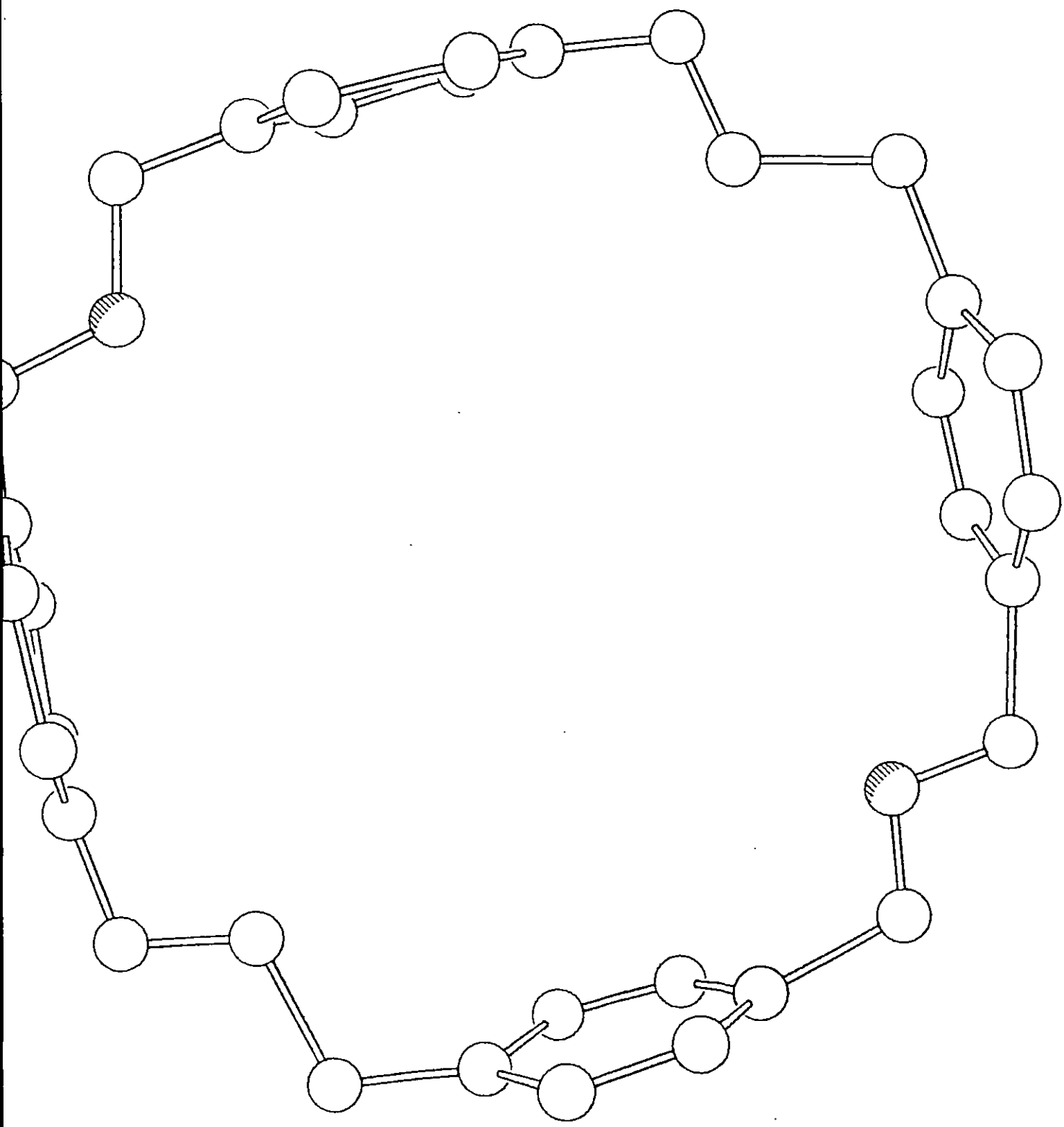
Crystal Data for 2,20-Di-aza[3.3.3.3]paracyclophane 1,4-Dioxan Complex.

Crystals of the complex $C_{34}H_{38}N_2.xC_4H_8O_2$, are tetragonal, a = 20.685(5), c = 10.158(2) Å, U = 4346 Å^3, space group $P\bar{4}$ 2,m, Z = 4. A total of 1620 independent reflections ($\theta \leqslant 55^\circ$) were measured on a diffractometer using Cu-K_α radiation (graphite monochromator) and of these 927 had $|Fo| > 3\sigma(|Fo|)$. The structure was solved by direct methods and refined anisotropically to R = 0.19.



X-ray view of compound (178) complex with dioxan.

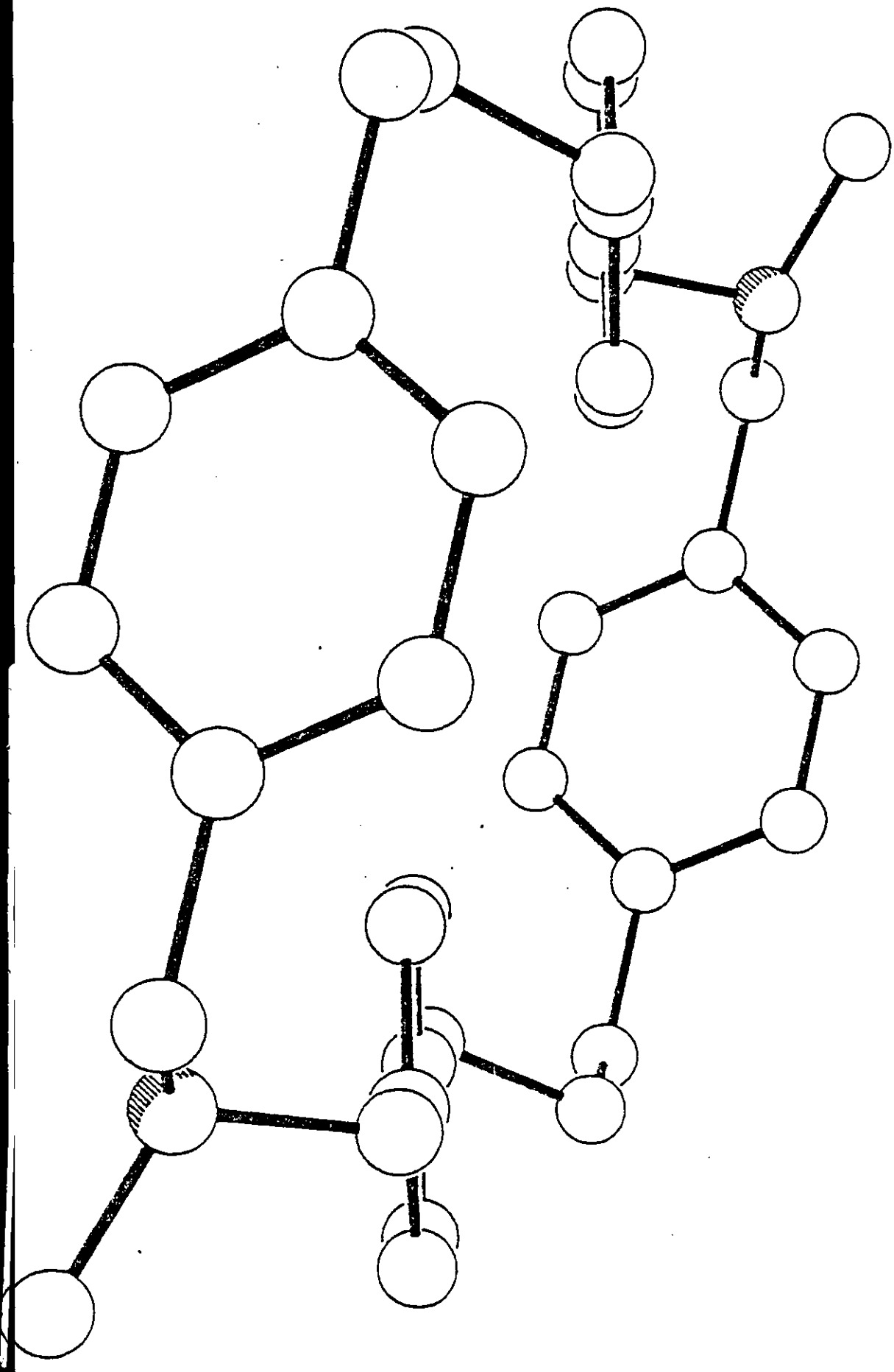
The dioxan molecules believed to be present were too disordered to be detected properly in this picture.



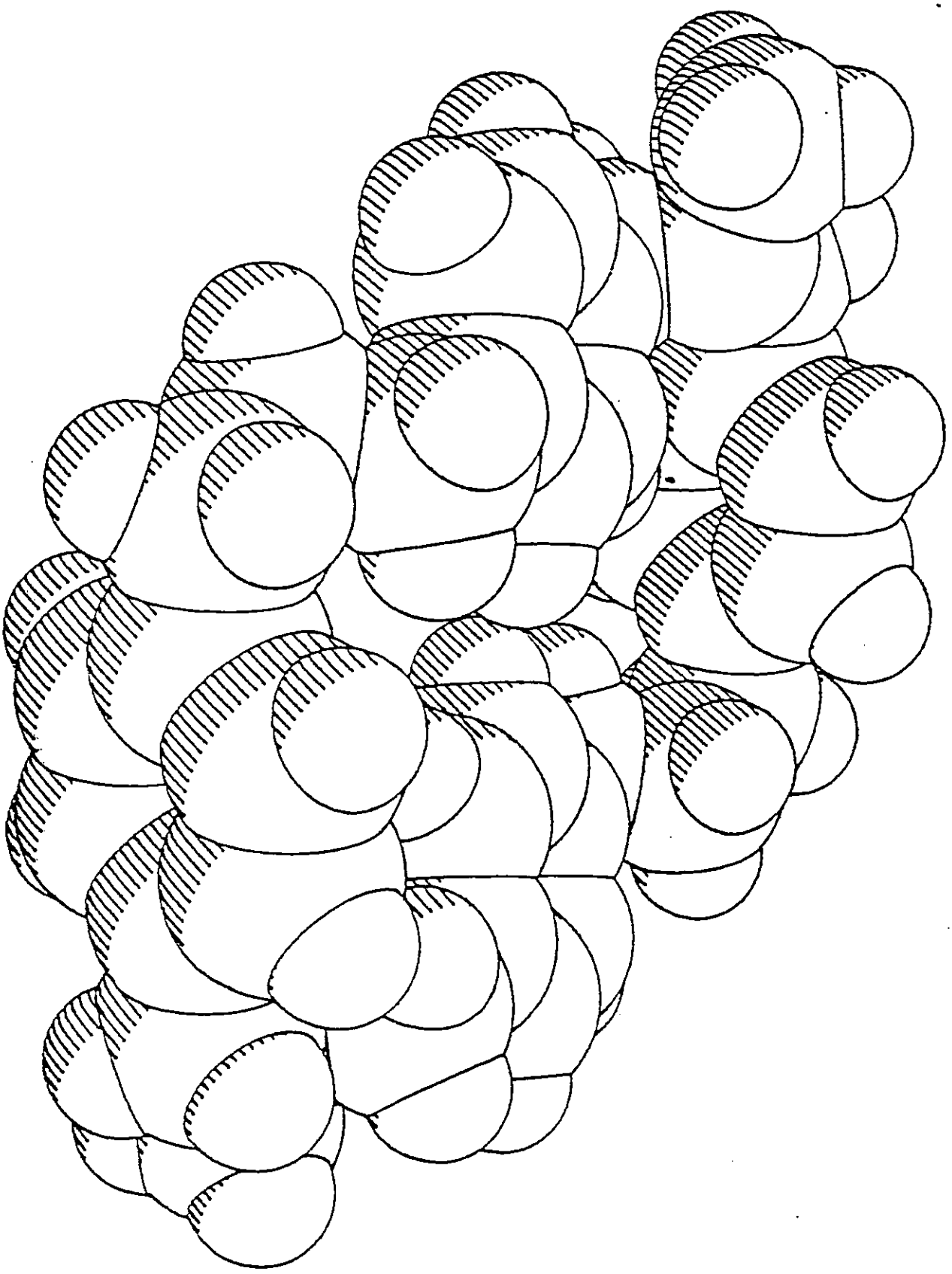
Another perspective view of the complex between compound (178) and dioxan.

Crystal Data for N,N′-Di-methyl-2,20-di-aza[3.3.3.3]paracyclophane (217).

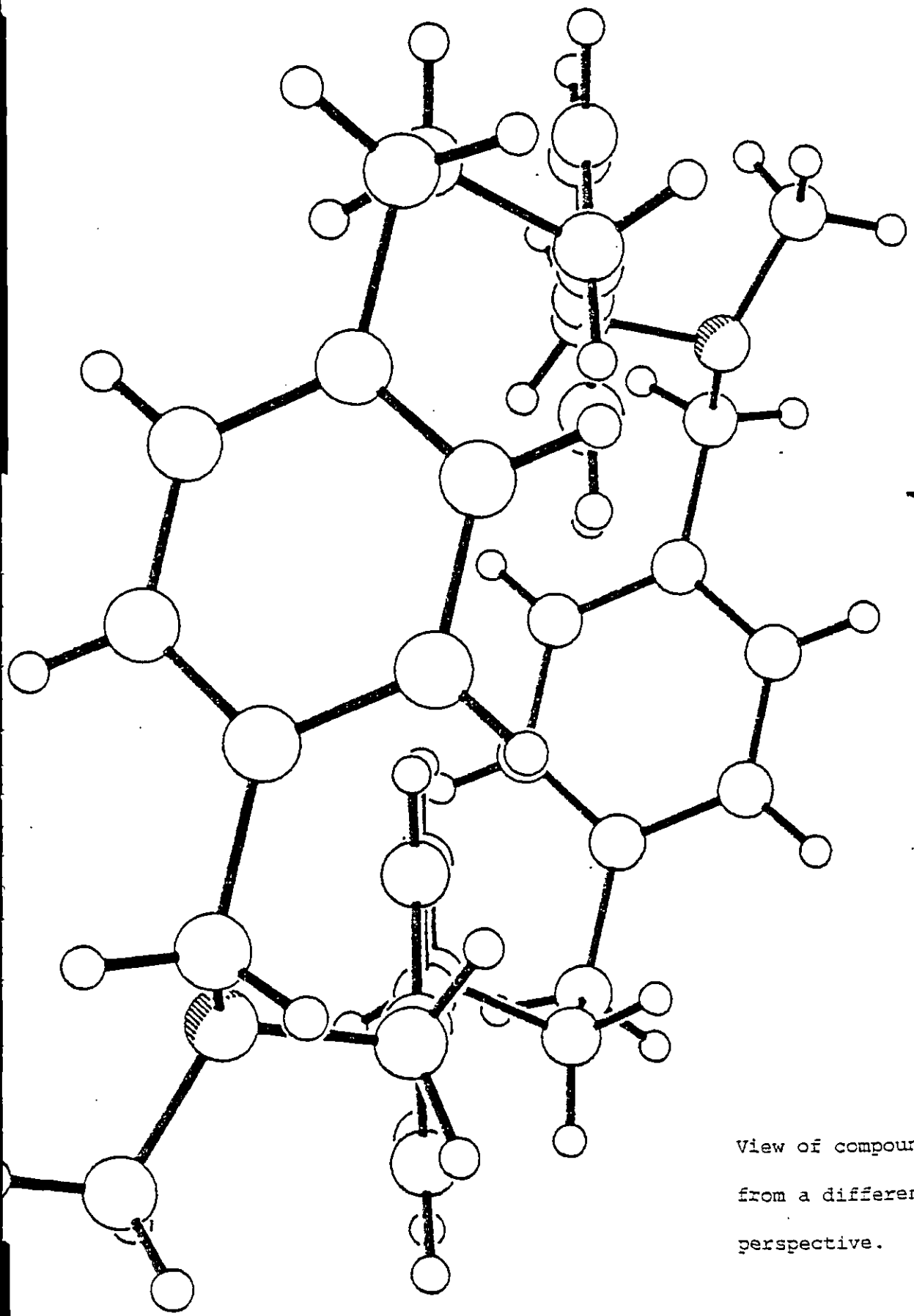
Crystals of $C_{36}H_{42}N_2$, M=502 are triclinic, a = 5.661(1), b = 10.823(2), c = 13.014(2) Å, α = 71.97(1)°, β = 88.33(1)°, γ 80.10(1)°, U = 747Å^3, space group $P\bar{1}$, Z = 1, molecule possesses a crystallographic centre of symmetry in centre of macrocycle. A total of 1855 independent reflections ($\theta \leqslant 55°$) were measured on a diffractometer using Cu-K_α radiation (graphite monochromator) and of these 1519 had $|Fo| > 3\sigma(|Fo|)$. The structure was solved by direct methods and refined anisotropically to R = 0.051.



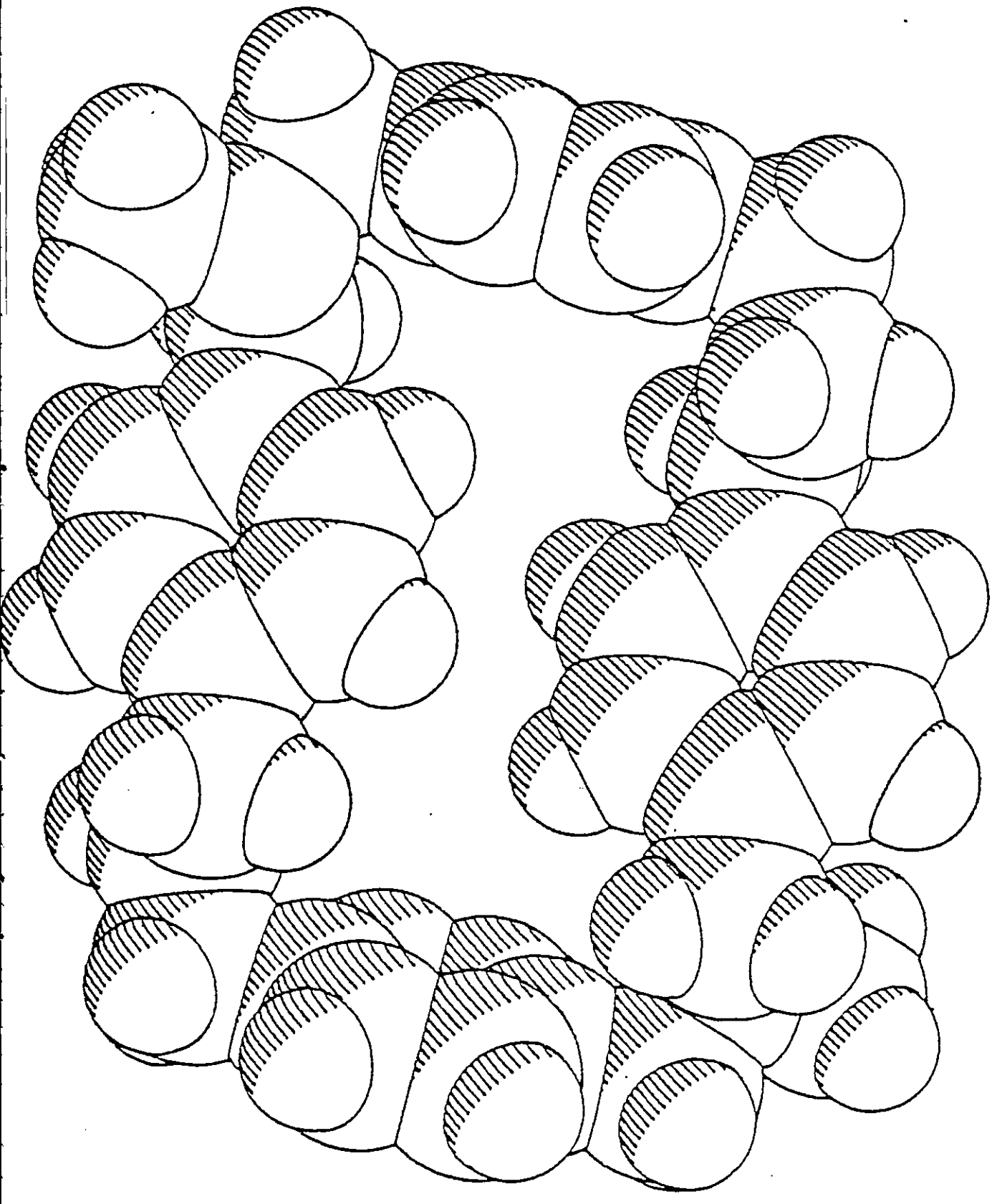
An X-ray view of compound (217)



Space-filling diagram of compound (217) from X-ray structure determination.



View of compound (217) from a different perspective.



Space-filling model view of compound (217) from a different perspective.

Inclusion Complexation of 1,4-Dioxan by an Azaparacyclophane; an *X*-Ray Crystallographic Study

Stephen J. Abbott,[a] Anthony G. M. Barrett,*[b] Christopher R. A. Godfrey,[b] S. Barret Kalindjian,[b] Gregory W. Simpson,[b] and David J. Williams*[b]

[a] *Imperial Chemical Industries, Heavy Chemicals New Science Group, P.L.C., PO Box No. 11, The Heath, Runcorn, Cheshire WA7 4QE, U.K.*

[b] *Department of Chemistry, Imperial College of Science & Technology, London SW7 2AY, U.K.*

An *X*-ray crystallographic study shows that 1,4-dioxan forms a 1 : 1 complex *via* incorporation within the dish cavity of the host *N,N',N'',N'''*-tetramethyl-2,11,20,29-tetra-aza[3.3.3.3]paracyclophane.

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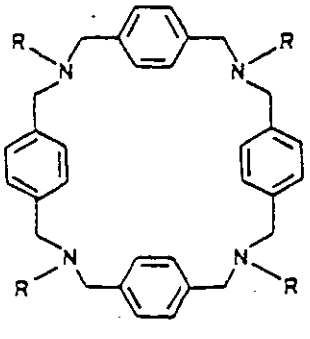
The design of polyfunctional host molecules for the *specific complexation* of guest species is an area of immense importance. In this context, we have had occasion to examine functionalised derivatives of the paracyclophane (1). Several di- and tetra-*N*-alkyl derivatives of this compound[1,2] and related systems[3,4] have been reported elsewhere. Urushigawa *et al.*[2] showed that the tetra-*N*-methyl derivative (1b) formed microanalytically pure benzene and 1,4-dioxan solvates. Herein, we report an *X*-ray crystallographic study of the latter, complex (2).



(1) a; R = H
b; R = Me

The host–guest complex (2) crystallised from dioxan to form a 1:1 solvate. *Crystal data:* Crystals of the complex, $C_{36}H_{44}N_4 \cdot C_4H_8O_2$, $M = 620.9$, are monoclinic, $a = 25.091(4)$, $b = 5.691(1)$, $c = 13.440(3)$ Å, $\beta = 112.06(2)°$, $U = 1779$ Å^3, space group $C2$, $Z = 2$, $D_c = 1.16$ g cm^{-3}. A total of 1340 independent reflections ($\theta \leqslant 58°$) were measured on a diffractometer using Cu-K_α radiation and of these 83 had $|F_o| < 3\sigma(|F_o|)$ and were classed as unobserved. The structure was solved by direct methods and refined anisotropically to $R = 0.056$.†

† The atomic co-ordinates for this work are available on request from the Director of the Cambridge Crystallographic Data Centre, University Chemical Laboratory, Lensfield Road, Cambridge CB2 1EW. Any request should be accompanied by the full literature citation for this communication.

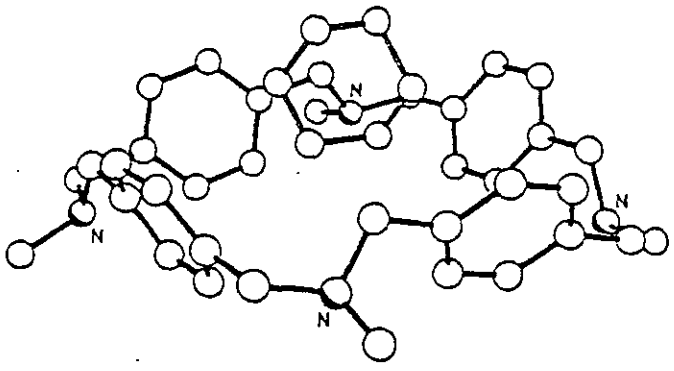


Figure 1. The molecular structure of the 1 : 1 complex of (1b) with 1,4-dioxan.

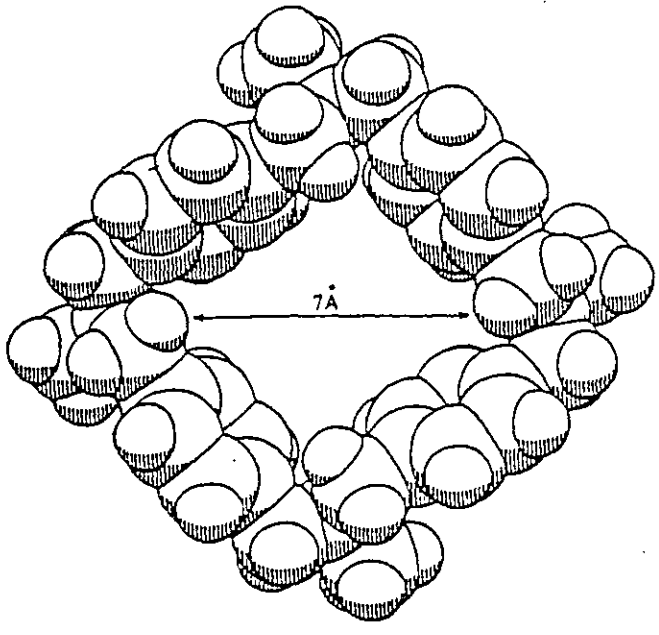


Figure 2. Space-filling drawing of the host in the complex (2) viewed down the crystallographic C_2 axis.

The complexed host molecule (Figure 1) adopts a 'dished' conformation with the planes of the aromatic rings nearly equally inclined (27.4 and 28.2°) to the crystallographic C_2 axis which passes through the centre of the macrocycle. Despite this dishing of the molecule, inspection of the space-filling representation of the host (Figure 2) shows there is still a significant free passage through the centre of the macrocycle. The molecules pack one above the other producing a continuous channel along the *b* direction. The maximum and minimum channel clear pathways are 7.0 and 4.4 Å respectively. A consequence of the dished conformation of the molecules and their packing one above another is the production of a 'cone in cone' structure (Figure 3) resulting in a widening of the channel from *ca.* 5 Å to a maximum of *ca.* 7 Å in the region between each layer of molecules and producing secondary cavities within which the guest dioxan molecules are located. These cavities are larger than are necessary to tightly hold the dioxan molecules which, as a consequence, adopt slightly differing orientations within each cavity.

This structural arrangement is similar to that observed for the complexation of durene by 1,6,20,25-tetra-aza[6.1.6.1]-paracyclophane.[4] However, in that instance the planes of the aromatic rings were parallel and the durene molecule inserted completely into the centre of the macrocycle. However in the complex (2) the host has appreciable conformational flexibility and hence the potential to adapt to include a wide range of guest species.

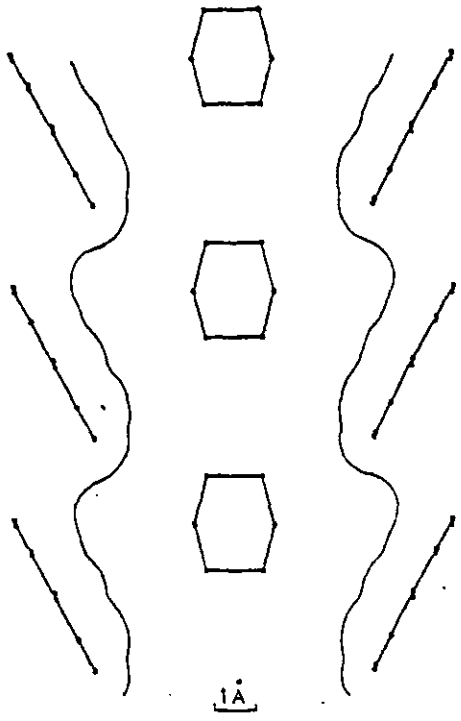


Figure 3. Cross-section of the channel showing the 'cone-in-cone' structure, the environment of the dioxan molecule, and the van der Waals' surface.

Inclusion complexation of this type is in striking contrast to that exhibited by the closely related tricyclic compounds such as tri-*o*-thymotide[5] and differently substituted trianthranilide derivatives.[6] In these, the channels or cavities are created by the packing of the molecules, *i.e.* in the intermolecular regions, whilst in the complex (2) they are created either partially or completely within the molecules themselves, *i.e.* intramolecularly.

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